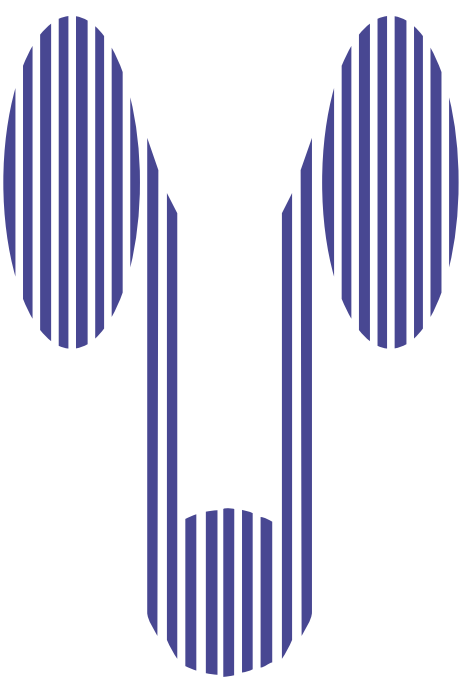
ISSN 1677-5538

INDEXED BY PubMed

International

Braz J Urol

Official Journal of the Brazilian Society of Urology
Official Journal of the Confederación Americana de Urologia
Volume 32, Number 2, March - April, 2006



International Braz J Urol

EDITOR'S COMMENT

The March - April 2006 issue of the International Braz J Urol presents interesting contributions, and as usual, the Editor's Comment highlights some important papers.

Doctors Evans and Morey, from the Brooke Army Medical Center, Fort Sam Houston, Texas, USA, well-known experts and pioneers in the field, present on page 131 a thorough review and state-of-the-art presentation on the current applications of fibrin sealant in urologic surgery. The authors verify that biosurgical preparations designed to promote surgical hemostasis and tissue adhesion are being increasingly employed in surgical specialties, and that fibrin sealant is the most widely studied and utilized biosurgical adjunct in urology. Complex reconstructive, oncologic, and laparoscopic genitourinary procedures are the most appropriate for sealant use. In this article, the authors detail the different urologic applications of fibrin sealant in the management of genitourinary injuries, surgery, and complications, and give several illustrative practical examples of its use. The authors draw attention to the fact that hemostatic agents and tissue sealants should not be viewed as a replacement for conventional sound surgical judgment or technique, but rather as complementary adjuncts to improve surgical outcome.

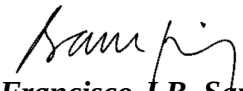
Doctor Romero and colleagues, from the James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Maryland, USA, present on page 196 a surgical technique article on the refinement of laparoscopic retroperitoneal lymph node dissection (L-RPLND) for testicular cancer. The authors have a 14-year experience on this procedure, initially for stage I nonseminomatous germ cell tumors (NSGCT) and later for post-chemotherapy patients who required resection of residual retroperitoneal masses. They have performed 92 L-RPLND for testicular cancer. Seventy-six (82.6%) patients underwent a complete template dissection, and sixteen (17.4%) patients underwent an abbreviated dissection due to positive lymph nodes found on frozen section. Median age was 30.5 years-old (range 15 to 45). Seventy-seven (83.7%) patients underwent L-RPLND for clinical stage I or II NSGCT of the testis, and 15 (16.3%) patients for residual retroperitoneal mass following chemotherapy. In this article, the authors describe the current technique employed at John Hopkins, and provide illustrations of all surgical steps, delineating the refinements of the technique over time.

Doctor Ziaee and co-workers, from Tehran University of Medical Sciences, Tehran, Iran, assessed on page 181 the effect of allopurinol in the treatment of chronic nonbacterial prostatitis. In this randomized double blind controlled trial an "intervention group" received allopurinol (100 mg tds for 3 months) with ofloxacin (200 mg tds) for 3 weeks (n = 29) and a "control group" received

placebo tablets with ofloxacin (n = 27). The results show that the 2 groups were similar regarding outcome variables. In the first month of study, a significant but similar improvement in symptom scores was observed in both groups. Microscopic examination of prostate massage and post-massage samples were also similar in both groups. No side effects due to allopurinol were observed in patients. The authors did not find any advantage for allopurinol in management of chronic prostatitis versus placebo in patients receiving routine antibacterial treatment. The present study is important, because this is the only additional study on allopurinol for chronic nonbacterial prostatitis, after the paper of Persson et al. (J Urol. 1996; 155: 961-4) which had concluded that allopurinol has a significant, positive effect on nonbacterial prostatitis, and many urologists did not trust that conclusion.

Doctor Billis and colleagues, from the State University of Campinas, Sao Paulo, Brazil, compared on page 165 the clinicopathologic characteristics and the time to PSA progression following radical retropubic prostatectomy of patients with clinical stage T1c tumors to those with stage T2, T2a or T2b tumors. They analyzed 186 patients submitted to prostatectomy with clinical stage T1c (33.52%) tumors, stage T2a (45.45%) and stage (T2b 21.02%). The variables studied were age, preoperative PSA, prostate weight, Gleason score, tumor extent, positive surgical margins, extraprostatic extension (pT3a), seminal vesicle invasion (pT3b), and time to PSA progression. It was found that patients with clinical stage T1c were younger and had the lowest mean preoperative PSA. In the surgical specimen, they had higher frequency of Gleason score < 7 and more organ confined cancer. In 40.54% of the patients with clinical stage T2b tumors, there was extraprostatic extension (pT3a). During the study period, 54 patients (30.68%) developed a biochemical progression. The authors concluded that clinicopathological features are not similar considering clinical stage T1c versus clinical stages T2, T2a or T2b.

Doctor Borden and colleagues, from the Wake Forest University School of Medicine, North Carolina, USA, on an interesting article, review on page 142 five adult renal allograft recipients with ureteral obstruction managed with successful repetitive ureteral stenting. The patients underwent an average of 8.8 stent changes over a mean of 34.5-month follow up. No decline in renal function was observed. The authors demonstrate that repetitive stenting is a viable treatment option for select patients with renal allograft ureteral obstruction. Doctor Ricardo J. Duarte, from University of Sao Paulo, provided an editorial comment on this paper.



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

Review Article
International Braz J Urol Vol. 32 (2): 131-141, March - April, 2006

Current Applications of Fibrin Sealant in Urologic Surgery

L. Andrew Evans, Allen F. Morey

Urology Service, Brooke Army Medical Center, Fort Sam Houston, Texas, USA

ABSTRACT

Biosurgical preparations designed to promote surgical hemostasis and tissue adhesion are being increasingly employed across all surgical disciplines. Fibrin sealant is the most widely studied and utilized biosurgical adjunct in urology. Complex reconstructive, oncologic, and laparoscopic genitourinary procedures are those most appropriate for sealant use. This article details the diverse urologic applications of fibrin sealant in the management of genitourinary injuries, surgery, and complications.

***Key words**: fibrin sealant; urology; hemostasis; complications; surgery; biologics*
Int Braz J Urol. 2006; 32: 131-41

INTRODUCTION

Although most applications are off-label, tissue sealants and hemostatic agents are being increasingly employed across all surgical disciplines. Biosurgical compounds can serve as adjuncts to primary surgical therapy or may assist in managing or preventing surgical complications. In urology, hemostatic agents and tissue sealants are finding increasing roles in managing traumatic and iatrogenic urologic injuries and promoting optimal wound healing.

Among the variety of hemostatic products now available in the United States (Table-1), fibrin sealant is the most widely utilized biosurgical agent in urologic surgery. This article details the diverse urologic applications of fibrin sealant for hemostasis, tissue adhesion, and urinary tract sealing.

FIBRIN SEALANT

Development

Mixtures of coagulation factors have been used in surgery for almost a century, dating back to the use of a fibrin emulsion by Bergel in 1909 to promote wound healing (1). Purified thrombin became available in 1938, and was first combined with fibrinogen in 1944 to enhance adhesion of skin grafts to burned soldiers (2). Although commercial fibrin sealant has been widely used in Europe since the 1970's, concerns about possible viral transmission limited sealant use in the United States until recently. In 1998, Tisseel® (Baxter Healthcare, Deerfield, Illinois) became the first fibrin sealant approved by the Food and Drug Administration (FDA) for use in the United States.

Although the three FDA approved indications for fibrin sealant are reoperative cardiac surgery, colon anastomosis, and treatment of splenic injury, fibrin sealants have been successfully employed in countless numbers of non-urologic surgical applications, including liver laceration, hepatic resection, bowel and vascular anastomoses, enterocutaneous and anorectal fistulae closure, cardiothoracic surgery, and neurosurgery. A review in 2002 by Shekarriz & Stoller (3) was the first major contemporary urological publication addressing the use of fibrin sealant in uro-

Table 1 – *Hemostatic agents and tissue adhesive available in the United States.*

Hemostatic Agents		
Component	**Brand Name**	**Manufacturer**
Fibrin sealant	Tisseel VH ® Crosseal®	Baxter Healthcare Omrix
Gelatin matrix thrombin	FloSeal®	Baxter Healthcare
Thrombin	Thrombin-JMI®	Jones Pharma
Gelatin sponge	Gelfoam®	Pharmacia Upjohn
Oxidized cellulose	Surgicel®	Ethicon
Collagen sponge	Actifoam®	CR Bard
Collagen fleece	Avitene®	CR Bard
Recombinant factor VIIa	NovoSeven®	Novo Nordisk A/S
	Tissue Adhesives	
Fibrin sealant	Tisseel VH ® Crosseal®	Baxter Healthcare Omrix
Polyethylene glycol	CoSeal®	Baxter Healthcare
Cyanoacrylate	Dermabond®	Ethicon

logic surgery, and an increasing number of urological sealant applications have followed.

Composition

Fibrin sealant contains 2 major components (thrombin and highly concentrated fibrinogen) which replicate and augment the final stage of the coagulation cascade—the cleavage of fibrinogen into fibrin by the action of thrombin—when mixed together. It is important to note that the fibrinogen concentration of sealant is supraphysiologic, 15 to 25 times higher than that of circulating plasma. The resultant clot tends to form more rapidly and more reliably than normal. Other key components of fibrin sealant are Factor XIII, which covalently crosslinks the fibrin polymer to produce an insoluble fibrin coagulum, and an antifibrinolytic agent which inhibits fibrinolysis thus preserving the stable fibrin clot (Figure-1).

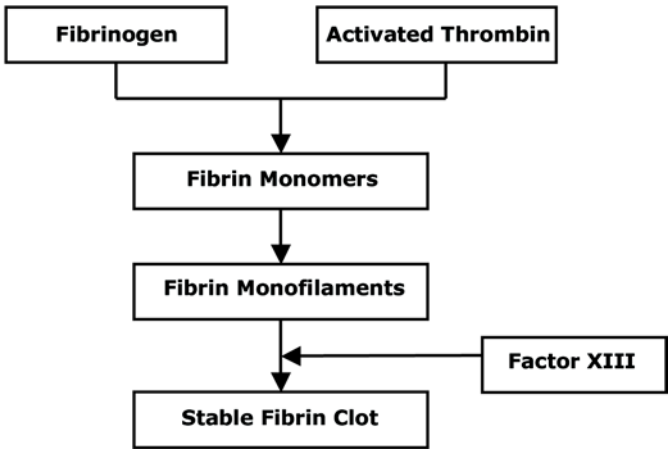


Figure 1 – *Mechanism of action of liquid fibrin sealant in recapitulating the terminal portion of the coagulation cascade.*

Tisseel® (Baxter Healthcare, Deerfield, Illinois) and Crosseal® (Omrix Biopharmaceuticals, Ltd, Israel) are the two fibrin sealants currently marketed in the United States. Tisseel® contains bovine aprotinin as its antifibrinolytic agent. Aprotinin is a serine protease inhibitor derived from bovine lung that works to limit fibrinolysis by inhibiting plasmin, kallikrein, and trypsin. Crosseal utilizes only human-derived proteins by including tranexamic acid as its antifibrinolytic agent instead of bovine aprotinin. Tranexamic acid is a synthetic analogue of the amino acid lysine and competes for lysine binding sites on plasminogen and plasmin, preventing binding to fibrin and inhibiting fibrinolysis (4).

Safety

All approved fibrin sealant preparations utilize a combination of donor screening, serum testing and retesting after 90 days storage, and a two-step vapor heating process to ensure viral safety (5,6). These steps are highly effective in ensuring viral safety and, to our knowledge, there are in 2005 still no reported transmissions of blood-borne viral pathogens associated with the use of FDA approved fibrin sealants (5). One parvovirus B19 transmission involving a non-FDA approved fibrin sealant was reported from Japan, but most adults have preexisting antibodies to this virus and the infection is usually a self-limited diarrhea (7).

Delivery Methods

Fibrin sealants are administered using a dual-chamber delivery system in which one chamber containing fibrinogen and factor XIII is admixed with the other chamber containing thrombin directly at the site of application using a "Y" adaptor, allowing an immediate conversion of fibrinogen to fibrin as the solutions exit the syringe. Dual lumen catheters ensure smooth, rapid sealant delivery, and a variety of specialized catheters and cannulae are available for endoscopic, laparoscopic, and open surgical application. We have also successfully used a dual lumen peripherally inserted central catheter (PICC) line for percutaneous transrenal application (8). Polymerization into the biocompatible fibrin clot is completed within 3 minutes (9), and the clot is gradually broken down and removed from the site by macrophages within 2-4 weeks, eventually becoming histopathologically invisible, without fibrosis or foreign-body reaction (10).

UROLOGICAL APPLICATIONS

Commercial fibrin sealant is employed for three major reasons in urologic surgery - as a hemostatic agent, a urinary tract sealant, and/or a tissue adhesive. A list of the most common urological applications is presented in Table-2. Fibrin sealant's unique properties as a hemostatic agent, urinary tract sealant, and tissue adhesive make it an effective adjunct for managing complex urologic injury and promoting wound healing in the genitourinary tract.

Table 2 – *Urological applications of fibrin sealant.*

I. Hemostasis
Partial nephrectomy
Open
Laparoscopic (13-16)
Percutaneous nephrolithotomy (22)
Management of splenic injury (23)
Hemophilia and other coagulopathy (24)
Circumcision (25)
Hemorrhagic cystitis (27)
II. Urinary Tract Sealant
Laparoscopic and open pyeloplasty (31-34)
Ureteral anastomoses (31-34)
Urethral reconstruction (37)
Simple retropubic prostatectomy (35)
Radical retropubic prostatectomy (36)
Bladder injury (24)
Lymphadenectomy (38,39)
Percutaneous nephrolithotomy tract closure (22)
III. Tissue Adhesion
Fournier's gangrene reconstruction (41,42)
Fistula closure (24,45,46)
Skin grafting (42)
Complex urethroplasty (37)

Hemostasis

Partial Nephrectomy

Fibrin sealant has been used since 1979 in open partial nephrectomy (11). The recent advent of minimally invasive techniques for nephron sparing surgery has resulted in widespread fibrin sealant use during laparoscopic partial nephrectomy today (12-15). A recent survey of 193 members of the World Congress of Endourology discovered 68% of surgeons routinely utilized fibrin sealant to assist with hemostasis during laparoscopic partial nephrectomy (16). Application of fibrin sealant to the cut surface of the renal parenchymal wound after segmental vascular and collecting system suture ligation during partial nephrectomy enhances hemostasis. The fibrin sealant layer can then be supported by a gelatin or collagen bolster, which is effectively glued into the renal defect by holding manual pressure on the bolster "sandwich". In vivo testing of fibrin sealant in a porcine model of open partial nephrectomy demonstrated supra-physiological sealing pressures of the renal parenchymal vasculature (mean 378 mm Hg) and collecting system (mean 166 mm Hg) compared to unsealed controls (17).

Renal Trauma

In 1989, Kram and colleagues first reported fibrin sealant use in 14 patients with traumatic renal injuries: renal salvage was achieved in all cases with no postoperative infection, delayed hemorrhage, or urinoma formation (18). In 2004, our laboratory reported the effective use of FDA-approved fibrin sealant in central porcine renal stab wounds when used in conjunction with a bolster of absorbable gelatin sponge or microfibrillar collagen (19). Though not yet commercially available, the absorbable fibrin adhesive bandage (AFAB), a similar product consisting of dry fibrin sealant on a polyglactin mesh backing developed in conjunction with the American Red Cross, significantly reduced bleeding in addition to operative and ischemic times in repair of porcine models of lower renal pole amputation (20) and grade IV renal stab wounds (21).

Miscellaneous Hemostatic Applications

Noller et al. reported no hemorrhagic complications in 10 consecutive renal units treated with fibrin sealant-assisted tubeless percutaneous nephrolithotomy (PCNL) (22). The instillation of 2 to 3 mL of fibrin sealant into the parenchymal defect is performed as the sheath is removed at the conclusion of PCNL in lieu of nephrostomy drainage. Postoperative computed tomography has confirmed the absence of perirenal hematomas in these "tubeless" procedures.

We have found that intraoperative splenic injury during left nephrectomy is easily managed with direct application of fibrin sealant to the bleeding parenchyma, thereby promoting prompt hemostasis and avoiding the need for splenectomy (23). Fibrin sealant has also been successfully used to control "medical" bleeding caused by warfarin use or other coagulopathies during urologic surgical procedures (24,25). Other urologic hemostatic applications include sealing the oral mucosal donor site during buccal graft urethroplasty (26) and cystoscopic application of fibrin sealant after fulguration to provide hemostasis in refractory radiation-induced hemorrhagic cystitis after supravesical urinary diversion (27).

Urinary Tract Sealant

A variety of non-urological studies has suggested the increased strength of sealed anastomoses. Skin sutures supported by a layer of fibrin sealant provided watertight anastomoses immediately after surgery and withstood significantly higher hydrostatic pressures than non-sealed anastomoses (28). Han et al. noted that microvascular sutured anastomoses supported by fibrin sealant had enhanced re-endotheliazation (29), and Park et al. reported significantly increased tensile strength in sealed skin closure versus controls (30).

Ureteral Anastomosis

Kram and colleagues first reported the successful use of fibrin sealant as a bolster over the suture line for ureteral anastomosis in 1989 (18). We have found fibrin sealant to be a useful adjunct in managing a variety of ureteral injuries, both iatrogenic and traumatic, and have frequently performed

"drain-free" sealed repairs. Between 2001 and 2003, 10 patients underwent definitive management of ureteral injury at our institution. Our experience has shown that sealant effectively prevents ureteral urinary extravasation and has not been associated with postoperative infection, leak, or scar formation (Figure-2). We believe that a sealed, stented ureteral repair is prudent in cases where a transabdominal approach has been performed because transabdominal drains are avoided. We also feel it is important to apply the sealant as a means of "suture support" by reinforcing standard suture lines, not in lieu of careful suture repair.

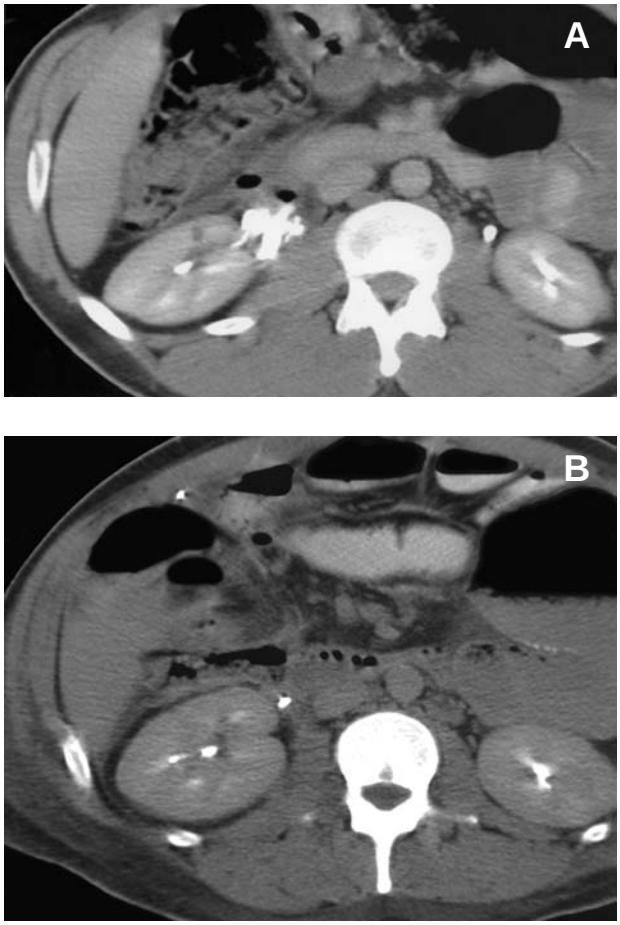


Figure 2 – *A) Stab wound to right flank with medial perirenal contrast material extravasation on preoperative trauma computed tomography (CT). A 4 cm laceration to the right renal pelvis was successfully repaired using 5-0 PDS suture with the application of a bolster of 5 cc of fibrin sealant over the suture line to reinforce urinary tract seal. No drain was placed. B) Postoperative CT image obtained 72 hours later demonstrates drain-free intact repair over ureteral stent without evidence of extravasation or urinoma.*

The increasing performance of laparoscopic renal reconstruction surgery may lead to increased sealant use. Fibrin sealant has been shown to successfully support approximating sutures in a porcine model of laparoscopic ureteral anastomoses (31) and has improved radiographic outcomes compared to free needle suturing and laser weld closure (32). A variety of studies have shown fibrin sealant to be effective as a bolster for laparoscopic pyeloplasty or collecting system repair (33), and satisfactory drainage has been confirmed by radiologic imaging at one to two years (34).

Prostatectomy

Drain-free simple retropubic prostatectomy has been successfully performed in over 25 cases in our institution, and we have demonstrated a faster return to regular diet and shortened hospital stay when compared with conventional simple prostatectomy (35). Again, we believe it is important to apply the sealant outside the urinary tract, over the sutured prostatic capsular closure, to ensure that the fibrin clot does not occlude urinary catheter drainage. Similarly, Diner et al. reported in 2004 that a significant decrease in postoperative drain output was noted in 16 patients following radical retropubic prostatectomy when 5 cc of fibrin sealant was applied to the suture line of the urethrovesical anastomosis (36). Earlier drain removal should facilitate a more expedient recovery and earlier discharge from the hospital leading to cost savings.

Urethroplasty

Fibrin sealant appears to allow earlier catheter removal, improved patient satisfaction, and enhanced wound healing after pendulous urethroplasty (37). In our experience of applying fibrin sealant directly over a suture line of 5-zero polydiaxanone during pendulous urethroplasty in 18 patients, a completely healed anastomosis was confirmed by voiding cystourethrography (VCUG) performed 1 week postoperatively in 83% of patients; all 18 patients demonstrated complete healing within 14 days, com-

pared to 8% of patients in the control group who had persistent extravasation at 21 days postoperatively ($p < 0.05$). Pendulous urethral reconstruction seems to be uniquely well-suited for sealant use because the superficial nature of the urethra in this location does not provide the robust surrounding spongy tissues that are routinely found in the bulbar urethra (Figure-3).

Complication Management

Fibrin sealant appears to promote the successful transvaginal management of iatrogenic cystotomy sustained during transvaginal hysterectomy. We observed that direct transvaginal fibrin sealant injection functions well as a bolster interposition over the cystotomy repair, thus preventing the additional time and morbidity required for abdominal bladder repair or tissue interposition with a Martius or omental flap (24). Fibrin sealant has also been utilized to prevent lymphocele formation after lymphadenectomy (38). Used as a sclerosant after percutaneous drainage of postoperative lymphoceles in renal transplantation, instillation of fibrin sealant achieved complete resolution of the lymphocele in 75% of patients without the need for open surgical management (39). Percutaneous transrenal application of 5 cc of fibrin sealant across a refractory calyceal urinary leak secondary to gunshot wound has proven effective in sealing refractory collecting system injury (8).

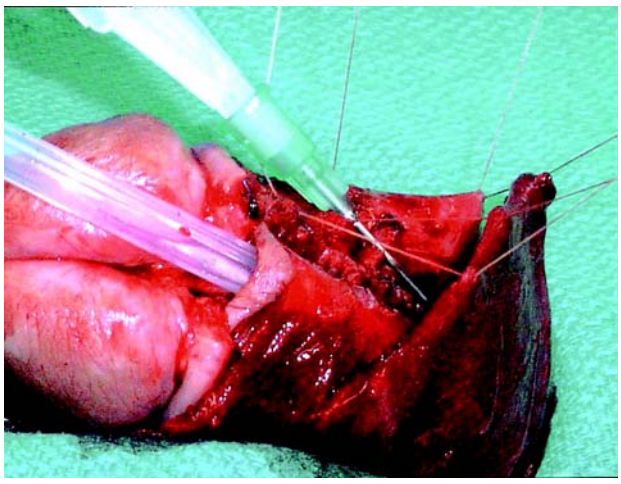


Figure 3 – *Application of fibrin sealant as a bolster over the suture line of pendulous urethroplasty. Redundant tunica dartos pedicle is glued in place over suture line.*

Tissue Adhesion

Tissue Planes

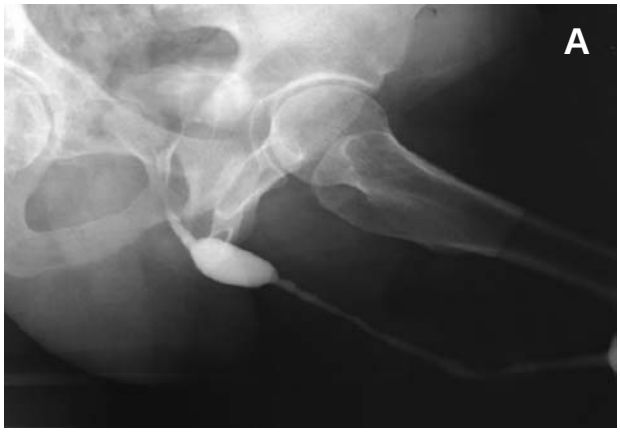
The fibrin polymer resulting from fibrin sealant application facilitates wound healing by increasing tissue plane adherence, thus eliminating dead space, accelerating revascularization, reducing hemorrhage, preventing seroma, and minimizing inflammation (40).

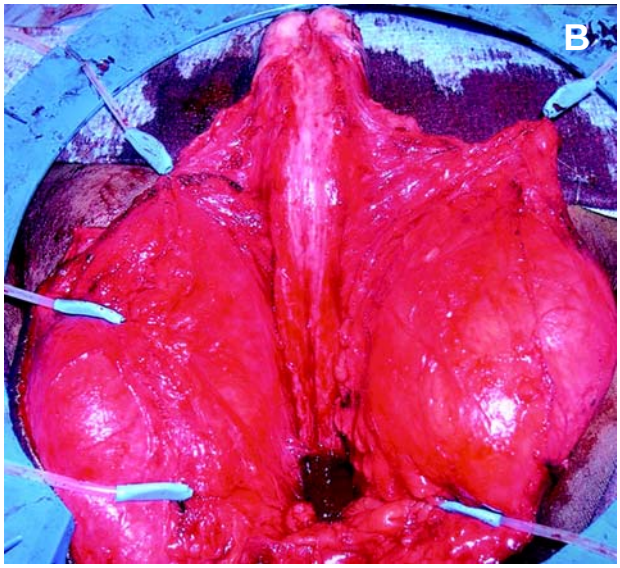
Tissue sealant properties of fibrin sealant have been applied to reduce air leaks and bronchopleural fistulae after pulmonary resection and decortication, secure skin grafts in reconstructive and burn surgery, and occlude chronic enterocutaneous and anorectal fistulous tracts.

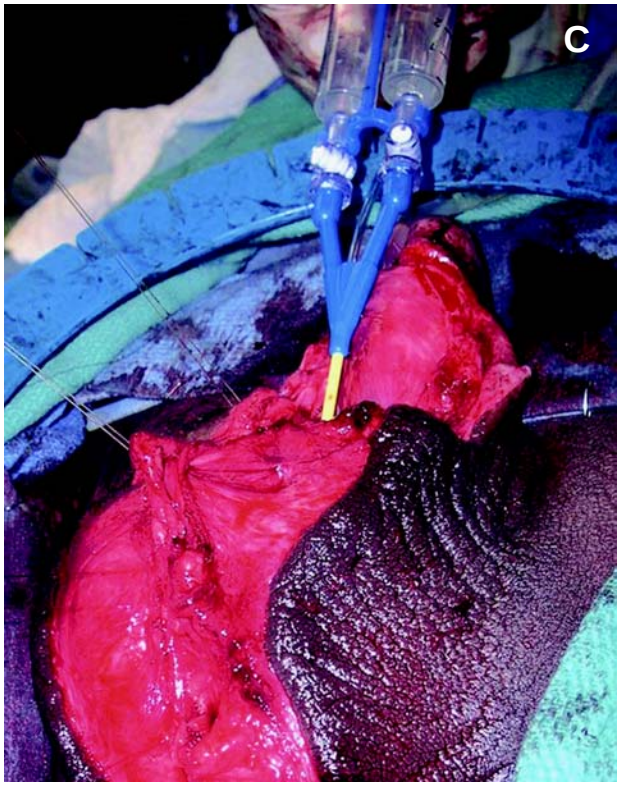
Fibrin sealant is now routinely used at our institution during complex urethroplasty, especially cases requiring panurethral reconstruction (Figure-4). The scrotum is completely bivalved to provide wide access to the underlying diseased urethra, and the scrotal wings are glued together with sealant after urethral repair to prevent edema and hematoma. Similar efficacy has been reported in 17 patients undergoing complex genital reconstructive surgery such as spit-thickness skin grafting and thigh flap surgery for Fournier's gangrene sequelae and invasive penile cancer: 94% of patients recovered without infection, seroma, hematoma, or other complications (Figure-5) (41,42).

Urinary Tract Fistulae

In addition to sealing tissue planes, fibrin sealant promotes closure of urinary fistulae by promoting the local proliferation of fibroblasts and subsequent replacement by connective tissue, allowing for occlusion of the fistulous tract (6). The fibrin polymer promotes the ingrowth of fibroblasts during wound healing and an influx of immune cells is stimulated in a paracrine fashion (43). The complex interaction of neutrophils, macrophages, and fibroblasts provides the basis of wound contraction and remodeling necessary for healthy wound healing. The recent application of the Vacuum Assisted Closure® (VAC®, Kinetic Concepts, Inc., San Antonio, Texas) device in closing larger complex wounds is believed to function through similar cellular mechanisms (44).







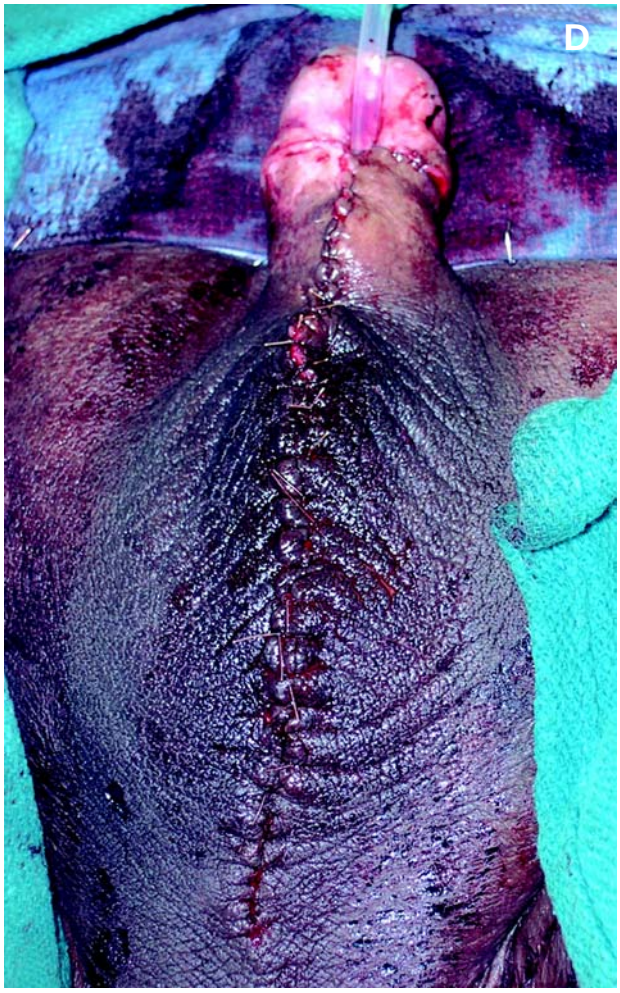


Figure 4 – *Panurethral reconstruction. A) Preoperative retrograde urethrogram shows extensive urethral stricture. B) Penile base, scrotum, and perineum are completely bivalved, thus allowing excellent exposure for urethral reconstruction. Buccal grafts were required in this case to reconstruct a 17 cm defect. Fibrin sealant is applied as a bolster to the suture lines and as a tissue adhesive to glue the scrotal wings back together with good hemostasis. C) Application of fibrin sealant to glue scrotal wings together after urethral reconstruction. D) Postoperative result after scrotum is glued and sutured back together shows no ecchymosis, edema, or drain requirement.*

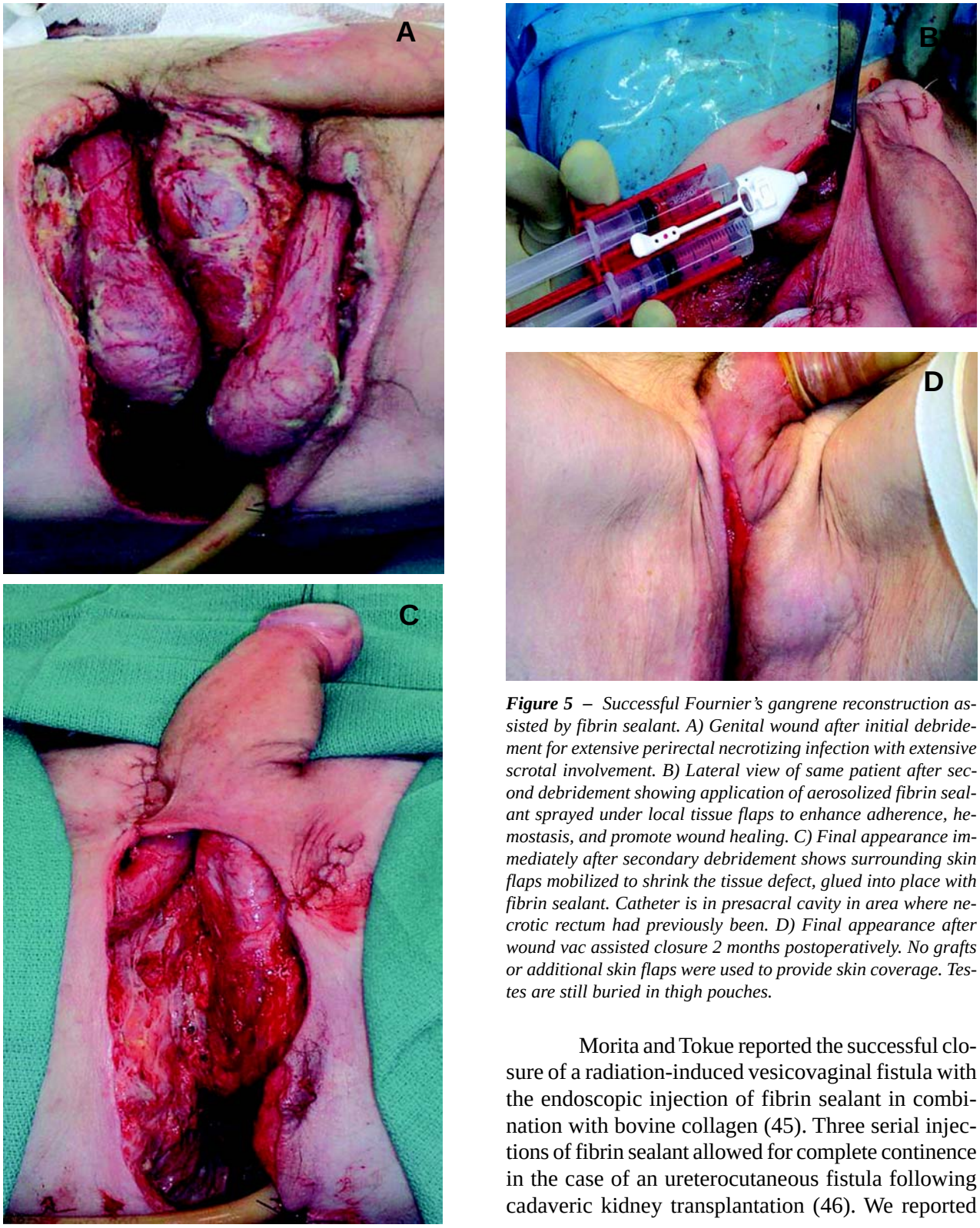


Figure 5 *– Successful Fournier's gangrene reconstruction assisted by fibrin sealant. A) Genital wound after initial debridement for extensive perirectal necrotizing infection with extensive scrotal involvement. B) Lateral view of same patient after second debridement showing application of aerosolized fibrin sealant sprayed under local tissue flaps to enhance adherence, hemostasis, and promote wound healing. C) Final appearance immediately after secondary debridement shows surrounding skin flaps mobilized to shrink the tissue defect, glued into place with fibrin sealant. Catheter is in presacral cavity in area where necrotic rectum had previously been. D) Final appearance after wound vac assisted closure 2 months postoperatively. No grafts or additional skin flaps were used to provide skin coverage. Testes are still buried in thigh pouches.*

Morita and Tokue reported the successful closure of a radiation-induced vesicovaginal fistula with the endoscopic injection of fibrin sealant in combination with bovine collagen (45). Three serial injections of fibrin sealant allowed for complete continence in the case of an ureterocutaneous fistula following cadaveric kidney transplantation (46). We reported

the successful definitive treatment of 6 cases of vesicocutaneous and urethrocutaneous fistulae by sealing the tract with the direct injection of 5 cc commercial fibrin sealant in conjunction with open or endoscopic fulguration (24) (Figure-6). We have not found sealant to be effective in vesicovaginal fistula, however, and this is probably because these fistulas are too short and broad compared with the long, thin fistulas typically found extending from the lower urinary tract in males.

SAFETY CONSIDERATIONS

Fibrin sealant should not be placed into large blood vessels due to the risk for potential thromboembolism. Repeat use of bovine thrombin preparations, which also contain bovine factor V, can induce the formation of antibodies that cross-react with human factor V and lead to a coagulopathic state (47). Pavlovich reported the postoperative development of coagulopathy due to repeat exposure to bovine thrombin during partial nephrectomy (48). The use of bovine-derived proteins carries a risk of allergic reaction upon re-exposure to the material, although bovine aprotinin (found in fibrin sealant) is much less immunogenic than thrombin (49).The reported incidence of hypersensitivity to intravenous aprotinin approaches 10%; thus, fibrin sealant containing bovine protein products should be used with caution in patients previously exposed to aprotinin (50).

CONCLUSIONS

Hemostatic agents and tissue sealants should not be viewed as a replacement for conventional sound surgical judgment or technique, but rather as complementary adjuncts to improve surgical outcome. Fibrin sealant offers an effective adjunct for hemostasis, reinforcement of urinary tract closure, and adhesion of tissue planes. Numerous reports in virtually all surgical disciplines have confirmed the reliable enhancement of wound healing promoted by fibrin sealant. Future development of novel biotherapeutic materials will continue to provide urologists with safe,

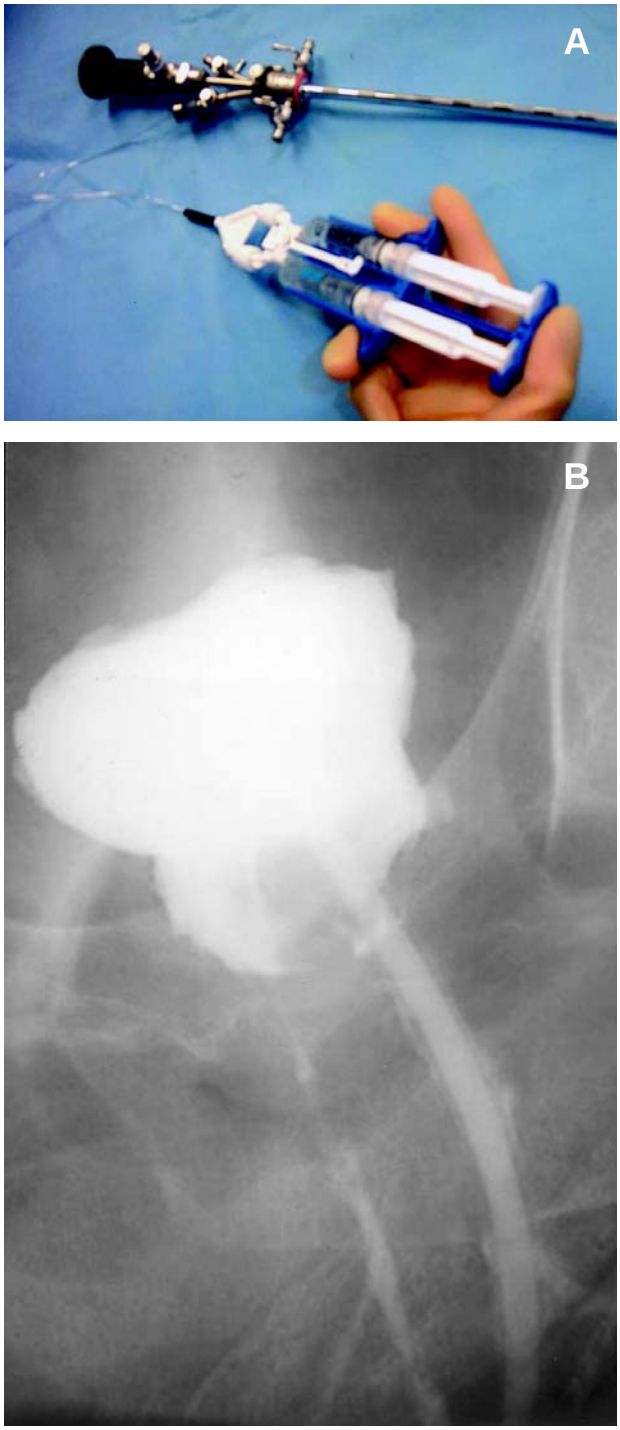


Figure 6 – *A) Cystoscopic injection via dual lumen catheter with "Y" adapter is one of several available devices for application of fibrin sealant. B) In this case, sealant was delivered cystoscopically to close a urethrocutaneous fistula after endoscopic fulguration.*

reliable agents for managing challenging urogenital injuries and complications.

DISCLAIMER

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of Defense or other departments of the U.S. Government.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Bergel S: Uber Wirkungen des Fibrins. Dtschr Med Wochenschr. 1909; 35: 633-65.
2. Cronkite EP, Lozner EL, Deaver J: Use of thrombin and fibrinogen in skin grafting. JAMA. 1944; 124: 976-8.
3. Shekarriz B, Stoller ML: The use of fibrin sealant in urology. J Urol. 2002; 167: 1218-25.
4. Dunn CJ, Goa KL: Tranexamic acid: a review of its use in surgery and other indications. Drugs. 1999; 57: 1005-32.
5. Jackson MR: Fibrin sealants in surgical practice: An overview. Am J Surg. 2001; 182: S1-S7.
6. Spotnitz WD: Commercial fibrin sealants in surgical care. Am J Surg. 2001; 182: 8S-14S.
7. Hino M, Ishiko O, Honda KI, Yamane T, Ohta K, Takubo T, et al.: Transmission of symptomatic parvovirus B19 infection by fibrin sealant used during surgery. Br J Haematol. 2000; 108: 194-5.
8. Baughman SM, Morey AF, Van Geertruyden PH, Radvany MG, Benson AE, Foley JP: Percutaneous transrenal application of fibrin sealant for refractory urinary leak after gunshot wound. J Urol. 2003; 170: 522-3.
9. Sapala JA, Wood MH, Schuhknecht MP: Anastomotic leak prophylaxis using a vapor-heated fibrin sealant: report on 738 gastric bypass patients. Obes Surg. 2004; 14: 35-42.
10. Martinowitz U, Saltz R: Fibrin sealant. Curr Opin Hematol. 1996; 3: 395-402.
11. Urlesberger H, Rauchenwald K, Henning K: Fibrin adhesives in surgery of the renal parenchyma. Eur Urol. 1979; 5: 260-1.
12. Wolf J, Seifman B, Montie J: Nephron sparing surgery for suspected malignancy: Open surgery compared to laparoscopy with selective use of hand assistance. J Urol. 2000; 163: 1659-64.
13. Janetschek G, Daffner P, Peschel R, Bartsch G: Laparoscopic nephron sparing surgery for small renal cell carcinoma. J Urol. 1998; 159: 1152-5.
14. Pruthi RS, Chun J, Richman M: The use of a fibrin tissue sealant during laparoscopic partial nephrectomy. BJU Int. 2004; 93: 813-7.
15. Finley DS, Lee DI, Eichel L, Uribe CA, McDougall EM, Clayman RV: Fibrin glue-oxidized cellulose sandwich for laparoscopic wedge resection of small renal lesions. J Urol. 2005; 173: 1477-81.
16. Gerber GS, Stockton BR: Laparoscopic partial nephrectomy. J Endourol. 2005; 19: 21-4.
17. Kouba E, Tornehl C, Lavelle J, Wallen E, Pruthi RS: Partial nephrectomy with fibrin glue repair: measurement of vascular and pelvicaliceal hydrodynamic bond integrity in a live and abbatoir porcine model. J Urol. 2004; 172: 326-30.
18. Kram HB, Ocampo HP, Yamaguchi MP, Nathan RC, Shoemaker WC: Fibrin glue in renal and ureteral trauma. Urology. 1989; 33: 215-8.
19. Griffith BC, Morey AF, Rozanski TA, Harris R, Dalton SR, Torgerson SJ, et al.: Central renal stab wounds: Treatment with augmented fibrin sealant in a porcine model. J Urol. 2004; 171: 445-7.
20. Cornum RL, Morey AF, Harris R, Gresham V, Daniels R, Knight RW, et al.: Does the absorbable fibrin adhesive bandage facilitate partial nephrectomy? J Urol. 2000; 164: 864-7.
21. Morey AF, Anema JG, Harris R, Gresham V, Daniels R, Knight RW, et al.: Treatment of grade 4 renal stab wounds with absorbale fibrin adhesive bandage in a porcine model. J Urol. 2001; 165: 955-8.
22. Noller MW, Baughman SM, Morey AF, Auge BK: Fibrin sealant enables tubeless percutaneous stone surgery. J Urol. 2004; 172: 166-9.
23. Canby-Hagino ED, Morey AF, Jatoi I, Perahia B, Bishoff JT: Fibrin sealant treatment of splenic injury during open and laparoscopic left radical nephrectomy. J Urol. 2000; 164: 2004-5.
24. Evans LA, Ferguson KH, Foley JP, Rozanski TA, Morey AF: Fibrin sealant for the management of genitourinary injuries, fistulas and surgical complications. J Urol. 2003; 169: 1360-2.
25. Martinowitz U, Varon D, Jonas P, Bar-Maor A, Brenner B, Leibovitch I, et al.: Circumcision in hemophilia:

the use of fibrin glue for local hemostasis. J Urol. 1992; 148: 855-7.
26. Riccabona M: Reconstruction or substitution of the pediatric urethra with buccal mucosa: indications, technical aspects and results. Tech Urol. 1999; 5: 133-8.
27. Ouwenga MK, Langston MD, Campbell SC: Use of fibrin sealant in recalcitrant Hemorrhagic cystitis. J Urol. 2004; 172: 1348.
28. Oosterlinck W, Cheng H, Hoebeke P, Verbeeck R: Watertight sutures with fibrin glue: an experimental study. Eur Urol. 1993; 23: 481-4.
29. Han SK, Kim SW, Kim WK: Microvascular anastomosis with minimal suture and fibrin glue: experimental and clinical study. Microsurgery. 1998; 18: 306-11.
30. Park W, Kim WH, Lee CH, Kim DY, Choi JH, Huh JW, et al.: Comparison of two fibrin glues in anastomoses and skin closure. J Vet Med A Physiol Pathol Clin Med. 2002; 49: 385-9.
31. McKay TC, Albala DM, Gehrin BE, Castelli M: Laparoscopic ureteral anastomosis using fibrin glue. J Urol. 1994; 152: 1637-40.
32. Wolf JS Jr, Soble JJ, Nakada SY, Rayala HJ. Humphrey PA. Clayman RV, et al.: Comparison of fibrin glue, laser weld, and mechanical suturing device for the laparoscopic closure of ureterotomy in a porcine model. J Urol. 1997; 157: 1487-92.
33. Patel R, Caruso RP, Taneja S, Stifelman M: Use of fibrin glue and gelfoam to repair collecting system injuries in a porcine model: implications for the technique of laparoscopic partial nephrectomy. J Endourol. 2003; 17: 799-804.
34. Eden CG, Sultana SR, Murray KH, Carruthers RK: Extraperitoneal laparoscopic dismembered fibrin-glued pyeloplasty: medium-term results. Br J Urol. 1997; 80: 382-9.
35. Morey AF, McDonough RC 3rd, Kizer WS, Foley JP: Drain-free simple retropubic prostatectomy with fibrin sealant. J Urol. 2002; 168: 627-9.
36. Diner EK, Patel SV, Kwart AM: Does fibrin sealant decrease immediate urinary leakage following radical retropubic prostatectomy? J Urol. 2005; 173: 1147-9.
37. Hick EJ and Morey AF: Initial experience with fibrin sealant in pendulous urethral reconstruction. Is early catheter removal possible? J Urol. 2004; 171: 1547-9.
38. Janetschek G, Hobisch A, Hittmair A, Holtl L, Peschel R, Bartsch G: Laparoscopic retroperitoneal lymphadenectomy after chemotherapy for stage IIB nonseminomatous testicular carcinoma. J Urol. 1999; 161: 477-81.
39. Chin AI, Ragavendra N, Hilborne L, Gritsch HA: Fibrin sealant sclerotherapy for treatment of lymphoceles following renal transplantation. J Urol. 2003; 170: 380-3.
40. Spotnitz WD, Falstrom JK, Rodeheaver GT: The role of sutures and fibrin sealant in wound healing. Surg Clin North Am. 1997; 77: 651-69.
41. Decastro BJ, Morey AF: Fibrin sealant for the reconstruction of fournier's gangrene sequelae. J Urol. 2002; 167: 1774-6.
42. Morris MS, Larson RJ, Santucci, RA, Morey AF: Role of fibrin sealant as tissue glue in complex genital reconstructive surgery. J Urol. 2004; 171: 19.
43. Gorodetsky R, Vexler A, An J, Mou X, Marx G: Haptotactic and growth stimulatory effects of fibrin(ogen) and thrombin on cultured fibroblasts. J Lab Clin Med. 1998; 131: 269-80.
44. Whelan C, Stewart J, Schwartz BF: Mechanics of wound healing and importance of Vacuum Assisted Closure in urology. J Urol. 2005; 173: 1463-70.
45. Morita T, Tokue A: Successful endoscopic closure of radiation induced vesicovaginal fistula with fibrin glue and bovine collagen. J Urol. 1999; 162: 1689.
46. Tsurusaki T, Sakai H, Nishikido M, Matsuya F, Kanetake H, Saito Y: Occlusion therapy for an intractable transplant-ureteral fistula using fibrin glue. J Urol. 1996; 155: 1698.
47. Christie RJ, Carrington L, Alving B: Postoperative bleeding induced by topical bovine thrombin: report of two cases. Surgery. 1997; 121: 708-10.
48. Pavlovich CP, Battiwalla M, Rick ME, Walther MM: Antibody induced coagulopathy from bovine thrombin use during partial nephrectomy. J Urol. 2001; 165: 1617.
49. Scheule AM, Beierlein W, Lorenz H, Ziemer G: Repeated anaphylactic reactions to aprotinin in fibrin sealant. Gastrointest Endosc. 1998; 48: 83-5.
50. MacGillivray TE: Fibrin sealants and glues. J Card Surg. 2003; 18: 480-4.

Accepted:
September 30, 2005

Correspondence address:
Dr. Allen F. Morey
Chief, Urology Service
Brooke Army Medical Center
3851 Roger Brooke Drive
Fort Sam Houston, TX, 78234, USA
Fax: + 1 210 916 – 5076
E-mail: allen.morey@amedd.army.mil

Clinical Urology
International Braz J Urol Vol. 32 (2): 142-146, March - April, 2006

Repetitive Ureteral Stenting for Management of Transplant Graft Ureteral Obstruction

Lester S. Borden Jr, Vernon M. Pais Jr, Dean G. Assimos

Department of Urology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

ABSTRACT

Purpose: To review the use of repetitive stenting in the management of patients with ureteral obstruction after renal transplantation, with an emphasis on technique and functional graft outcome.
Materials and Methods: Five adult renal allograft recipients with ureteral obstruction were managed with repetitive ureteral stenting. Their hospital records, office notes, and operative reports were reviewed.
Results: All patients were successfully managed with retrograde ureteral stenting. They underwent an average of 8.8 stent changes over a mean 34.5 month follow up. No decline in renal function was observed.
Conclusions: Repetitive stenting is a viable treatment option for select patients with renal allograft ureteral obstruction.

***Key words**: kidney transplantation; ureteral obstruction; catheterization; stent; graft survival*
Int Braz J Urol. 2006; 32: 142-6

INTRODUCTION

The most common urological complication following renal transplantation is ureteral obstruction with a reported incidence of 3-10% (1-3). Percutaneous drainage with or without antegrade ureteral stent placement provides a temporary solution for such problems. Open surgical reconstruction is often the preferred method for correcting this problem. However, there are patients who either fail an open surgical reconstructive or endourologic approaches, or who are deemed not to be good candidates for these procedures. Repetitive ureteral stenting may be a viable option in this setting. Herein, we present our experience with this form of management.

MATERIALS AND METHODS

From November 1997 to April 2003, 460 renal transplant procedures and 26 combined pancreas and renal transplant operations were performed at the Wake Forest University Baptist Medical Center. Five adult male patients were diagnosed with ureteral obstruction following renal transplantation and were managed with repetitive ureteral stenting. The mean patient age was 50.4 years (range 27-67). Ureteral obstruction was diagnosed by new onset hydronephrosis demonstrated by ultrasonography and increasing serum creatinine levels. Three patients received deceased donor renal transplants, one received a living-related transplant, and one received a living-unrelated transplant. Three had failed attempts at open surgical reconstruction, Boari flap reconstruction in 1 and uretero-pyelostomy with native ureter in 2, and declined further attempts at open surgical repair. Two had strictures longer than 2 cm, were not thought to be good candidates for an endourological approach and declined open surgical repair. Three patients underwent initial endoscopic retrograde stent placement and two had initial percutaneous nephrostomy drain-

age followed by antegrade stent placement. All subjects were then managed with retrograde stent changes. It is necessary to explain why some patients were poor candidates for such repair. Why did not you try nay endoscopic method like dilation or cold knife incision or laser incision?

The following approach was employed. Patients were administered prophylactic antibiotics prior to the induction of general or regional anesthesia. They were placed in the dorsal lithotomy position and cystoscopic removal of the indwelling ureteral stent was performed. The transplant ureteral orifice was identified and cannulated with a 5F angiographic catheter through which a hydrophilic guide wire was inserted and then manipulated into the renal collecting system. These maneuvers were monitored with fluoroscopy. Methylene blue or indigo carmine was administered intravenously to help identify the ureteral orifice when it was obscured by surrounding edema. A 5F, 12-14 cm double J stent was passed over the wire using both endoscopic and fluoroscopic guidance. The wire was subsequently removed and coiling of both ends of the stent was confirmed with fluoroscopy. The initial stent change interval was every 3 months and this was increased if there was no evidence of encrustation up to a maximum period of 6 months.

RESULTS

An average of 8.8 stent changes were performed per patient and the mean duration of ureteral stenting was 34.5 months (range 9.7-75.5). Which were the catheter caliber? How much time it remained in the place? Glomerular filtration rates were calculated by the Cockcroft-Gault formula and measured at baseline and at the time of the most recent stent change (Table-1). There was no significant decline in renal function during the period of stenting. There were no procedure related complications. One patient had periodic, recurrent urinary tract infections, which were managed with antibiotic therapy. Which were the symptoms related to double J? It could be interesting to know about the costs per procedure and per patient/year. I think that it is elevated.

COMMENTS

Ureteral complications can develop after both cadaveric and living donor renal transplantation. They have been reported to occur in up to 10% of patients undergoing such procedures. Which was the incidence in your casuistic (1-3)? These complications include urine leak, ureteral necrosis, ureteral stricture and extrinsic obstruction from lymphocele. The underlying etiology may be due to surgical technique or compromised vascular integrity of the ureter. Some of these problems are transient and the patients can be successfully managed with antegrade or retrograde stent placement, or nephrostomy tube insertion (4,5). Our cohort included patients who developed ureteral obstruction who had failed open surgical reconstruction or had long strictures and declined an open surgical repair. Why not? While other endourological approaches such as balloon dilation, endoureterotomy and cutting balloon incision have been used to manage patients developing ureteral obstruction after renal transplantation, our patient cohort were not thought to be good candidates for such treatments

Table 1 – *Demographics and maintenance of glomerular filtration rates (GFR) in patients with renal allograft ureteral obstruction managed with chronic ureteral stent.*

Patient	Age in Years	Number of Stent Changes	Baseline GFR	Most Recent GFR
1	61	19	55.9	57.9
2	44	8	31.7	39.0
3	53	7	58.6	60.4
4	27	8	51.0	53.0
5	67	2	37.3	35.9

based on the aforementioned factors. (6,7). Why? Probably the costs of changing the double J frequently is more expensive than try a definitive endoscope procedure.

Our results indicate that repetitive stenting can be a successful form of management for this highly select group; those who fail open surgical reconstruction, those who are not thought to good candidates for definitive endourological therapy, and those who decline open surgical reconstruction. Which kind of patients? In the material and methods, the patients were not well characterized. Graft function was maintained at a mean follow-up of almost three years. There were no complications associated with the stent change procedures. Which were the criteria for choose the double J caliber? Which was the best caliber? Which caused fewer symptoms? It was used catheter shorter than the normal one?

There are great difference between 3 and 6 months. Which the used criterion to make the exchange in 3 or 6 months? The duration of stenting is a unique feature of our study. Patients were stented for a mean duration of almost 3 years and a range extending to 75 months. This is the longest reported duration of ureteral stenting in this population. The only comparable series was reported by Pappas and associates and the mean duration of stenting was 15 months with a range of 12 to 21 months (8).

We found that certain technical maneuvers facilitated stent placement when the ureteral orifice is located in the dome area of the bladder. Identification of the orifice when bladder inflammation or bullous edema is present may be aided by the intravenous administration of indigo carmine or methylene blue. This promotes the excretion of blue colored urine from the targeted orifice thus facilitating its identification. Furosemide may also be administered to promote a diuresis if ureteral efflux is not promptly identified with the latter measures. Alignment of the scope with the allograft ureteral orifice can be achieved with any of several maneuvers. The utilization of a 5F angiographic catheter with a curved tip facilitates guide wire cannulation of the orifice. Manual suprapubic compression of the bladder may improve the alignment of an anteriorly located orifice with the angiographic catheter. Finally, flexible cystoscopy may also allow improved access to the orifice if these prior maneuvers are unsuccessful. The cannulation itself is aided by the use of a hydrophilic guidewire. Finally, we strongly recommend that fluoroscopy be used to monitor these procedures, as the course of the transplanted ureter may be variable.

CONCLUSIONS

Ideally, definitive correction of transplant graft ureteral obstruction with an open surgical or endourological approach should be considered for most patients with ureteral obstruction after renal transplantation. There is, however, a group of patients who either have failed these approaches or who are not candidates for them. This group was not studied and you cannot conclude on it. Repetitive ureteral stenting is a viable treatment option in this setting and may allow preservation of renal function.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Faenza A, Nardo B, Catena F, Scolari MP, d'Arcangelo GL, Buscaroli A, et al.: Ureteral stenosis after kidney transplantation. A study on 869 consecutive transplants. Transpl Int. 1999; 12: 334-40.
2. Shoskes DA, Hanbury D, Cranston D, Morris PJ: Urological complications in 1,000 consecutive renal transplant recipients. J Urol. 1995; 153: 18-21.
3. Kinnaert P, Hall M, Janssen F, Vereerstraeten P, Toussaint C, Van Geertruyden J: Ureteral stenosis after kidney transplantation: true incidence and long-term followup after surgical correction. J Urol. 1985; 133: 17-20.
4. Sigman DB, Del Pizzo JJ, Sklar GN: Endoscopic retrograde stenting for allograft hydronephrosis. J Endourol. 1999; 13: 21-5.
5. Bosma RJ, van Driel MF, van Son WJ, de Ruiter AJ, Mensink HJ: Endourological management of ureteral obstruction after renal transplantation. J Urol. 1996; 156: 1099-100.

6. Kristo B, Phelan MW, Gritsch HA, Schulam PG: Treatment of renal transplant ureterovesical anastomotic strictures using antegrade balloon dilation with or without holmium:YAG laser endoureterotomy. Urology. 2003; 62: 831-4.
7. Schwartz BF, Chatham JR, Bretan P, Goharderakhshan R, Stoller ML: Treatment of refractory kidney transplant ureteral strictures using balloon cautery endoureterotomy. Urology. 2001; 58: 536-9.
8. Pappas P, Stravodimos KG, Adamakis I, Leonardou P, Zavos G, Constantinides C, et al.: Prolonged ureteral stenting in obstruction after renal transplantation: long-term results. Transplant Proc. 2004; 36: 1398-401.

Accepted after revision:
January 25, 2006

Correspondence address:
Dr. Dean G. Assimos
Department of Urology
Wake Forest Univ. Sch. Med.
Medical Center Boulevard
Winston-Salem, NC 27157, USA
Fax: + 1 336 716-5711
E-mail: dassimos@wfubmc.edu

EDITORIAL COMMENT

The authors describe their interesting experience with patients with ureteral stenosis after renal transplantation and treated by repetitive ureteral stenting. Among 460 grafts, 5 cases were included in the program (1.08%). Three had failed to a previous reimplant surgery and 2 had refused a new surgical approach.

Ureteral stenosis occurs in 2 to 10% of renal grafts, being 80% in the uretero-vesical junction and 71% occurring in the first 3 months after transplantation (1). Lesions less than 2 cm of extension have better prognosis as well as those treated during the first 3 months post transplantation (2).

There are some proposals for the management of ureteral stenosis in graft patients, but the gold standard approach is the re-anastomosis with the native ureter (3). However, the minimally invasive or endourological techniques have been considered to reduce the impact of this complication. Among these techniques, the balloon dilation, the balloon cutting endoureterotoy (Acucise®), the Holmium laser endoureterotomy and the prolonged use of double-J stent are emphasized.

It is worthy to point out that the retrograde placement of ureteral stent can be challenging in kidney transplant patients. Nahas et al. described their experience with retrograde catheterization in patients with renal graft and ureteral dilation. In 9 of 12 cases (75%), it was possible to perform successfully retrograde catheterization. The remaining cases were treated by percutaneous approach (4).

Ureteral re-implant in kidney transplant patients is object of discussion in medical literature. Gauleria et al. compared the Leadbetter-Politano ureteral implant technique with the anterior ureteroneocystostomy and demonstrated with the second procedure a reduction in the stenosis index (7.7% to 3.8%) (5).

Kristo and cols. described the technique of dilation of ureteral stenosis with a balloon, by anterior approach, in 9 kidney transplant patients. Six cases were treated exclusively with the balloon and in 3 cases the author included the Holmium laser for incision. He was successful in all cases, but all patients presented a stenosis of less than 0.5 cm extension (6).

Balloon cautery was used by Erturk et al. He reported an 86% resolution index, but severe bleeding was observed as a complication in one case (7).

The long-term use of ureteral catheter, described by Pappas et al., is promising. The stents were replaced each 3 months and remained for a median time of 15 months. The authors reported 90% of cure of ureteral stenosis in kidney transplant patients (8).

In this issue of the International Braz J Urol the authors contribute to the experience with periodical replacement of ureteral catheter for the treatment of ureteral stenosis in transplanted patients. In this study, the use of double-J stent allowed the preservation of renal function in all cases.

REFERENCES

1. Shoskes DA, Hanbury D, Cranston D, Morris PJ: Urological complications in 1,000 consecutive renal transplant recipients. J Urol. 1995; 153: 18-21.
2. Goldfischer ER, Gerber GS: Endoscopic management of ureteral strictures. J Urol. 1997; 157: 770-5.
3. Schwartz BF, Chatham JR, Bretan P, Goharderakhshan R, Stoller ML: Treatment of refractory kidney transplant ureteral strictures using balloon cautery endoureterotomy. Urology. 2001; 58: 536-9.
4. Nahas WC, Gil AO, Mazzucchi E, et al. Retrograde pyelography in transplant kidney: a reliable method. Urol Panamericana. 1995; 7: 39-40.
5. Guleria S, Chahal R, Madaan S, Irving HC, Newstead CG, Pollard SG, et al.: Ureteric complications of renal transplantation: the impact of the double J stent and the anterior extravesical ureteroneocystostomy. Transplant Proc. 2005; 37: 1054-6.
6. Kristo B, Phelan MW, Gritsch HA, Schulam PG: Treatment of renal transplant ureterovesical anastomotic strictures using antegrade balloon dilation with or without holmium:YAG laser endoureterotomy. Urology. 2003; 62: 831-4.
7. Erturk E, Burzon DT, Waldman D: Treatment of transplant ureteral stenosis with endoureterotomy. J Urol. 1999; 161: 412-4.
8. Pappas P, Stravodimos KG, Adamakis I, Leonardou P, Zavos G, Constantinides C, et al.: Prolonged ureteral stenting in obstruction after renal transplantation: long-term results. Transplant Proc. 2004; 36: 1398-401.

Dr. Ricardo Jordão Duarte
Assistant Professor of Urology
University of Sao Paulo, SP, Brazil
E-mail: ricjordao@uol.com.br

Clinical Urology
International Braz J Urol Vol. 32 (2): 147-154, March - April, 2006

Virtual Computed Tomography Cystoscopy in Bladder Pathologies

Halil Arslan, Kadir Ceylan, Mustafa Harman, Yuksel Yilmaz, Osman Temizoz, Saban Can

Departments of Radiology and Urology, Yuzuncu Yil University School of Medicine, Van, Turkey

ABSTRACT

Objective: Assessed the usefulness of virtual cystoscopy performed with multidetector computed tomography (CT) in patients with different urinary bladder pathologies compared to the conventional cystoscopy.
Materials and Methods: Eighteen patients with different bladder pathologies, which consisted of 11 tumors, 3 diverticula, 2 trabecular changes and 2 stones, were assessed with conventional cystoscopy and virtual CT cystoscopy. The results of virtual CT cystoscopy were compared with the findings of conventional cystoscopy. We determined the detection rate and positive predictive value of CT imaging based virtual cystoscopy in the diagnosis of urinary bladder lesions.
Results: CT scanning was well tolerated by all patients, and no complications occurred. Images in 16 (88%) of the 18 virtual cystoscopic examinations were either of excellent or good quality. All tumors except one, 2 trabecular changes and 2 stones were characterized with similar findings in the both of methods. The masses ranged from 0.4 to 7.0 cm in diameter. While conventional cystoscopy could not evaluate interior part of the diverticulum, virtual CT cystoscopy could demonstrate clearly within it. There were no false-positive findings in our series.
Conclusion: Virtual CT cystoscopy is a promising technique to be used in the detection of bladder lesions. It should be considered especially at the evaluation of bladder diverticula. In the future, it may be possible or even advantageous to incorporate into the imaging algorithm for evaluation of bladder lesion.

***Key words**: bladder; cystoscopy; tomography, spiral computed; tumors; diverticula; stones*
Int Braz J Urol. 2006; 32: 147-54

INTRODUCTION

Bladder pathologies are consisted of the important group of genitourinary tract diseases. The most common complaints in bladder disease are microscopic and macroscopic hematuria, disuria and other voiding symptoms. All these symptoms may be related to inflammatory, neoplastic, stones, neurologic, obstructive or congenital abnormalities. Urogram, sonography (US), computed tomography (CT), magnetic resonant imaging (MRI) and some other radiological modality have been used for a long time in all these pathologies. However, conventional cystoscopy is a standard diagnostic approach for urinary bladder evaluation, its primary indication is the diagnosis of lower urinary tract disease, sings, and symptoms that may be related to the urinary tract are evaluated using cystoscopy to directly visualize lower urinary tract anatomy and macroscopic pathology. However, this procedure has drawbacks, including its high costs and an invasiveness that may lead to iatrogenic bladder injury and urinary sepsis. CT is usually recommended as a useful radiologic approach for assessing bladder disease, but CT has low sensitivity for detection of small bladder lesions. For CT to depict a small bladder lesion, optimal imaging conditions, including

adequate bladder distention and thin-slice scanning, must be satisfied. Therefore, negative findings on CT warrant performance of conventional cystoscopy in patients with bladder pathology (1-4).

Recently, three-dimensional computer-rendering techniques with rapid image acquisition have led to the development of virtual-reality imaging. With commercially available software, virtual reality imaging allows interactive intraluminal navigation through any hollow viscus, simulating conventional cystoscopy. This technique of virtual endoscopy has been applied to many organs, including the colon, bronchus, stomach, and bladder (3-6).

Currently, most authors have been studied with virtual cystoscopy about the bladder tumor. Few reports are found in the literature regarding different bladder pathology such as diverticulum or inflammatory pseudotumor based virtual cystoscopy of the urinary bladder (7,8).

The purpose of this study was to evaluate the usefulness of virtual cystoscopy using a volume rendering algorithm performed with multidetector CT in patients with different urinary bladder pathology compared with the gold standard that is, conventional cystoscopy and to determine the modality's detection rate and positive predictive value.

MATERIALS AND METHODS

Eighteen patients (mean age 56 ± 11 years, range 40 to 72 years) were referred from the urology department because of the different urinary bladder disease, which consisted of 11 tumors, 3 diverticula, 2 trabecular changes and 2 stones for this study. We carried out both conventional and virtual cystoscopy in all patients. Time interval between conventional and CT cystoscopy ranged from zero to 7 days. Each patient had various clinical histories. Most of the patients presented painless hematuria or dysuria. Conventional cystoscopies were carried out with unaware of virtual cystoscopic findings. The conventional cystoscopies were performed with rigid 21F cystoscope (Storz, Germany) with a field of view of 30 degrees in all patients under general or local anesthesia. Virtual cystoscopic examinations were started with obtaining adequate bladder distention in supine position. Helical CT was performed with 4 channel CT scanner (Somatom Sensation 4, Siemens Medical Systems, Erlangen, Germany), in single breath hold, with 1 mm collimation, 1 mm reconstruction interval and 3 mm thickness. Other scanning parameters were as follows: 1 mm reconstruction interval, mAs 153, and 120 kV, feed/rotation 5 mm. The scanning time was only 8-12 second. Prior to the scan, adequate filling of the bladder with approximately 250-450 mL of air was required. At the same time, IV 100 mL contrast medium was administered in all patients by a power injector at a rate of 2.0-2.5 mL/s for possible extravesical invasion of the tumor or some other pathology. The patients were then turned to the prone position, and CT of the bladder was repeated with use of the same parameters after a repeated scout view was obtained. Additional bladder distention with approximately 80-120 mL of air was necessary in some of the patients, since repositioning led to leakage of some of the insufflated gas from the bladder.

The data were downloaded to an independent workstation (Leonardo; Siemens Medical Systems) equipped with software for interactive intraluminal navigation. Using multiplanar reformation from source images, a central observation point was defined in the middle of the lumen of the bladder. The camera for virtual cystoscopy was placed in the center of the bladder lumen and thereafter was advanced to each quadrant in turn. When a possible abnormality was discovered, it was fully evaluated from various angles.

The number, location, and size of the tumors were individually determined and noted after cystoscopy for later comparison with the results of CT imaging-based virtual cystoscopy. The virtual and conventional cystoscopic findings for each patient were documented on separate worksheets. The number, size, location, and morphologic features of the masses, mucosal thickness, trabeculations and diverticula and other luminal pathology were also noted in both methods. On transverse section and virtual CT images obtained with the patients in both supine and prone positions, each mass lesion was characterized as a focal polypoid lesion, a sessile mass, or wall thickening. A discrete lesion was considered polypoid, if it was taller rather than wider, while a sessile mass was

defined as a lesion when it was wider at the base. A lesion was characterized as wall thickening when there was elevation of the bladder wall without a discrete mass. The quality of each CT image was also evaluated in terms of the residual urine, which may obscure the bladder mucosa, and the degree of distention. Complications due to CT cystoscopy were recorded.

Three radiologists (HA,MH,OT) blinded to the findings of conventional cystoscopy, independently interpreted the images prospectively, and any discrepant readings were resolved by consensus. The results of virtual CT cystoscopy were compared with the findings of conventional cystoscopy, which is considered the standard. The lesions that were not prospectively identified at CT cystoscopy were retrospectively evaluated for visibility on transverse and virtual images. The pathology report in each patient with bladder tumor was also reviewed for further correlation. Using conventional cystoscopy as the gold standard, we analyzed them to determine the detection rate of CT imaging-based virtual cystoscopy in the diagnosis of urinary bladder lesions.

RESULTS

CT scanning was well tolerated by all patients, and no complication occurred. Images in 16 (88%) of the 18 virtual cystoscopic examinations were of excellent or good quality, with adequate bladder distention and minimum residual urine. Images in 2 examinations were suboptimal due to either moderate residual urine or inadequate bladder distention. Tumoral lesions were seen in one of them. However, in other patient, a smaller-than-4 mm polypoid tumoral lesion could not be detected.

On conventional cystoscopy, 11 tumors were found in 18 patients. These masses ranged from 0.4 to 7.0 cm in diameter (mean, 1.5 cm). Out of 11 polypoid lesions, 8 were larger than 5 mm, and 3 were 5 mm or smaller. Eight out of the polypoid lesions were larger than 5 mm, and 3 were 5 mm or smaller. One of the polypoid lesions was calcified. Six out of the 11 lesions were located on the lateral wall (Figures-1 and 2); 2 on the posterior wall; 2 on the anterior wall and 1 in the bladder neck. All lesions were diagnosed as transitional cell carcinoma in the pathology reports. All these tumors had been described by the virtual cistoscopy with nearly similar findings in size localization and surface of the tumor except one lesion, which was smaller than 5 mm 90% of the tumors were diagnosed by virtual cystoscopy as compared to conventional cystoscopy. Mucosal thickness and trabeculations were also seen in the virtual CT cystoscopy and the appearance was similar in both modalities (Figure-3). Bladder stone could not differentiate the tumor or polyp without adjustment of the lowest and highest point of the density value in the volume-rendering method in two patients (Figure-4).

Three diverticula were diagnosed, but the interior of the diverticula could not be evaluated by conventional cystoscopy. Their lumens were easily detected by virtual cystoscopy. In three diverticula, virtual CT cystoscopies were superior to conventional

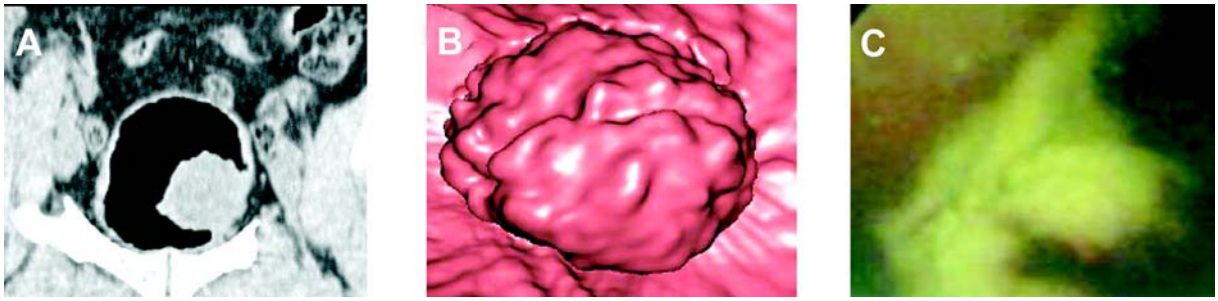


Figure 1 *– 50-year-old man with transitional cell carcinoma obtained in area toward left wall shows polypoid lesion. A) Coronal multiplanar reconstruction section. B) Virtual CT cystoscopy appearance. C) Conventional cystoscopy. Vegetative surface of the tumor was clearly identified in virtual CT cystoscopy. Surrounding mucosal surface appears normal both of the conventional and virtual CT cystoscopy.*

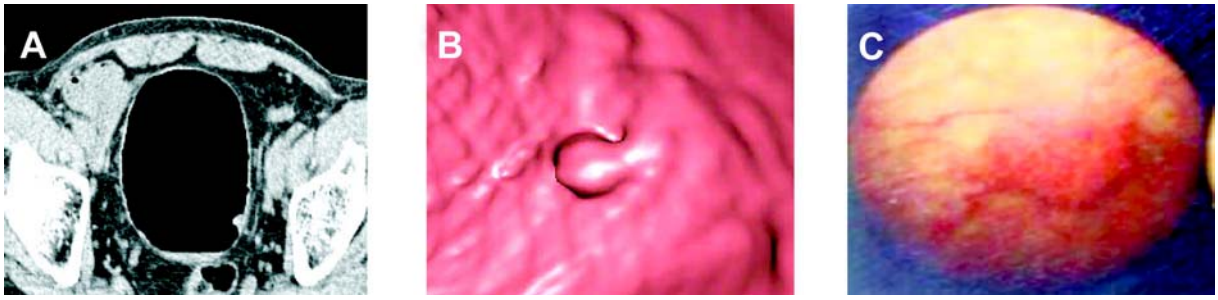


Figure 2 – *60 year-old man with primary urinary bladder cancer. A) Transverse section. B) Virtual CT cystoscopy appearance. C) Conventional cystoscopy. Virtual CT cystoscopic image focused on polyp with 12 mm located near left urethral orifice. Internal urethral orifice can be identified only polyp with 12mm located near left urethral orifice. Internal urethral orifice can be identified in lower midportion.*

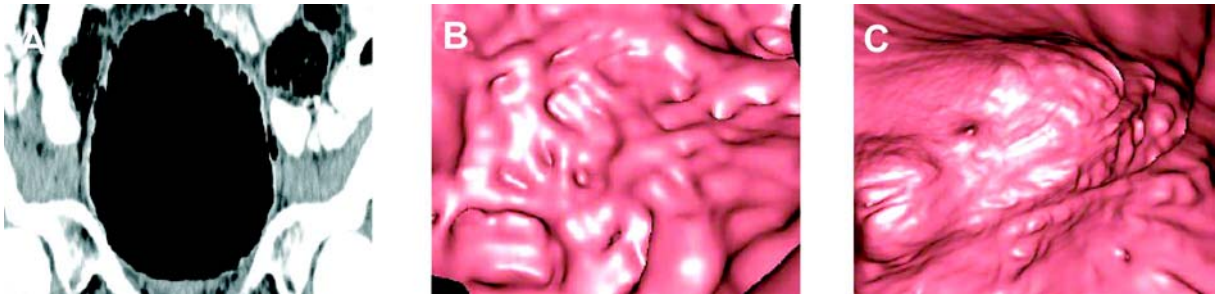


Figure 3 – *71 year-old man with trabeculation because of the prostate hypertrophy. A) Coronal multiplanar reconstruction image. B) Magnified virtual CT cystoscopy appearance. C) General trabecular appearance of mucosal surface in virtual CT cystoscopy. Virtual CT cystoscopy shows mucosal thickness and trabeculation similar with the conventional cystoscopy.*

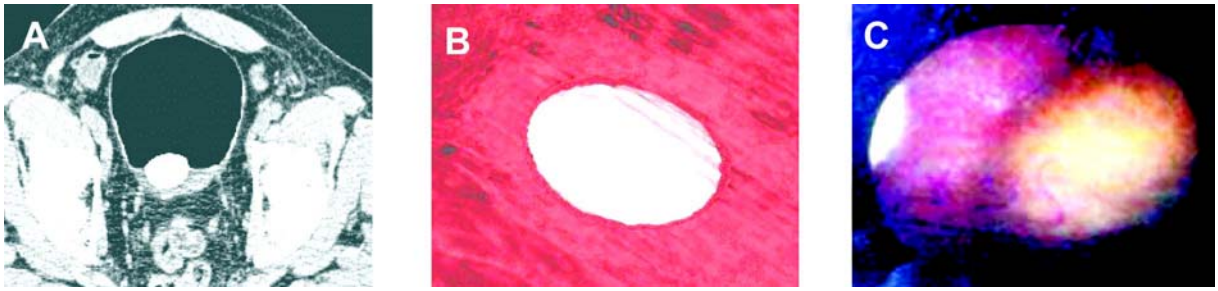


Figure 4 – *55 year-old man with solitary bladder stone. A) Transverse section. B) Virtual CT cystoscopy appearance. C) Conventional cystoscopy. Stone could be easily differentiated from the surrounding tissue in virtual CT cystoscopy appearance after the adjustment threshold value of density.*

cystoscopy in demonstration of the interior of the diverticula (Figure-5).

Transverse section and virtual CT images were complementary in lesion detection and characterization. Although areas of wall thickening and trabeculation were seen on the virtual images, they were more conspicuous on the transverse views. However, the lobulated morphologic characteristics of a small polypoid lesion were better depicted on the virtual image. There were no false-positive findings in our series. The presence of every lesion seen at virtual cystoscopy was confirmed at conventional cystoscopy. Virtual cystoscopy time, including catheter placement, was approximately 20-25 minutes. Con-

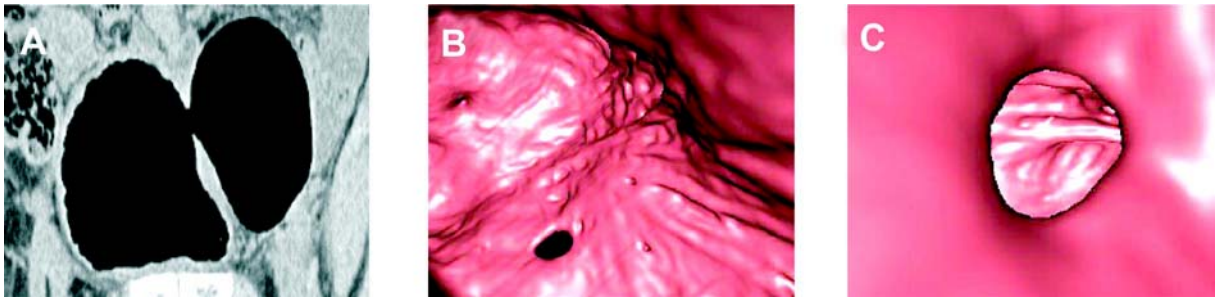


***Figure 5** – 45 year-old men with virtual CT cystoscopic images of bladder wall diverticulum. A) Sagittal multiplanar reconstruction image. B) Virtual CT cystoscopy appearance of the neck of the diverticulum. C) Interior appearance of the diverticulum. Diverticulum could be evaluated both of the multiplanar reconstruction images and virtual CT cystoscopy, but could not in the conventional cystoscopy.*

sidering conventional cystoscopy to be the gold standard, we found the following diagnostic values for the identification of bladder lesions on virtual cystoscopy. In 17 out of 18 patients (94.4%), lesions were detected by using virtual CT cystoscopy.

COMMENTS

Several imaging techniques are available for use in the detection of bladder pathology. US, urogram, CT, MRI and conventional cystoscopy could be used in the bladder disease. Conventional cystoscopy was accepted as a gold standard in bladder (3,5). However, there are several disadvantages of the conventional cystoscopy. It is often difficult to perform adequately when exploring the anterior bladder wall or a diverticulum cavity. Primary intradiverticular carcinomas are rare, but diagnosis is often difficult with conventional method (6,9,10,11). There are some contraindications for the conventional cystoscopy such as bacteriuria, acute cystitis, urethritis, prostatitis, obstructive prostatic hypertrophy, and stricture or rupture of the urethra. Marked hematuria is another factor that limits the technical success of cystoscopy, thereby decreasing its reliability. On the other hand, cystoscopy is performed in general or local anesthesia and it is an invasive and uncomfortable procedure for patients, and complications such as infections, uretral or bladder perforation, scarring, and stricture of the urethra have been observed (3,6,12-14).

Virtual endoscopy is a recently developed noninvasive method to detect tumors protruding from the walls of hollow organs. A promising advantage of this imaging modality is that views not possible in conventional endoscopic examination can be created. The volumetric data obtained with helical CT or MR imaging are computer-rendered to generate three-dimensional images, and with commercially available software, intraluminal navigation through any hollow viscus is possible. There are two main techniques for the reconstruction of virtual image. One of them is volume rendering and the other is surface-rendering algorithm. Of the different three-dimensional rendering techniques available, the perspective volume rendering provides more information because the entire data set is incorporated (15-19). We used a volume-rendering algorithm in this study.

Virtual endoscopy has been most widely applied to imaging of the colon and many investigators report its feasibility in the depiction of colorectal polyps (20,21). After the first report of virtual cystoscopy, in the study by Vining at al., there have been a lot of studies on the utility of virtual cystoscopy of the bladder. The urinary bladder is a good candidate for virtual cystoscopy because of its simple luminal morphology, its relatively small volume, and the absence of involuntary peristalsis. Therefore, a virtual cystoscopic rendering of the bladder takes a short time to navigate and does not require great skill on the part of the operator (4-6,18). On the other hand, according to a study by Kim et al., virtual cystoscopy was found superior than multiplanar reconstruction and source CT images for lesion detection in the contrast material-filled bladder (22). However, most stud-

ies were performed in bladder tumor and previous studies have focused solely on known bladder lesion. There have been no enough studies on different pathologies. We carried out this study on different bladder pathologies and evaluated the capabilities of virtual cystoscopy, such as diverticula, trabeculation and stone.

As a minimally invasive procedure, virtual CT cystoscopy provides many advantages as compared to conventional cystoscopy. The virtual CT cystoscopy images could be stored in file and the lesion could be compared in follow up period with based images. The size of a tumor is measured objectively. Access to the anterior bladder wall or the lumen of a diverticulum is not restricted in virtual cystoscopy because various software reconstruction tools can be used and the tumor can be easily detected (23). Patients with a severe urethral stricture or marked prostatic hypertrophy, who may be poor candidates for conventional cystoscopy, can safely undergo virtual CT cystoscopy. It is also indicated for patients who are at risk of complications such as hemorrhage, perforation, infection, or pain, and for the examination of young patients (3,5,6). In our group, diverticula were very well examined by virtual CT cystoscopy while conventional cystoscopy could not evaluate the interior of lesions. However, we had some difficulties in bladder stone using virtual cystoscopy. It was very difficult to differentiate the polyp without setting the threshold density value. This also showed us that axial images and virtual cystoscopy images should be evaluated together.

Two techniques have been used to obtain the CT source data for reconstructed virtual cystoscopic images, scanning the bladder that has been filled with either air or contrast material. Both methods have some advantages and disadvantages when compared with one another. Most previous studies have been chosen to scan the air-filled bladder. However, virtual cystoscopy of the air-filled bladder is inherently invasive because catheterization is required to introduce air into the bladder. Supine and prone examination is another disadvantage of the air-filled bladder method. On the other hand, filling the bladder with IV contrast material has been easily achieved in many studies. In this method, there is no need for examination in prone and supine position. Therefore, this means lesser radiation and cost (3,22). However, urine and contrast could not be mixed properly with this method for virtual cystoscopy. This is one of the disadvantages. Secondly, IV contrast application is mandatory and this is another difficulty. Waiting for bladder filling and inadequate distention is another disadvantage. In addition to these disadvantages, possible scheduling problems may arise in a busy CT practice because of the repeated patient positioning and scanning required (3,4,5). In our study, like many others, we used air-filled bladder for virtual cystoscopy. If there is already a Foley catheter inside the bladder, the air-filled bladder method might be preferable. However, when there is no catheter and a IV contrasted examination has already been planned, the second method can be used for virtual cystoscopy.

Virtual cystoscopy has several limitations. A major limitation is that it is unable to depict flat lesions, which appear as subtle mucosal color changes on conventional cystoscopy. However, various factors influence the detection of sessile lesions, including the method used to acquire the CT data, interactive navigational skill of the operator, attenuation-coefficient ranges used for voxel categorization, and degree of bladder distention. Sessile lesions usually have an irregular surface that must be minutely depicted on virtual cystoscopy. So if the examination parameter is appropriate and distention is adequate, sessile lesions also could be easily detected. Secondly, the differentiation between small tumors and inflammatory swelling of the mucosa could be difficult, especially in patients with unsatisfactory bladder filling. Inflammatory swelling of the mucosa thus could be misdiagnosed as a tumor, or small tumors could be missed on virtual cystoscopy. Insufficient distention of the bladder may also cause the mucosa to wrinkle. Third, mucosal thickening secondary to fibrosis cannot be distinguished from a neoplasm. Of course, one faces a similar problem on conventional cystoscopy because biopsy is often required to determine whether a bladder lesion is inflammatory, fibrotic, or neoplastic. A fourth disadvantage of virtual cystoscopy is that it lacks the ability to provide tissue for histologic evaluation, an ability that is possible on conventional cystoscopy and biopsy. Fifth, it is difficult to visualize the lumen of the urethra as is routinely done with conventional cystoscopy. How-

ever, it was reported that urethra could also be evaluated by virtual cystoscopy (24).

In conclusion, virtual CT cystoscopy is a promising technique for tumor and some other bladder lesions, such as diverticula. Virtual CT cystoscopy is likely superior to demonstrate the interior part of the diverticulum. Adequate bladder distention and analysis of virtual images are required for optimal evaluation. This minimally invasive method can be of value for screening, primary diagnosis and surveillance of bladder lesions. Virtual CT cystoscopy may be indicated as a clinical routine when conventional cystoscopy is contraindicated or restricted in feasibility and interpretation or there is risk of hemorrhage, perforation, or pain especially in young patients. In the future, it may be possible or even advantageous to incorporate into the imaging algorithm for evaluation of bladder lesion through continued development and advancement of hardware and software. To determine the clinical value of virtual CT cystoscopy in the different bladder pathology, however, larger prospective studies in the general patient population are necessary.

REFERENCES

1. Carter HB: Basic Instrumentation and Cystoscopy. Walsh PC, Retik BA,Vaughan ED, Wein AJ (eds.). Campbell's Urology, Saunders, Philadelphia. 8 ed., 2002; vol. 1, pp. 111-21.
2. Bernhardt TM, Schmidl H, Philipp C, Allhoff EP, Rapp-Bernhardt U: Diagnostic potential of virtual cystoscopy of the bladder: MRI vs CT. Preliminary report. Eur Radiol. 2003; 13: 305-12.
3. Kim JK, Ahn JH, Park T, Ahn HJ, Kim CS, Cho KS: Virtual cystoscopy of the contrast material-filled bladder in patients with gross hematuria. AJR Am J Roentgenol. 2002; 179: 763-8.
4. Vining DJ, Zagoria RJ, Liu K, Stelts D: CT cystoscopy: an innovation in bladder imaging. AJR Am J Roentgenol. 1996; 166: 409-10.
5. Song JH, Francis IR, Platt JF, Cohan RH, Mohsin J, Kielb SJ, et al.: Bladder tumor detection at virtual cystoscopy. Radiology. 2001; 218: 95-100.
6. Lammle M, Beer A, Settles M, Hannig C, Schwaibold H, Drews C: Reliability of MR imaging-based virtual cystoscopy in the diagnosis of cancer of the urinary bladder. AJR Am J Roentgenol. 2002; 178: 1483-8.
7. Zantl N, Beer A, van Randenborgh H, Hartung R: Virtual endoscopy of the urinary tract. Urologe A. 2002; 41: 552-8.
8. Sakamoto Y, Tanaka H, Kawabata G: Inflammatory pseudotumor of the urinary bladder diagnosed using 3D-CT cystoscopy. Hinyokika Kiyo. 2003; 49: 587-90.
9. Durfee SM, Schwartz LH, Panicek DM, Russo P: MR imaging of carcinoma within urinary bladder diverticulum. Clin Imaging. 1997; 21: 290-2.
10. Stephenson WT, Holmes FF, Noble MJ, Gerald KB: Analysis of bladder carcinoma by subsite. Cystoscopic location may have prognostic value. Cancer. 1990; 66: 1630-5.
11. Baniel J, Vishna T: Primary transitional cell carcinoma in vesical diverticula. Urology. 1997; 50: 697-9.
12. Bavetta S, Olsha O, Fenely J: Spreading sepsis by cystoscopy. Postgrad Med J. 1990; 66: 734-5.
13. Mosbah A, Kane A, Zhani R, Hattab C: Iatrogenic urethral strictures of the male urethra. Acta Urol Belg. 1990; 58: 87-93.
14. Golomb J, Waizbard E, Iellin A, Merimsky E: Recurrent bladder perforation in chronic irradiation cystitis. J Urol. 1986; 92: 47-8.
15. Blezek DJ, Robb RA: Evaluating virtual endoscopy for clinical use. J Digit Imaging. 1997; 10(Suppl 1): 51-5.
16. Rubin GD, Beaulieu CF, Argiro V, Ringl H, Norbash AM, Feller JF, et al.: Perspective volume rendering of CT and MR images: applications for endoscopic imaging. Radiology. 1996; 199: 321-30.
17. Calhoun PS, Kuszyk BS, Heath DG, Carley JC, Fishman EK: Three-dimensional volume rendering of spiral CT data: theory and method. Radiographics. 1999; 19: 745-64.
18. Yazgan C, Fitoz S, Atasoy C, Turkolmez K, Yagci C, Akyar S: Virtual cystoscopy in the evaluation of bladder tumors. Clin Imaging. 2004; 28: 138-42.
19. Hopper KD, Iyriboz AT, Wise SW, Neuman JD, Mauger DT, Kasales CJ: Mucosal detail at CT virtual reality: surface versus volume rendering. Radiology. 2000; 214: 517-22.
20. Hara AK, Johnson CD, Reed JE, Ahlquist DA, Nelson H, MacCarty RL, et al.: Detection of colorectal polyps with CT colography: initial assessment of sensitivity and specificity. Radiology. 1997; 205: 59-65.
21. Chen SC, Lu DS, Hecht JR, Kadell BM: CT colonography: value of scanning in both the supine and prone positions. AJR Am J Roentgenol. 1999; 172: 595-9.
22. Kim JK, Park SY, Kim HS, Kim SH, Cho KS: Comparison of virtual cystoscopy, multiplanar reformation,

and source CT images with contrast material-filled bladder for detecting lesions. AJR Am J Roentgenol. 2005; 185: 689-96.
23. Prando A: CT-virtual endoscopy of the urinary tract. Int Braz J Urol. 2002; 28: 317-22.
24. Chou CP, Huang JS, Wu MT, Pan HB, Huang FD, Yu CC, et al.: CT voiding urethrography and virtual urethroscopy: preliminary study with 16-MDCT. AJR Am J Roentgenol. 2005; 184: 1882-8.

Accepted after revision:
January 25, 2006

Correspondence address:
Dr. Halil Arslan
YYÜ Týp Fakültesi Hastanesi
Radyoloji Anabilim Dalý
Maras. Cad, 65200, Van, TURKEY
Fax: + 90 432-2167519
E-mail: drhalilarslan@hotmail.com

EDITORIAL COMMENT

CT-cystoscopy has been shown to be a very accurate technique since it is able to detect lesions larger than 0.5 cm and is able to show mucosal abnormalities as small as 2 mm.

CT-cystoscopy can be obtained either with gas-filled bladder or with contrast-material-filled bladder. Usually the sensitivity of this technique is higher for the detection of polypoid lesions in comparison with sessile lesions. In our institution we routinely evaluate the axial images together with virtual images since this combination, allows a significant increase in the overall sensitivity of this technique.

Virtual cystoscopy can also be obtained using magnetic resonance imaging (MR-cystoscopy). MR-cystoscopy has some advantages over CT-cystoscopy since there is no need for bladder catheterization or intravenous injection of contrast material, but has lower spatial resolution (better for lesions larger than 1 cm in diameter).

In this report, 18 patients with bladder pathologies were evaluated by CT-cystoscopy using distension of the bladder with gas after bladder catheterization. All patients were evaluated in both prone and supine position. The size of detected lesions ranged from 0.4 to 7.0 cm in diameter and there were no false-positive findings.

Bladder tumors can be noninvasively diagnosed using CT-cystoscopy or MR-cystoscopy, since both give comparable views to conventional cystoscopy. Virtual cystoscopy is helpful in cases where conventional cystoscopy is inconclusive or cannot be performed. One of the strengths of this technique is to add diagnostic information to conventional cystoscopy in the evaluation of bladder diverticula. Tumor within bladder diverticulum with narrow lumen can be easily demonstrated by virtual endoscopy.

Our goal for the future is to improve spatial resolution of CT-cystoscopy, reduce the radiation dose to the patient and provide useful information in order to allow conventional cystoscopy guided by the ct-cystoscopic findings.

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

Clinical Urology
International Braz J Urol Vol. 32 (2): 155-164, March - April, 2006

A New Nomogram to Predict Pathologic Outcome Following Radical Prostatectomy

Alexandre Crippa, Miguel Srougi, Marcos F. Dall'Oglio, Alberto A. Antunes, Katia R. Leite, Luciano J. Nesrallah, Valdemar Ortiz

Division of Urology, Federal University of Sao Paulo, UNIFESP, Sao Paulo, SP, Brazil

ABSTRACT

Objective: To develop a preoperative nomogram to predict pathologic outcome in patients submitted to radical prostatectomy for clinical localized prostate cancer.
Materials and Methods: Nine hundred and sixty patients with clinical stage T1 and T2 prostate cancer were evaluated following radical prostatectomy, and 898 were included in the study. Following a multivariate analysis, nomograms were developed incorporating serum PSA, biopsy Gleason score, and percentage of positive biopsy cores in order to predict the risks of extraprostatic tumor extension, and seminal vesicle involvement.
Results: In univariate analysis there was a significant association between percentage of positive biopsy cores ($p < 0.001$), serum PSA ($p = 0.001$) and biopsy Gleason score ($p < 0.001$) with extraprostatic tumor extension. A similar pathologic outcome was seen among tumors with Gleason score 7, and Gleason score 8 to 10. In multivariate analysis, the 3 preoperative variables showed independent significance to predict tumor extension. This allowed the development of nomogram-1 (using Gleason scores in 3 categories - 2 to 6, 7 and 8 to 10) and nomogram-2 (using Gleason scores in 2 categories - 2 to 6 and 7 to 10) to predict disease extension based on these 3 parameters. In the validation analysis, 87% and 91.1% of the time the nomograms-1 and 2, correctly predicted the probability of a pathological stage to within 10% respectively.
Conclusion: Incorporating percent of positive biopsy cores to a nomogram that includes preoperative serum PSA and biopsy Gleason score, can accurately predict the presence of extraprostatic disease extension in patients with clinical localized prostate cancer.

***Key words**: prostatic neoplasms; neoplasm staging; nomograms; prostate-specific antigen; needle biopsy*
Int Braz J Urol. 2006; 32: 155-64

INTRODUCTION

Gleason grade from biopsy, along with serum PSA and tumor extent at digital rectal examination, are the current most common parameters used to predict the risk of organ confined disease and choose a definitive treatment in patients with prostate cancer (1).

However, some studies show that clinical stage as defined at digital rectal examination is neither the ideal method to choose a definitive therapy (2) nor to predict biochemical outcome after treatment (3-6). The percentage of patients staged as T1c increased from less than 1% in the eighties to 60% in the nineties. Furthermore, a study of more than 1000 patients that underwent radical retropubic

prostatectomy did not find statistical difference in disease recurrence rates among patients staged as T2a, T2b or T2c at digital rectal examination after a 10 years follow up period (7).

New variables to predict the probabilities of organ confined disease and disease recurrence after treatment have been widely studied (8-10), and the percentage of positive biopsy cores (PPBC) for cancer has emerged as an independent prognostic factor (11-13). Probably, the reason for this importance is based on its straight relation with tumor volume in radical prostatectomy specimens (14).

As discussed above, several individual parameters have the power to preoperatively predict the risk of the actual pathologic stage and biochemical outcome after treatment. For this reason, many authors have analyzed the use of pre- and postoperative nomograms in order to find patients in which a high risk of extra-prostatic disease (15) or high rates of disease progression are expected (16,17).

The first nomogram developed by Partin et al. (18), to predict the risks of nomogram confined disease and involvement of seminal vesicles and iliac lymph nodes in patients that underwent radical retropubic prostatectomy, included the biopsy Gleason score, clinical stage and serum PSA levels.

Considering that the percent positive biopsy cores represent an important prognostic factor (19), clinical stage as defined at digital rectal examination is not as relevant as it was thought before (4) and some studies incorporated the PPBC into models of prognostic value (8), in the present study we analyzed the predictive power of a new nomogram including the preoperative serum PSA and the biopsy Gleason score along with the PPBC.

MATERIALS AND METHODS

Between September 1988 and December 2002, 960 patients with clinically localized prostate cancer who underwent radical retropubic prostatectomy were retrospectively studied. All the patients underwent clinical and pathological staging according to the TNM staging system (20).

From the 960 patients, only those men with complete information regarding the total number of biopsy cores, number of fragments with cancer, biopsy Gleason score, serum PSA levels and pathologic analysis of the surgical specimen were studied. Fifty-four patients that received neoadjuvant androgen deprivation therapy or were diagnosed through transurethral resection or transvesical prostatectomy were excluded. A total of 898 remained in study. Table-1 shows the patients characteristics.

The same surgeon (MS) performed all the surgical procedures according to the Walsh technique (21), modified by Srougi (22). The same pathologist (KRL) analyzed all the surgical specimens, including the prostate gland, seminal vesicles and obturatory lymph.

Macroscopic Analysis

The specimens of radical prostatectomy were fixed in buffered formalin 10% for a period of 6h. After weighting and measuring the gland, thin transversal sections were performed in the surgical margins related to the bladder neck and the prostate apex. The seminal vesicles were sectioned in the base and longitudinal sections were submitted to histological examination. The entire gland was included for study after having their margins painted with India ink. The right and left lobes were separated, with sequential transversal sections being performed every 3 mm, designed from the proximal region towards the distal one. Between 10 and 12 sections from each lobe were included for histological study. The lymph nodes from the fat related to the resection of the iliac chain were dissected and sections representative of each nodular structure were included for study.

Microscopic Analysis

The specimens underwent the usual processing with inclusion in paraffin. Sections of 4 to 6 mm were stained by hematoxylin-eosin. The analyzed parameters were:

Histological pattern and Gleason score - The Gleason histological grade was used for evaluating the histological differentiation, considering only the acinar pattern (23).

Table 1 *– Demographic and clinical features of the 898 patients.*

N Patients	898
Age (years)	
Mean ± SD	62.9 ± 7.4
Median	63.5
Minimum – maximum	40 - 83
PSA (ng/mL)	
Mean ± SD	10.1 ± 7.3
Median	8.0
Minimum – Maximum	0.3 - 63.5
0 to 4.0	84 (9.4%)
4.1 to 10.0	512 (57.0%)
10.1 to 20.0	236 (26.3%)
> 20.0	66 (7.3%)
Gleason	
2 to 6	653 (72.7%)
7	165 (18.4%)
8 to 10	80 (8.9%)
Clinical Stage	
T1c	432 (48.1%)
T2	459 (51.1%)
T3a	7 (0.8%)
Pathologic Stage	
T2	599 (66.7%)
T3	296 (33.0%)
T4	3 (0.3%)
Total Number of Cores	
Mean ± SD	8.1 ± 3.3
Median	7.0
Minimum – maximum	2.0 - 22.0
Number of Positive Cores	
Mean ± SD	3.2 ± 2.1
Median	3.0
Minimum – maximum	1.0 - 20.0
Percent Positive Biopsy Cores	
Mean ± SD	41.2% ± 24.1%
Median	33.3%
Minimum – maximum	5.0% - 100.0%
0 to 25.0%	290 (32.3%)
25.1 to 50.0%	392 (43.7%)
50.1 to 75.0%	134 (14.9%)
75.1 to 100.0%	82 (9.1%)

Surgical margins - Positive margin was defined if carcinoma was within the bladder neck or distal urethral shave tissues, or if India ink was identified on tumor cells at a peripheral margin.

Extra-prostatic involvement - The invasion of adipose tissue and the periprostatic neurovascular plexus was considered as involvement of extra-prostatic tissue and, therefore, non organ-confined disease.

Seminal vesicle involvement - The involvement of seminal vesicle parenchyma and not only the adventitial tissue was considered seminal vesicle involvement.

Lymph node metastasis - The obturatory lymph nodes involved with cancer were designated as metastatic lymph nodes, and no difference regarding micro or macro-metastasis was considered.

To final analysis, the TNM 2002 (20) staging system was used.

The finding of an organ-confined disease was compared to the PPBC, serum PSA levels and Gleason score through a logistic regression model.

A multinomial logistic regression analysis (24) with 3 answers was performed: organ-confined disease, extraprostatic extension and seminal vesicle involvement. The predictive variables were the serum PSA levels, divided in categories of 0 to 4 ng/mL; 4.1 to 10.0 ng/mL; 10.1 to 20 ng/mL and greater than 20 ng/mL, the biopsy Gleason score, divided in categories of 2 to 6; 7 and 8 to 10, and then analyzed in groups of 2 to 6 and 7 to 10, and the PPBC, divided in categories of 0 to 25%; 25.1 to 50%; 50.1 to 75%; 75.1 to 100%. PPBC was defined using the formula, number of positive cores / total biopsy cores X 100.

Considering the association of the 3 parameters with disease extension on univariate and multivariate analysis, nomograms were developed based on the probabilities predicted by the adjusted model. A 95% confidence interval for the final model was obtained by repeating the analysis on 1000 bootstrap samples from the original cohort (25). The percentage of the bootstrap observed probabilities that were within 10% of the nomogram value was shown. Sensitivity, specificity, positive predictive value and negative predictive value were also determined. A significance level of 5% was adopted, and therefore, statistical significance was set as a $p \leq 0.05$. Statistical analysis was performed in the R for Windows software.

RESULTS

Table-2 shows that number of cores retrieved from biopsy and patient age was not related to the pathologic findings of the surgical specimen. Conversely, the PPBC, biopsy Gleason score and initial PSA levels showed relation with disease extension. According to multivariate analysis, these three studied variables were independent prognostic factors for predicting prostate cancer extension (Table-2).

Table-3 shows a nomogram-1 that allows prediction of organ-confined disease according to preoperative PSA levels, biopsy Gleason score and PPBC. However, nomogram-1 also shows that if we keep unchanged the PSA and PPBC values, the confidence intervals of patients with Gleason score 7 are the same of those with Gleason score 8 to 10 regarding the finding of organ-confined disease. This fact led us to develop a nomogram-2 (Table-4), using Gleason categories of 2 to 6 and 7 to 10, without losing predictive power and making it more practical for clinical use.

A validation analysis compared the predicted probabilities from the nomogram-1 with the observed probabilities from additional 1000 bootstrap samples

Table 2 – *Univariate and multivariate analysis for predicting organ-confined disease.*

	Univariate Analysis		
	OR	**95% CI**	**p Value**
N. of cores	0.99	[0.95 - 1.03]	0.669
Age (years)	1.02	[0.99 - 1.04]	0.091
Serum PSA			0.011
4.1-10 versus 0-4.0	1.67	[0.96 - 2.90]	0.071
10.1-20 versus 0-4.0	2.39	[1.33 - 4.27]	0.003
> 20.0 versus 0-4.0	2.38	[1.16 - 4.89]	0.018
Gleason			< 0.001
7 / 2-6	3.19	[2.25 - 4.54]	< 0.001
8-10 / 2-6	3.01	[1.88 - 4.83]	< 0.001
Percentage of positive cores			< 0.001
25.1-50.0 versus 0-25.0	1.48	[1.05 - 2.08]	0.025
50.1-75 versus 0-25.0	2.02	[1.30 - 3.13]	0.002
75.1-100 versus 0-25.0	3.94	[2.36 - 6.58]	< 0.001
	Multivariate Analysis		
	OR	**95% CI**	**p Value**
PSA			0.057
4.0-10 versus 0-4.0	1.58	[0.89 - 2.80]	0.120
10.0-20 versus 0-4.0	2.17	[1.18 - 3.97]	0.012
> 20.0 versus 0-4.0	1.99	[0.94 - 4.25]	0.074
Gleason			< 0.001
7 / 0-6	2.96	[2.06 - 4.26]	< 0.001
8-10 / 2-6	2.86	[1.76 - 4.64]	< 0.001
Percentage of positive cores			< 0.001
25.0-50.0 versus 0-25.0	1.35	[0.95 - 1.93]	0.096
50.0-75 versus 0-25.0	1.58	[0.99 - 2.50]	0.053
75.0-100 versus 0-25.0	3.04	[1.78 - 5.20]	< 0.001

Table 3 – Nomogram - *Prediction of organ-confined disease according to preoperative PSA levels, biopsy Gleason score and percent positive biopsy cores (PPBC)**

	Gleason Score 2 to 6 PSA (ng/mL)				Gleason Score 7 PSA (ng/mL)				Gleason Score 8 to 10 PSA (ng/mL)			
PPBC	**0 to 4.0**	**4.1 to 10.0**	**10.1 to 20.0**	**> 20.0**	**0 to 4.0**	**4.1 to 10.0**	**10.1 to 20.0**	**> 20.0**	**0 to 4.0**	**4.1 to 10.0**	**10.1 to 20.0**	**> 20.0**
0 to 25%	86 (78-93)	80 (75-85)	75 (68-82)	78 (65-87)	69 (55-83)	59 (48-69)	51 (39-63)	53 (35-70)	70 (53-84)	59 (47-71)	52 (38-65)	x
25.1 to 50%	82 (74-90)	75 (69-80)	69 (61-75)	71 (59-82)	63 (50-77)	51 (42-60)	42 (31-52)	43 (28-60)	64 (46-79)	52 (38-64)	43 (30-56)	45 (27-63)
50.1 to 75%	80 (67-90	72 (63-80)	66 (55-76)	68 (53-82)	59 (43-76)	47 (36-59)	39 (27-51)	40 (25-58)	x	48 (33-62)	40 (25-55)	42 (25-61)
75.1 to 100%	72 (55-85)	59 (46-71)	50 (37-63)	51 (34-67)	46 (29-68)	31 (21-44)	22 (13-34)	22 (12-37)	x	33 (20-48)	24 (13-38)	24 (12-42)

** Numbers represent percent predictive probability (95% confidence interval), X = lack of sufficient data to calculate probability.*

Table 4 – Nomogram - *Prediction of organ-confined disease according to preoperative PSA levels, biopsy Gleason score and percent positive biopsy cores (PPBC)*.*

	Gleason Score 2 to 6 PSA (ng/mL)				Gleason Score 7 to 10 PSA (ng/mL)			
PPBC	**0 to 4.0**	**4.1 to 10.0**	**10.1 to 20.0**	**> 20.0**	**0 to 4.0**	**4.1 to 10.0**	**10.1 to 20.0**	**> 20.0**
0 to 25%	86 (78-92)	80 (75-85)	75 (69-82)	78 (66-87)	70 (57-81)	59 (50-67)	51 (40-62)	54 (37-69)
25.1 to 50%	82 (75-90)	75 (70-80)	69 (63-76)	71 (59-83)	64 (51-77)	51 (43-59)	42 (33-52)	44 (30-60)
50.1 to 75%	80 (68-89)	72 (63-80)	66 (55-75)	68 (53-81)	59 (43-75)	47 (36-58)	39 (27-51)	41 (26-57)
75.1 to 100%	72 (57-84)	59 (47-71)	50 (37-62)	51 (35-67)	47 (29-66)	32 (21-44)	23 (14-33)	23 (12-36)

** Numbers represent percent predictive probability (95% confidence interval).*

from the study group. In the validation study, 87.0% of the time the nomograms correctly predicted the probability of a pathological stage to within 10%. The same was applied to validation of nomogram-2, which used Gleason score categories of 2 to 6 and 7 to 10. In this case, the validation study showed that in 91.1% the time the nomogram correctly predicted the probability of a pathological stage to within 10%. Tables-5 and 6 shows the sensitivity, specificity, positive predictive value, and negative predictive value achieved for various predicted probability cutoff values for organ-confined cancer when assessed in the 1000 validation bootstrap samples.

COMMENTS

After Partin's pioneer idea of creating nomograms to predict prostate cancer extension in 1993 (18), several other models using different variables were developed to predict disease extension and/or recurrence. However, some of them are not practical for clinical use due to the complexity of its interpretation and most present a lack of significant accuracy due to the relative imprecision of the prognostic variables utilized.

Our study presents a nomogram to predict disease extension in patients with clinical localized prostate cancer on the basis of preoperative serum PSA, biopsy Gleason score and PPBC as a new parameter to be included, with more accurate results than the isolated analysis of each variable separately.

The finding of an organ-confined disease after radical retropubic prostatectomy varies from 13 to 82% of cases (18,26). In the present study, we found a 66.7% rate. This variation depends on the biopsy Gleason score, serum PSA levels and PPBC, however even with all these variables being favorable, there is still a chance of 20% of extra-prostatic extension (19).

The development of the present nomogram was not based on the clinical stage as proposed by Partin et al. (15), because we believe this variable is losing clinical significance as more than 60% of patients with prostate cancer are staged as T1c (27). This distribution differs from what was observed during the eighties, where less than 1% of cases were detected due to serum PSA level elevation (28). Furthermore, in prostate screening programs, only 10% of patients underwent transrectal needle biopsy due to abnormalities on digital rectal examination (29).

Since tumoral volume has emerged as an important prognostic factor of pathologic findings and disease recurrence, the PPBC has been used to predict pathologic (12) and biochemical outcome after treatment (19,30). This idea gained support after the demonstration of a linear relationship between PPBC and tumoral volume at radical prostatectomy specimen (31).

There is also a relation between the presence of Gleason patterns 4 or 5 on biopsy and on surgical specimens, showing that this finding at biopsy samples has prognostic value for the patient (31). In fact, 13% of the patients with biopsy Gleason score less than 7 show disease recurrence while almost 60% with a Gleason score was 7 to 10 did (32). In our series, only 48.8% of patients with a Gleason score between 8 to 10 had an organ-confined disease, while this finding occurred in 74.1% of patients with scores under 7. Thus, if we apply the nomogram in a patient with all favorable variables (PSA less than 4 ng/mL, less than 25% positive biopsy cores and Gleason score less than 7), this number reaches 86% of chances of an organ-confined disease.

When comparing patients with Gleason score 7 to patients with Gleason score 8 to 10, we noted that when keeping serum PSA values between 4 and 10 ng/mL and positive biopsy cores under 25%, the probability of finding an organ-confined disease was 60% and 61% respectively. For this reason, we decided to construct an easier nomogram considering only categories of 2 to 6 and 7 to 10. This finding demonstrates that tumors with Gleason score 7 can present a similar behavior when compared to scores 8 to 10, probably due to the fact that patients with Gleason score 7 also own different percentages of patterns 4 or even 5.

Despite all these evidences, there are still some controversies regarding cases with Gleason score 7 presenting a different behavior when compared to patients with Gleason scores 8 to 10 (33). As we know, the Gleason score 7 is composed by the

Table 5 – *Predictive performance (median [95% confidence interval]) of organ-confined disease nomograms in 1000 validation bootstrap samples (nomogram-1).*

Probability	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
≥ 0.10	100 (100-100)	0 (0-0)	66.8 (63.7-69.9)	100 (91.3-100)
≥ 0.15	100 (99.7-100)	0 (0-3.7)	66.9 (63.8-70.0)	100 (50.0-100)
≥ 0.20	100 (99.2-100)	1.0 (0-6.1)	67.1 (64.1-70.5)	88.9 (33.3-100)
≥ 0.25	99.7 (98.8-100)	3.3 (0-10.1)	67.6 (64.5-70.9)	83.3 (50.0-100)
≥ 0.30	99.3 (97.7-100)	5.6 (1.0-12.6)	68.0 (64.9-71.3)	80.0 (50.0-100)
≥ 0.35	98.7 (96.3-99.7)	9.2 (2.8-17.4)	68.7 (65.5-71.9)	76.9 (55.9-92.3)
≥ 0.40	97.2 (93.5-99.4)	13.6 (6.0-24.5)	69.5 (66.4-72.8)	71.0 (58.6-87.5)
≥ 0.45	94.8 (88.6-98.1)	20.0 (9.9-35.8)	70.7 (67.4-74.0)	65.3 (56.1-77.3)
≥ 0.50	90.1 (83.8-95.7)	29.8 (16.1-44.3)	72.2 (69.1-75.8)	60.2 (53.9-68.1)
≥ 0.55	84.6 (79.2-91.6)	39.9 (25.1-49.4)	73.8 (70.4-77.3)	56.3 (51.0-61.9)
≥ 0.60	80.3 (75.2-85.8)	45.8 (34.7-53.7)	74.9 (71.7-78.1)	53.5 (47.9-58.7)
≥ 0.65	76.0 (65.7-81.4)	51.5 (42.1-62.6)	75.9 (72.7-79.3)	51.1 (45.8-56.4)
≥ 0.70	66.5 (45.3-77.8)	61.8 (49.1-75.8)	77.5 (74.2-81.0)	47.6 (41.7-53.9)
≥ 0.75	47.6 (23.1-67.6)	76.0 (60.9-89.8)	80.2 (76.4-84.6)	41.6 (36.8-48.7)
≥ 0.80	21.7 (0-48.5)	91.4 (77.4-100)	83.6 (70.4-90.9)	36.3 (32.6-40.8)
≥ 0.85	3.3 (0-12.8)	98.6 (95.9-100)	85.6 (67.9-95.6)	33.9 (30.5-37.0)
≥ 0.90	0 (0-5.2)	100 (98.2-100)	87.0 (72.1-98.1)	33.3 (30.1-36.4)

Table 6 – *Predictive performance (median [95% confidence interval]) of organ-confined disease nomograms in 1000 validation bootstrap samples (nomogram-2).*

Probability	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
≥ 0.10	100 (100-100)	0 (0-0)	66.8 (63.9-69.8)	100 (84.0-100)
≥ 0.15	100 (99.7-100)	0 (0-3.4)	66.9 (63.9-69.8)	100 (60.5-100)
≥ 0.20	100 (99.1-100)	0 (0-6.1)	67.2 (64.2-70.1)	88.2 (50.0-100)
≥ 0.25	99.5 (98.7-100)	3.3 (0-10.7)	67.6 (64.6-70.6)	80.0 (44.4-100)
≥ 0.30	99.3 (98.1-100)	5.6 (0-12.4)	68.1 (65.2-71.1)	80.0 (50.0-100)
≥ 0.35	98.8 (96.1-99.8)	9.1 (2.1-18.3)	68.7 (65.7-71.6)	77.2 (52.6-94.1)
≥ 0.40	97.3 (94.0-99.5)	13.0 (5.2-23.3)	69.5 (66.5-72.6)	71.1 (54.3-88.6)
≥ 0.45	94.8 (88.7-98.8)	19.4 (8.9-34.5)	70.5 (67.7-73.8)	64.9 (54.5-81.1)
≥ 0.50	90.3 (83.5-95.8)	28.9 (15.1-44.6)	72.0 (69.0-75.8)	59.7 (53.1-67.4)
≥ 0.55	84.1 (79.0-91.9)	40.2(24.0-49.8)	73.8 (70.5-77.1)	55.7 (50.3-61.5)
≥ 0.60	79.9 (74.0-85.1)	46.1 (36.0-54.4)	74.9 (71.9-77.9)	53.1 (47.7-58.1)
≥ 0.65	75.7 (65.4-80.6)	51.7 (43.5-63.7)	76.0 (73.2-79.2)	50.9 (45.7-56.0)
≥ 0.70	66.6 (50.7-77.8)	61.4 (49.3-73.1)	77.6 (74.6-81.1)	47.7 (42.4-53.4)
≥ 0.75	48.5 (26.5-68.0)	75.5 (61.4-89.2)	80.2 (76.8-84.6)	41.7 (36.9-48.7)
≥ 0.80	23.5 (0-39.7)	90.6 (82.5-100)	83.7 (73.1-92.4)	36.3 (32.6-41.2)
≥ 0.85	3.2 (0-12.1)	98.7 (95.7-100)	86.6 (67.4-96.7)	33.6 (30.8-37.0)
≥ 0.90	0 (0-5.0)	100 (98.2-100)	86.7 (69.6-99.2)	33.2 (30.2-36.3)

sum of the two most prevalent glandular patterns that most frequently can be 3+4 or 4+3. Some studies have shown that the percentage of Gleason pattern 4 is related to extension and severity of the disease (31), motivating comparisons of these two scores. Chan et al. (34) found an organ-confined disease rate of 34.7% among patients with surgical Gleason score 7 that underwent radical prostatectomy. However, the risk of disease progression after surgery was 20% greater for patients with Gleason 4+3 when compared to patients with Gleason score 3+4 after 10 years follow up. It is important to point out that these results were based on analysis of the surgical specimens and not on biopsy samples as we discussed before (33). Conversely, Groeber et al. (35) did not find any difference between the groups with Gleason score 3+4 or 4+3 regarding extra-prostatic extension or seminal vesicle involvement.

In the present study we ratify the greater accuracy of the nomograms when compared to the analysis of a single prognostic variable. In patients with serum PSA between 0 to 4 ng/mL, the chance of an organ-confined disease was 78.6%, however, when considering biopsy Gleason score and PPBC, we found that the finding of an organ-confined disease can be observed in 70 to 86% of cases. Gancarczyk et al. (8), developed a nomogram based on the same variables and showed a 72% rate of an organ-confined disease when serum PSA was 4 ng/mL or lower. However, as shown in our series, when considering the biopsy Gleason score and PPBC, this rate varied from 54 to 80%. The same reasoning can be applied when considering biopsy Gleason score as a single variable that defines a 74.1% chance of an organ-confined disease in a patient with score 2 to 6. However, when all these three variables are considered together, we found that the same patient present a 51 to 86% chance of an organ confined disease. We also noted that patients with more than 75% positive biopsy cores have a 43.9% chance of presenting an organ-confined disease, the same number found by Gancarczyk et al. (8) considering a cut point of 60% for positive biopsy cores. However, this probability rises to 71% with favorable PSA levels and Gleason scores and reduces to 26% when both variables were unfavorable.

Finally, in the present study, we confirmed the superiority of the nomograms when compared to the analysis of a single prognostic factor. We emphasize that the PPBC is a very important parameter that should be incorporated in preoperative models, and that patients with biopsy Gleason score 7 can show the same disease extension when compared to patients with Gleason score 8 to 10.

ACKNOWLEDGEMENTS

Adriana Sañudo made the statistical analysis.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC: Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol. 2003; 169: 517-23.
2. Peller PA, Young DC, Marmaduke DP, Marsh WL, Badalament RA: Sextant prostate biopsies. A histopathologic correlation with radical prostatectomy specimens. Cancer. 1995; 75: 530-8.
3. Freedland SJ, Terris MK, Csathy GS, Kane CJ, Amling CL, Presti JC Jr, et al.: Preoperative model for predicting prostate specific antigen recurrence after radical prostatectomy using percent of biopsy tissue with cancer, biopsy Gleason grade and serum prostate specific antigen. J Urol. 2004; 171: 2215-20.
4. Freedland SJ, Aronson WJ, Csathy GS, Kane CJ, Amling CL, Presti JC Jr, et al.: Comparison of percentage of total prostate needle biopsy tissue with cancer to percentage of cores with cancer for predicting PSA recurrence after radical prostatectomy: results from the SEARCH database. Urology. 2003; 61: 742-7.
5. San Francisco IF, Regan MM, Olumi AF, DeWolf WC: Percent of cores positive for cancer is a better preoperative predictor of cancer recurrence after radical prostatectomy than prostate specific antigen. J Urol. 2004; 171: 1492-9.

6. Graefen M, Ohori M, Karakiewicz PI, Cagiannos I, Hammerer PG, Haese A, et al.: Assessment of the enhancement in predictive accuracy provided by systematic biopsy in predicting outcome for clinically localized prostate cancer. J Urol. 2004; 171: 200-3.
7. Hull GW, Rabbani F, Abbas F, Wheeler TM, Kattan MW, Scardino PT: Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol. 2002; 167: 528-34.
8. Gancarczyk KJ, Wu H, McLeod DG, Kane C, Kusuda L, Lance R, et al.: Using the percentage of biopsy cores positive for cancer, pretreatment PSA, and highest biopsy Gleason sum to predict pathologic stage after radical prostatectomy: the Center for Prostate Disease Research nomograms. Urology. 2003; 61: 589-95.
9. Sebo TJ, Cheville JC, Riehle DL, Lohse CM, Pankratz VS, Myers RP, et al.: Predicting prostate carcinoma volume and stage at radical prostatectomy by assessing needle biopsy specimens for percent surface area and cores positive for carcinoma, perineural invasion, Gleason score, DNA ploidy and proliferation, and preoperative serum prostate specific antigen: a report of 454 cases. Cancer. 2001; 91: 2196-204.
10. Tombal B, Tajeddine N, Cosyns JP, Feyaerts A, Opsomer R, Wese FX, et al.: Does site-specific labelling and individual processing of sextant biopsies improve the accuracy of prostate biopsy in predicting pathological stage in patients with T1c prostate cancer? BJU Int. 2002; 89: 543-8.
11. Grossfeld GD, Latini DM, Lubeck DP, Broering JM, Li YP, Mehta SS, et al.: Predicting disease recurrence in intermediate and high-risk patients undergoing radical prostatectomy using percent positive biopsies: results from CaPSURE. Urology. 2002; 59: 560-5.
12. Quinn DI, Henshall SM, Brenner PC, Kooner R, Golovsky D, O'Neill GF, et al.: Prognostic significance of preoperative factors in localized prostate carcinoma treated with radical prostatectomy: importance of percentage of biopsies that contain tumor and the presence of biopsy perineural invasion. Cancer. 2003; 97: 1884-93.
13. Sebo TJ, Bock BJ, Cheville JC, Lohse C, Wollan P, Zincke H: The percent of cores positive for cancer in prostate needle biopsy specimens is strongly predictive of tumor stage and volume at radical prostatectomy. J Urol. 2000; 163: 174-8.
14. Cagiannos I, Karakiewicz P, Eastham JA, Ohori M, Rabbani F, Gerigk C, et al.: A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. J Urol. 2003; 170: 1798-803.
15. Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD: Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology. 2001; 58: 843-8.
16. Egawa S, Suyama K, Arai Y, Matsumoto K, Tsukayama C, Kuwao S, et al.: A study of pretreatment nomograms to predict pathological stage and biochemical recurrence after radical prostatectomy for clinically resectable prostate cancer in Japanese men. Jpn J Clin Oncol. 2001; 31: 74-81.
17. Kattan MW, Zelefsky MJ, Kupelian PA, Cho D, Scardino PT, Fuks Z, et al.: Pretreatment nomogram that predicts 5-year probability of metastasis following three-dimensional conformal radiation therapy for localized prostate cancer. J Clin Oncol. 2003; 21: 4568-71.
18. Partin AW, Yoo J, Carter HB, Pearson JD, Chan DW, Epstein JI, et al.: The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. J Urol. 1993; 150: 110-4.
19. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Fondurulia J, Chen MH, et al.: Clinical utility of the percentage of positive prostate biopsies in defining biochemical outcome after radical prostatectomy for patients with clinically localized prostate cancer. J Clin Oncol. 2000; 18: 1164-72.
20. Schroder FH, Hermanek P, Denis L, Fair WR, Gospodarowicz MK, Pavone-Macaluso M: The TNM classification of prostate cancer. Prostate Suppl. 1992; 4: 129-38.
21. Walsh PC, Donker PJ: Impotence following radical prostatectomy: insight into etiology and prevention. 1982. J Urol. 2002; 167: 1005-10.
22. Srougi M: Radical Prostatectomy with Potency Preservation. In: Srougi M, Simon SD (ed.), Urological Cancer. Sao Paulo, Platina. 1996; pp. 357-65. [in Portuguese]
23. Gleason DF: Classification of prostatic carcinomas. Cancer Chemother Rep. 1966; 50: 125-8.
24. Hosmer DW, Lemeshow S: Applied logistic regression. New York, John Wiley. 1989; pp. 369.
25. Efron B, Tibshirabi RJ: Na introduction to be bootstrap. New York; Chapman & Hall. 1993; pp. 430.
26. Freedland SJ, Csathy GS, Dorey F, Aronson WJ: Percent prostate needle biopsy tissue with cancer is more predictive of biochemical failure or adverse pathology after radical prostatectomy than prostate

specific antigen or Gleason score. J Urol. 2002: 167: 516-20.
27. Rioux-Leclercq NC, Chan DY, Epstein JI: Prediction of outcome after radical prostatectomy in men with organ-confined Gleason score 8 to 10 adenocarcinoma. Urology. 2002; 60: 666-9.
28. Han M, Partin AW, Piantadosi S, Epstein JI, Walsh PC: Era specific biochemical recurrence-free survival following radical prostatectomy for clinically localized prostate cancer. J Urol. 2001; 166: 416-9.
29. Yan Y, Carvalhal GF, Catalona WJ, Young JD: Primary treatment choices for men with clinically localized prostate carcinoma detected by screening. Cancer. 2000; 88: 1122-30.
30. Ravery V, Chastang C, Toublanc M, Boccon-Gibod L, Delmas V, Boccon-Gibod L: Percentage of cancer on biopsy cores accurately predicts extracapsular extension and biochemical relapse after radical prostatectomy for T1-T2 prostate cancer. Eur Urol. 2000; 37: 449-55.
31. Rubin MA, Mucci NR, Manley S, Sanda M, Cushenberry E, Strawderman M, et al.: Predictors of Gleason pattern 4/5 prostate cancer on prostatectomy specimens: can high grade tumor be predicted preoperatively? J Urol. 2001; 165: 114-8.
32. Sakr WA, Tefilli MV, Grignon DJ, Banerjee M, Dey J, Gheiler EL, et al.: Gleason score 7 prostate cancer: a heterogeneous entity? Correlation with pathologic parameters and disease-free survival. Urology. 2000; 56: 730-4.
33. Herman CM, Kattan MW, Ohori M, Scardino PT, Wheeler TM: Primary Gleason pattern as a predictor of disease progression in gleason score 7 prostate cancer: a multivariate analysis of 823 men treated with radical prostatectomy. Am J Surg Pathol. 2001; 25: 657-60.
34. Chan TY, Partin AW, Walsh PC, Epstein JI: Prognostic significance of Gleason score 3+4 versus Gleason score 4+3 tumor at radical prostatectomy. Urology. 2000; 56: 823-7.
35. Grober ED, Tsihlias J, Jewett MA, Sweet JM, Evans AJ, Trachtenberg J, et al.: Correlation of the primary Gleason pattern on prostate needle biopsy with clinico-pathological factors in Gleason 7 tumors. Can J Urol. 2004; 11: 2157-62.

Accepted after revision:
January 3, 2006

Correspondence address:
Dr. Alexandre Crippa
Rua Barata Ribeiro, 414 – 7o. andar
São Paulo, SP, 01308-000, Brazil
Fax: + 55 11 3257-9006
E-mail: drcrippa@uol.com.br

Clinical Urology
International Braz J Urol Vol. 32 (2): 165-171, March - April, 2006

Are Prostate Carcinoma Clinical Stages T1c and T2 Similar?

Athanase Billis, Luis A. Magna, Isabela C. Watanabe, Matheus V. Costa, Gilliatt H. Telles, Ubirajara Ferreira

Department of Anatomic Pathology (AB, ICW, MVC, GHT), Department of Medical Genetics and Biostatistics (LAM), and Department of Urology (UF), School of Medicine, State University of Campinas (Unicamp), Campinas, SP, Brazil

ABSTRACT

Purpose: A recent study has found that PSA recurrence rate for clinical T1c tumors is similar to T2 tumors, indicating a need for further refinement of clinical staging system. To test this finding we compared clinicopathologic characteristics and the time to PSA progression following radical retropubic prostatectomy of patients with clinical stage T1c tumors to those with stage T2, T2a or T2b tumors.
Materials and Methods: From a total of 186 consecutive patients submitted to prostatectomy, 33.52% had clinical stage T1c tumors, 45.45% stage T2a tumors and 21.02% stage T2b tumors. The variables studied were age, preoperative PSA, prostate weight, Gleason score, tumor extent, positive surgical margins, extraprostatic extension (pT3a), seminal vesicle invasion (pT3b), and time to PSA progression. Tumor extent was evaluated by a point-count method.
Results: Patients with clinical stage T1c were younger and had the lowest mean preoperative PSA. In the surgical specimen, they had higher frequency of Gleason score < 7 and more organ confined cancer. In 40.54% of the patients with clinical stage T2b tumors, there was extraprostatic extension (pT3a). During the study period, 54 patients (30.68%) developed a biochemical progression. Kaplan-Meier product-limit analysis revealed no significant difference in the time to PSA progression between men with clinical stage T1c versus clinical stage T2 ($p = 0.7959$), T2a ($p = 0.6060$) or T2b ($p = 0.2941$) as well as between men with clinical stage T2a versus stage T2b ($p = 0.0994$).
Conclusion: Clinicopathological features are not similar considering clinical stage T1c versus clinical stages T2, T2a or T2b.

***Key words**: prostatic neoplasms; pathology; neoplasm staging; prostate-specific antigen*
Int Braz J Urol. 2006; 32: 165-71

INTRODUCTION

A recent study (1) has found that PSA recurrence rate for clinical T1c tumors is similar to T2 tumors, indicating a need for further refinement of clinical staging system. To test this finding we compared clinicopathologic characteristics and the time to PSA progression following radical prostatectomy of patients with clinical T1c tumors to those with T2 tumors as well as subclassifying stage T2 into stages T2a and T2b.

MATERIAL AND METHODS

The study was done on 59 patients with clinical stage T1c tumors and 127 patients with clinical stage T2 tumors submitted to radical retropubic pros-

tatectomy from January 1997 to July 2004 in our Institution. The variables studied were age, preoperative PSA, prostate weight and pathologic findings in the surgical specimens: Gleason score, tumor extent, positive surgical margins, extraprostatic extension (pT3a), and seminal vesicle invasion (pT3b). Time to biochemical progression following surgery was studied comparing the groups: T1c versus T2, T1c versus T2a, T1c versus T2b, and T2a versus T2b.

The surgical specimen previously fixed was weighed, measured and the entire surface inked. The bladder neck and apical margins were amputated. From each cone-shaped amputated margin, 8 fragments were processed through perpendicular sections relative to the margins. The rest of the prostate was serially cut in transverse sections at 3 to 5mm intervals. The prostate slices were subdivided into quadrants and labeled to allow for reconstruction as whole-mount sections.

Blocks were embedded in paraffin, cut at 6 μm, and one section from each block was stained with hematoxylin and eosin. Presence of adenocarcinoma was diagnosed according to the criteria of Mostofi and Price (2). The diagnosis was based on invasion or architectural disturbance. Histological grading was performed according to the Gleason system (3). Prostatic carcinomas with final score < 7 were considered low-intermediate grade; and, with final score ≥ 7 were considered high-grade (4). Extraprostatic extension was diagnosed according to Bostwick & Montironi (5), whenever cancer was seen in adipose tissue, and corresponds to pT3a in the TNM staging system (6). Seminal vesicle invasion was defined as an invasion of the muscular wall, as described by Epstein et al. (7), corresponding to pT3b in the TNM staging system.

Tumor extent was estimated by use of a point-count method (8). Drawn on a sheet of paper, each quadrant of the whole mount sections contained 8 equidistant points. During the microscopic examination of the slides, the tumor area was drawn on the correspondent quadrant seen on the paper. At the end of the examination the amount of positive points represented an estimate of the tumor extent.

The 59 patients with stage T1c had clinically unapparent tumor not palpable or visible by imaging identified by needle biopsy. The 127 patients with clinical stage T2 had tumor confined within the prostate; 80 had stage T2a (tumor involving one lobe) and 37 had stage T2b (tumor involving both lobes). In 10 patients there was no information regarding subclassification of clinical stage T2.

Biochemical progression was defined as PSA ≥ 0.4 ng/mL. From January 1997 to July 2005, 54 patients (30.68%) developed a biochemical progression. The mean and median follow-up for these patients was 24.74 and 16 months, respectively (range 2 to 89 months).

The data were analyzed using the Mann-Whitney test for comparison of independent samples and Fisher's exact test for evaluating differences between proportions. Time to PSA progression was studied using the Kaplan-Meier product-limit analysis; the comparison between the groups was done using the log-rank test. For the analysis of time to biochemical progression, 18 patients without tests for PSA level following radical prostatectomy were excluded. The mean and median follow-up for 122 men without biochemical progression (censored patients) was 33.50 and 30.50 months, respectively (range 3 to 94 months). P value < 0.05 was considered statistically significant. All statistical analyses were performed using Statistica 5.5 software (StatSoft, Inc., Tulsa, OK, USA).

RESULTS

Table-1 compares clinicopathologic features between 59 patients with stage T1c and 127 patients with stage T2. There were no statistically significant differences related to age ($p = 0.0788$), preoperative PSA ($p = 0.3791$), prostate weight ($p = 0.6301$), tumor extent ($p = 0.1857$), positive surgical margins ($p = 0.3163$), extraprostatic extension ($p = 0.1020$) and seminal vesicle invasion ($p = 0.2481$). There was a statistically significant higher number of patients with Gleason score ≥ 7 in stage T2 ($p = 0.0212$).

Table-2 compares clinicopathologic features between 59 patients with stage T1c and 80 patients with stage T2a. There were no statistically significant differences related to preoperative PSA ($p = 0.8068$), prostate weight ($p = 0.4777$), Gleason score

Table 1 – *Clinicopathologic features of men undergoing radical prostatectomy, by clinical stage.*

Characteristic	Clinical Stage T1c (%)	Clinical Stage T2 (%)	p Value
Number of patients	59 (31.72)	127 (68.28)	
Age			
Mean ± SD	61.96 ± 7.17	64.07 ± 5.91	0.0788[1]
Preoperative PSA (ng/mL)			
Mean ± SD	9.32 ± 4.04	10.89 ± 7.29	0.3791[1]
Median	7.8	9.12	
Prostate weight (g)			
Mean ± SD	37.77 ± 14.52	39.28 ± 16.37	0.6301[1]
Median	35	36	
Gleason score			
< 7	28 (47.46)	37 (29.60)	0.0212[2]
≥ 7	31 (52.54)	88 (70.40)	
Tumor extent			
Mean ± SD	33.89 ± 34.77	39.75 ± 39.46	
Median	25	29	0.1857[1]
Positive surgical margins	23 (38.98)	39 (30.70)	0.3163[2]
Extraprostatic extension (pT3a)	10 (16.94)	37 (29.13)	0.1020[2]
Seminal vesicle invasion (pT3b)	5 (8.47)	20 (15.74)	0.2481[2]

SD = standard deviation; [1] Mann-Whitney; [2] Fisher exact-test.

Table 2 – *Clinicopathologic features of men undergoing radical prostatectomy, by clinical stage T1c and stage T2a.*

Characteristic	Clinical Stage T1c (%)	Clinical Stage T2a (%)	p Value
Number of patients	59 (42.45)	80 (57.55)	
Age			
Mean ± SD	61.96 ± 7.17	64.60 ± 5.75	0.0411[1]
Preoperative PSA (ng/mL)			
Mean ± SD	9.32 ± 4.04	11.00 ± 11.32	0.8068[1]
Median	7.8	9.30	
Prostate weight (g)			
Mean ± SD	37.77 ± 14.52	40.20 ± 17.24	0.4777[1]
Median	35	40	
Gleason score			
< 7	28 (47.46)	24 (30.37)	0.0511[2]
≥ 7	31 (52.54)	55 (69.62)	
Tumor extent			
Mean ± SD	33.89 ± 34.77	38.68 ± 38.63	0.2979[1]
Median	25	28	
Positive surgical margins	23 (38.98)	35 (43.75)	0.8638[2]
Extraprostatic extension (pT3a)	10 (16.94)	19 (23.75)	0.4006[2]
Seminal vesicle invasion (pT3b)	5 (8.47)	12 (15.00)	0.3014[2]

SD = standard deviation; [1] Mann-Whitney; [2] Fisher exact-test.

(p = 0.0511), tumor extent (p = 0.2979), positive surgical margins (p = 0.8638), extraprostatic extension (p = 0.4006) and seminal vesicle invasion (p = 0.3014). Patients with clinical T2a tumors were significantly older than patients with stage T1c cancer (p = 0.0411).

Table-3 compares clinicopathologic features between 59 patients with stage T1c and 37 patients with stage T2b. There were no statistically significant differences related to age (p = 0.6693), preoperative PSA (p = 0.0616), prostate weight (p = 0.8185), Gleason score (p = 0.1336), tumor extent (p = 0.0948), positive surgical margins (p = 0.6756), and seminal vesicle invasion (p = 0.3264). There was a statistically significant higher number of patients with clinical stage T2b showing extraprostatic extension (pT3a) in the surgical specimen (p = 0.0161).

Figure-1 shows the time to PSA progression using the Kaplan-Meier product-limit analysis. There was no statistical significance between patients with stage T1c versus T2 (p = 0.7959).

Figure-2 shows the time to PSA progression using the Kaplan-Meier product-limit analysis. There was no statistical significance between patients with stage T1c versus T2a (p = 0.6060) and T1c versus T2b (p = 0.2941) as well as between patients with clinical stage T2b versus stage T2a (p = 0.0994).

COMMENTS

The TNM staging system (6) places men with tumors detected because of elevated prostate-specific antigen in the T1c group and those with palpable nodule confined within the prostate in stage T2. The latter is subclassified into stage T2a (tumor involving one lobe) and stage T2b (tumor involving both lobes).

In a recent study, Armatys et al. (1) found that patients with clinical stage T2 tumors have higher Gleason score and final pathologic stage compared to those tumors detected because of elevated serum PSA (T1c). In our series, there was a statistically significant higher number of patients with Gleason score ≥ 7 in clinical stage T2, however, there was no difference regarding pathologic stage. Armatys et al. (1) suggested a need for further refinement of clinical

Table 3 – *Clinicopathologic features of men undergoing radical prostatectomy, by clinical stage T1c and T2b.*

Characteristic	Clinical Stage T1c (%)	Clinical Stage T2b (%)	p Value
Number of patients	59 (61.46)	37 (38.54)	
Age			
Mean ± SD	61.96 ± 7.17	62.76 ± 6.58	0.6693[1]
Preoperative PSA (ng/mL)			
Mean ± SD	9.32 ± 4.04	13.44 ± 10.07	0.0616[1]
Median	7.8	10.00	
Prostate weight (g)			
Mean ± SD	37.77 ± 14.52	37.21 ± 14.88	0.8185[1]
Median	35	30	
Gleason score			
< 7	28 (47.46)	11 (30.56)	0.1336[2]
≥ 7	31 (52.54)	25 (69.44)	
Tumor extent			
Mean ± SD	33.89 ± 34.77	46.52 ± 44.99	0.0948[1]
Median	25	34	
Positive surgical margins	23 (38.98)	15 (40.55)	0.6756[2]
Extraprostatic extension (pT3a)	10 (16.94)	15 (40.54)	0.0161[2]
Seminal vesicle invasion (pT3b)	5 (8.47)	6 (16.21)	0.3264[2]

SD = standard deviation; [1] Mann-Whitney; [2] Fisher exact-test.

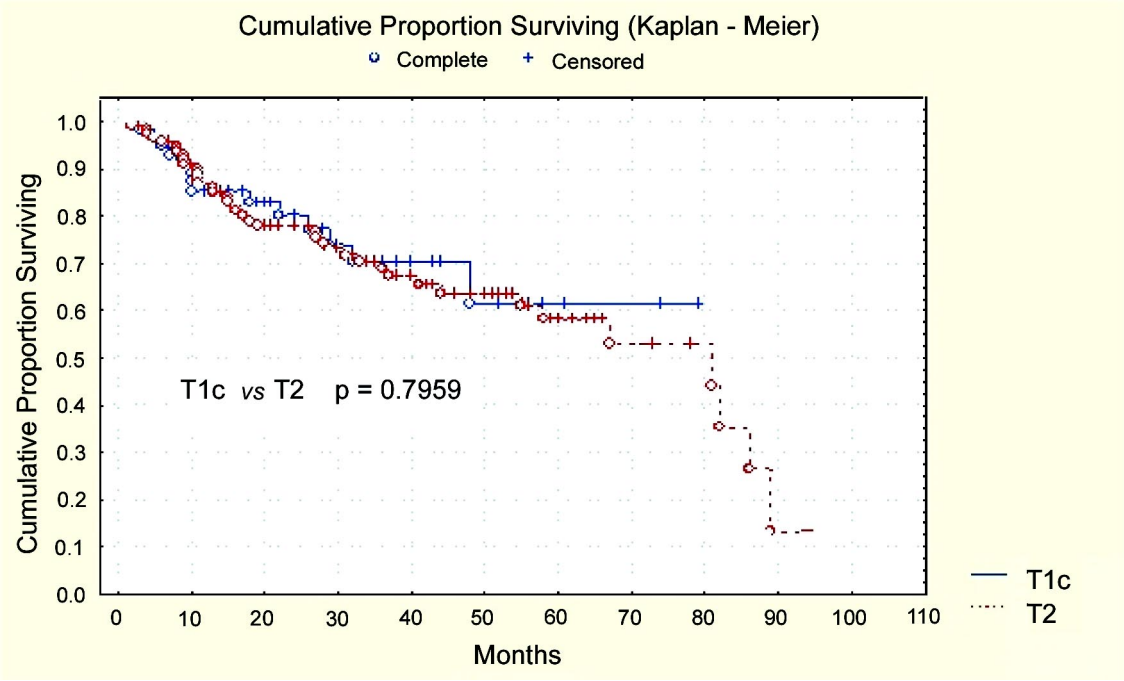


Figure 1 *– Time to PSA progression according to clinical stages T1c and T2. Kaplan-Meier product-limit analysis.*

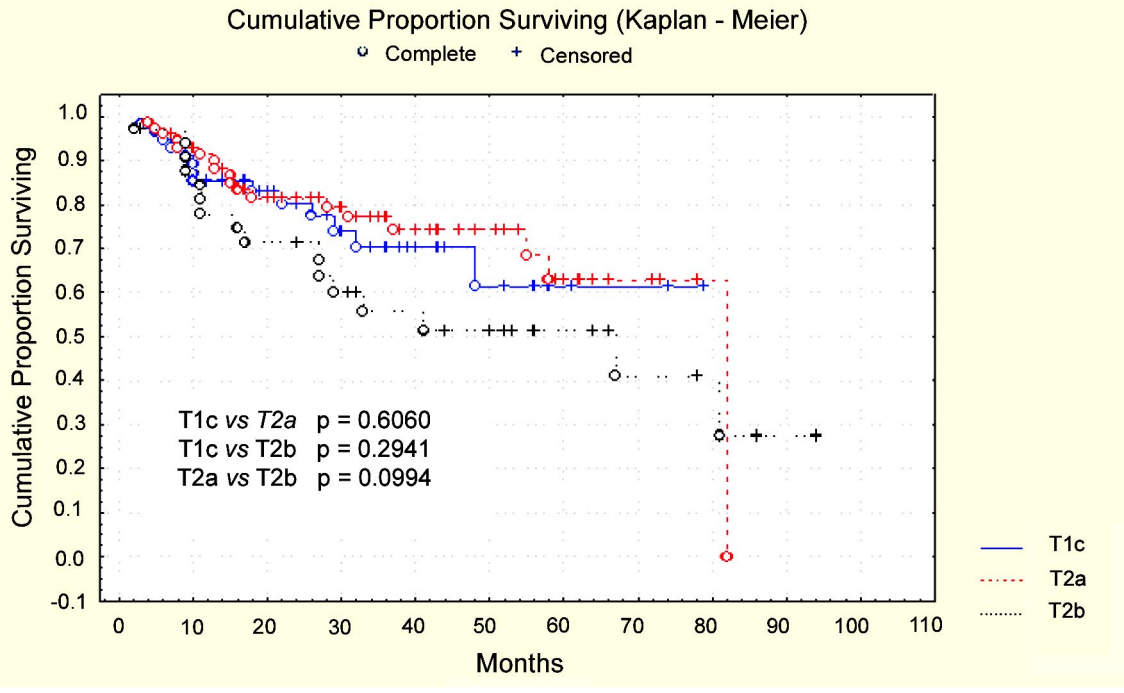


Figure 2 *– Time to PSA progression according to clinical stages T1c, T2a and T2b. Kaplan-Meier product-limit analysis.*

staging system because the PSA recurrence rate for T1c tumors was similar to cT2 tumors. This finding is similar to our study; however, the authors did not considered the subclassification of stage T2 into stages T2a and T2b.

Jack et al. (9) compared tumor location and pathological parameters in the radical prostatectomy specimens of stages T1c versus T2 cases in a 3-year period. Prostate specific antigen detected stage T1c tumors had a lower grade, stage and volume than stage T2 tumors during the same period. Lower tumor grade in stage T1c cases were due at least in part to the increased detection of Gleason pattern 2 containing transition zone tumors. The authors did not study the PSA progression rate for T1c and cT2 tumors as well as did not subclassified clinical stage T2.

Furuya et al. (10), in order to examine the characteristics of men with nonpalpable prostate cancer (T1c cancer) in Japan, compared patients treated with radical prostatectomy with those with palpable (T2) cancer. Prostate-specific antigen level in patients with T2b disease was significantly higher than those with T1c and T2a tumors. At the time of radical prostatectomy, 78%, 71% and 31% of patients with T1c, T2a, and T2b, respectively, had organ-confined disease. T1c cancers were clinically significant and clinicopathological features of T1c tumors were similar to T2a tumors. In our study, the mean preoperative PSA was 9.32, 11.00 and 13.44 in patients with stage T1c, T2a and T2b, respectively. Extraprostatic extension in the surgical specimen (pT3a) was found in 16.94%, 23.75% and 40.54% of the patients in stage T1c, T2a and T2b, respectively. These clinicopathologic findings are in accordance with Furuya et al. The authors did not study time to biochemical progression following surgery.

The definition of the serum PSA level for biochemical progression is controversial and varies from 0.2ng/mL to 0.6ng/mL in the literature (11-15). We considered as biochemical progression serum PSA level of 0.4ng/mL. Using the Kaplan-Meier product-limit analysis, there was no statistically significant difference in the time to PSA progression between patients with clinical stage T1c versus stage T2 ($p = 0.7959$), T1c versus T2a ($p = 0.6060$), T1c versus T2b ($p = 0.2941$) as well as between patients with clinical stage T2b versus stage T2a ($p = 0.0994$).

Ramos et al. (16) compared clinicopathological features, and cancer recurrence and survival rates in men with stage T1c versus T2a or T2b prostate cancer. The 5-year recurrence-free survival was similar for T1c versus T2a, and higher versus T2b cancers. Clinical stage was T1c in 39%, T2a in 22% and T2b in 39% of their patients; in our study, was 33.52%, 45.45% and 21.02%, respectively. Mean patient age was younger for the clinical stage T1c group (61 years) in their study as well as in ours (61 years).

Ghavamian et al. (17) compared clinicopathologic findings and PSA progression following radical retropubic prostatectomy in patients with clinical stage T1c, T2a or T2b cancer. Survival rates for T1c tumors were similar to T2a lesions, but significantly better than T2b lesions. Clinical T1c tumors were more likely to be organ confined and with a Gleason score less than 7. Considering tumor volume, T1c tumors were comparable to T2a lesions. Our findings showed that patients with stage T1c were more likely to have organ confined, Gleason score < 7 and less extensive tumors. Using a point-count method for estimating tumor extent the mean was 33.89, 38.68 and 46.52 positive points for stages T1c, T2a and T2b, respectively.

CONCLUSIONS

Clinicopathological features are not similar considering clinical stage T1c versus clinical stages T2, T2a or T2b. A statistically higher number of patients have Gleason score ≥ 7 in stage T2; are older in stage T2a; and, are not organ confined in stage T2b. Time to PSA progression following radical prostatectomy is similar between men in clinical stage T1c versus stages T2, T2a or T2b as well as between patients with clinical stage T2b versus stage T2a.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Armatys A, Koch MO, Bihrle R, Gardner TA, Eble JN, Patel NB, et al.: A clinicopathologic comparison of clinical stages T1c versus T2 prostate adenocarcinoma: Lack of differences in PSA recurrence, Mod Pathol. 2004; 17(suppl 1):138A.
2. Mostofi, FK, Price EB Jr: Tumors of the Male Genital System, Atlas of Tumor Pathology, Second Series, Fascicle 8. Washington DC, Armed Forces Institute of Pathology. 1973; pp. 202-17.
3. Gleason DF, Mellinger GT: Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol. 1974; 111: 58-64.
4. Gleason DF: Histologic grading of prostate cancer: a perspective. Hum Pathol. 1992; 23: 273-9.
5. Bostwick DG, Montironi R: Evaluating radical prostatectomy specimens: therapeutic and prognostic importance. Virchows Arch. 1997; 430: 1-16.
6. International Union Against Cancer: Prostate. In: Sobin LH, Wittekind Ch. (eds.), TNM Classification of Malignant Tumours, 6th ed. New York, Wiley-Liss. 1997; pp. 170-3.
7. Epstein JI, Carmichael M, Walsh PC: Adenocarcinoma of the prostate invading the seminal vesicle: definition and relation of tumor volume, grade and margins of resection to prognosis. J Urol. 1993; 149: 1040-5.
8. Billis A, Magna LA, Ferreira U: Correlation between tumor extent in radical prostatectomies and preoperative PSA, histological grade, surgical margins, and extraprostatic extension: application of a new practical method for tumor extent evaluation. Int Braz J Urol. 2003; 29: 113-9; discussion 120.
9. Jack GS, Cookson MS, Coffey CS, Vader V, Roberts RL, Chang SS, et al.: Pathological parameters of radical prostatectomy for clinical stages T1c versus T2 prostate adenocarcinoma: decreased pathological stage and increased detection of transition zone tumors. J Urol. 2002; 168: 519-24.
10. Furuya Y, Ohta S, Sato N, Kotake T, Masai M: Comparison of T1c versus T2 prostate cancers in Japanese patients undergoing radical prostatectomy. Int Urol Nephrol. 2002; 33: 73-6.
11. Amling CL, Bergstralh EJ, Blute ML, Slezak JM, Zincke H: Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? J Urol. 2001; 165: 1146-51.
12. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC: Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol. 2003; 169: 517-23.
13. Sofer M, Savoie M, Kim SS, Civantos F, Soloway MS: Biochemical and pathological predictors of the recurrence of prostatic adenocarcinoma with seminal vesicle invasion. J Urol. 2003; 169: 153-6.
14. Moul JW, Douglas TH, McCarthy WF, McLeod DG: Black race is an adverse prognostic factor for prostate cancer recurrence following radical prostatectomy in an equal access health care setting. J Urol. 1996; 155: 1667-73.
15. Andersson J, Ekman P, Egevad L, Hellstrom M: Relatively high risk of treatment failure after prostatectomy: tumour grade, histopathological stage and the preoperative serum PSA level are key prognosticators. Scand J Urol Nephrol. 2001; 35: 453-8.
16. Ramos CG, Carvalhal GF, Smith DS, Mager DE, Catalona WJ: Clinical and pathological characteristics, and recurrence rates of stage T1c versus T2a or T2b prostate cancer. J Urol. 1999; 161: 1525-9.
17. Ghavamian R, Blute ML, Bergstralh EJ, Slezak J, Zincke H: Comparison of clinically nonpalpable prostate-specific antigen-detected (cT1c) versus palpable (cT2) prostate cancers in patients undergoing radical retropubic prostatectomy. Urology. 1999; 54: 105-10.

Accepted after revision:
October 26, 2005

Correspondence address:
Dr. Athanase Billis
Dept. de Anatomia Patológica, UNICAMP
Caixa Postal 6111
Campinas, SP, 13084-971, Brazil
E-mail: athanase@fcm.unicamp.br

Clinical Urology
International Braz J Urol Vol. 32 (2): 172-180, March - April, 2006

Prospective Randomized Controlled Trial Comparing Three Different Ways of Anesthesia in Transrectal Ultrasound-Guided Prostate Biopsy

M. Tobias-Machado, Mauricio J. Verotti, Augusto J. Aragao, Alexandre O. Rodrigues, Milton Borrelli, Eric R. Wroclawski

Section of Urology, ABC Medical School, Santo Andre, Sao Paulo, Brazil

ABSTRACT

Purpose: To make an objective controlled comparison of pain tolerance in transrectal ultrasound-guided prostatic biopsy using intrarectal topic anesthesia, injectable periprostatic anesthesia, or low-dose intravenous sedation.
Materials and Methods: One hundred and sixty patients were randomized into 4 groups: group I, intrarectal application of 2% lidocaine gel; group II, periprostatic anesthesia; group III, intravenous injection of midazolam and meperidine; and group IV, control, patients to whom no sedation or analgesic was given. Pain was evaluated using an analogue pain scale graded from 0 to 5. Acceptance of a repetition biopsy, the side effects of the drugs and complications were also evaluated.
Results: 18/20 (90%) and 6/20 (30%) patients reported strong or unbearable pain in the group submitted to conventional biopsy and topical anesthesia ($p = 0.23$, chi-square = 1.41); whereas those submitted to periprostatic blockade and sedation, severe pain occurred in only 2/60 (3%) patients ($p < 0.001$, chi-square = 40.19) and 3/60 (5%) patients ($p < 0.001$, chi-square = 33.34). Acceptance of repetition of the biopsy was present in only 45% of the patients submitted to conventional biopsy, 60% of those that were given topical anesthesia ($p = 0.52$, chi-square = 0.4), compared to 100% of those submitted to periprostatic anesthesia ($p < 0.01$, chi-square = 15.17), and 95% of those who were sedated ($p < 0.001$, chi-square = 25.97%).
Conclusions: Transrectal ultrasound-guided prostatic biopsy is an uncomfortable experience; however application of periprostatic blockade and intravenous analgesia are associated to higher tolerance of the exam and patient comfort. Low dose sedation by association of intravenous meperidine and midazolam is an emerging and safe outpatient option.

***Key words**: prostate; biopsy; needle; ultrasonography; anesthesia and analgesia*
Int Braz J Urol. 2006; 32: 172-80

INTRODUCTION

From introduction by Hodge et al. in 1989 (1) to 2000, the ultrasound-guided biopsy was usually performed under no kind of anesthesia. Several authors report different indices of pain acceptance during biopsy without anesthesia, 11 to 90% of the patients complaining of some degree of pain during the exam (2,3). It was only after Soloway's report that the growing use of periprostatic blockade in clinical practice gained acceptance (4). In a recent review of the best scientific evidences, Autorino et al. concluded that periprostatic infiltration should be considered the gold standard at the present time (5).

Some authors believe that transrectal probe, a factor not alleviated by periprostatic blockade, is

an important component of pain during prostate biopsy. In this context, the use of sedation for prostate biopsy in outpatient regimen was recently described (6,7).

Our objective was to compare, in a randomized study, the use of periprostatic blockade, topical anesthesia with intrarectal lidocaine gel, intravenous sedation, and the traditional method (without analgesia) in the performance of transrectal ultrasound-guided prostatic biopsy.

MATERIAL AND METHODS

One hundred and sixty patients were submitted to transrectal ultrasound-guided prostatic biopsy from October 2000 to October 2001. The size of sample was calculated by Epi info 2000 considering confidence interval of 95% and significant pain frequency of 30%, based in previous reports (8,9).

Patients included signed the Instrument of Informed Consent of the Study according to the guidance of the Institution's Ethics Committee in Research. All the patients received a single dose of ciprofloxacin and were advised to be with a family member. The patients were randomized into 4 groups by picking their names on envelopes:

Group I (topical anesthesia): Intrarectal application of 20 mL of 2% gel lidocaine hydrochloride 10 minutes prior to the procedure.

Group II (periprostatic blockade): Transrectal application of lubricating hydrophilic gel. Ten minutes later, anesthesia was administered by four periprostatic injections of 2.5 mL of 1% lidocaine, guided by ultrasound using a 25 cm x 22 G needle introduced by the biopsy guide. Applications were made bilaterally in the neurovascular bundle region and in the prostatic apex, and biopsy was made ten minutes later (2,4).

Group III (sedation): Intrarectal application of 20 mL of lubricating hydrophilic gel with concomitant intravenous administration of 1.5 mg of midazolam maleate and 2 mg of meperidine hydrochloride, 10 minutes prior to the procedure. All patients received oxygen offered by nasal catheter (1-2 liters/ minute). Material for cardiopulmonary resuscitation and antagonists of benzodiazepine and opioid agents were available on the room.

Group IV (control): Single intrarectal application of 15 mL of lubricating hydrophilic gel 10 minutes prior to the procedure.

All of the biopsies were guided by transrectal ultrasound, using a Dornier 6.5 MHz end-fire probe, obtaining 12 prostatic fragments with an 18 G needle.

After a preliminary analysis of the first eighty procedures, our Institution's Ethics Committee in Research suggested that we abandoned the use of topical anesthesia and placebo (control group). The remaining patients were also randomized through groups II and III, until the total sample of 160 patients was completed.

With the intention of using objective parameters to analyze pain, we made a visual analogue scale graded from 0 to 5 correlating numbers, colors, and intensity of pain (10). After the exam was performed, the pain scale was presented by a different physician (who was not aware of the type of anesthesia used), and the patient was questioned about the presence and intensity of pain during the exam and acceptance of a repetition of the biopsy and the possible side effects of the drugs used.

Patients were reevaluated after 7 days and questions were asked regarding complications of the exam.

For the statistical analysis of pain, patients were regrouped into two groups: those without pain, with very light or light pain, which were considered as individuals with good acceptance of pain; and the cases with moderate, strong, and unbearable pain, where were considered as individuals with poor acceptance of pain in the exam. Statistical analysis was done in the software Epi info 2000® using the chi-square test and the exact Fisher test, with a confidence interval of 95% ($p < 0.05$).

RESULTS

Out of the 160 patients, 20 were included in group I (topical anesthesia), 60 in group II (periprostatic blockade), 60 in group III (sedation), and 20 in group IV (control). Mean age of the patients was 68.77

(± 8.37) years, mean PSA value was 15.19 (± 14) ng/mL, and the prostate volume evaluated by transrectal ultrasound was 35.67 (± 18.20) g, with no statistical difference as to these parameters among the 4 groups ($p > 0.05$), (Table-1).

Among the patients submitted to biopsy without analgesia (group IV), 19 (95%) reported some type of pain, one (5%) reported light pain, 4 (20%) moderate pain, 9 (45%) strong but bearable pain, and 5 (25%) reported unbearable pain (Figure-1).

The pain evaluation in patients submitted to intrarectal anesthesia showed no statistical difference when compared to the control group (Table-2).

In the periprostatic group, 47 (78.33%) reported pain, of which majority reported very light pain or no pain (86.7%) and only 2 patients (3.33%) defined the pain as strong but bearable (Figure-1). No patient complained of unbearable pain and there was a significant reduction of pain when compared to the group, in which no anesthesia was used ($p < 0.001$, chi-square = 40.19), (Table-2).

Out of the 60 patients submitted to intravenous sedation, 76% reported some degree of pain, most of them with a very light pain or no pain (81.6%) and only 3 (4.99%) related strong or unbearable pain. When compared to the control group, pain reduction

Table 1 – *Distribution of patients according to age, PSA values, and prostatic volume in the 4 groups studied, confirming homogeneity among the samples.*

Group	Mean Age (SD)*	Mean PSA (SD)*	Prostatic Volume* (mean)
I	69.45 (± 9.93)	15.225 (± 14.30)	37.2 (23.2)
II	70.95 (± 8.5)	14.05 (± 13.31)	35.8 (15.8)
III	67.7 (± 7.8)	22.01 (± 23.61)	38.5 (18.3)
IV	69 (± 7.3)	16.47 (± 13.88)	36.5 (17.2)

**p > 0.05*

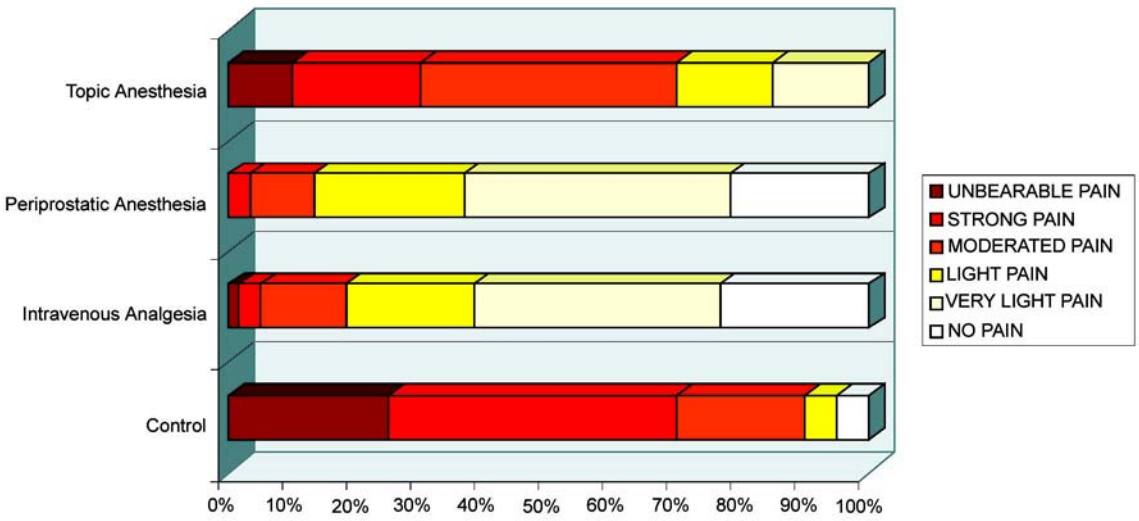


Figure 1 – *Distribution of pain intensity according to the analogue pain scale and modality of analgesia used.*

Table 2 – *Comparison of pain tolerance between the control and the anesthesia groups studied.*

	Good Pain Tolerance N (%)	Poor Pain Tolerance N (%)	p Value
Topical anesthesia (N = 20)	6 (30)	14 (70)	p = 0.23
Periprostatic blockade (N = 60)	52 (86.70)	8 (13.30)	p < 0.001
Sedation (N = 60)	49 (81.60)	11 (18.40)	p < 0.001
Control (N = 20)	2 (10)	18 (90)	
Total	109 (68.10)	51 (31.90)	

was significant (p < 0.001, chi-square = 33.34), (Table-2).

Considering the impact of pain upon acceptance of a possible repetition of the biopsy, 9 (45%) patients of the control group would accept a new biopsy, as well as 12 (60%) patients submitted to topical anesthesia (p = 0.52, chi-square = 0.4), 59 (98.33%) of the periprostatic blockade group (p < 0.001, chi-square = 29.41) and 57 (95%) of the sedation group (p < 0.001, chi-square = 25.97), (Table-3).

The main complications were hematuria (91 patients, 37.91%), rectal bleeding (76 patients, 31.25%), urinary retention (15 patients, 6.25%), febrile UTI (16 patients, 6.66%) and vasovagal reaction (24 patients, 10%). No cardiac or respiratory complication related to the use of the drug was evidenced. No morbidity prevailed among the groups studied (Table-4).

COMMENTS

Advancement in the knowledge of the rich prostatic innervation allowed the clinical use of local anesthesia in urological procedures (11).

Table 3 – *Acceptance of a possible repetition biopsy. Comparison between control group and analgesia group.*

	Acceptance N (%)	Refusal N (%)	p Value
Topical Anesthesia (N = 20)	12 (60)	8 (40)	p = 0.52
Periprostatic Blockade (N = 60)	59 (98.30)	1 (1.70)	p < 0.001
Sedation (N = 60)	57 (95)	3 (5)	p < 0.001
Control (N = 20)	9 (45)	11 (55)	
Total	137 (85.60)	23 (14.40)	

Table 4 – *Comparison in the incidence of different types of biopsy- related complications among the 4 groups studied.*

Group	Hematuria	UTI (febrile)	Rectal Bleeding	Urinary Retention	Vasovagal Reaction
I	40%	6.66%	30%	5%	8.33%
II	36.66%	5%	33.33%	5%	10%
III	38.33%	6.66%	31.66%	6.66%	10%
IV	36.33%	8.33%	30%	8.33%	11.66%
Total	91 patients	16 patients	75 patients	15 patients	24 patients

Most reports of non-randomized series describe a sextant prostatic biopsy as a procedure with good pain tolerance, with moderate or severe pain in 7-22% (8,9,12).

The main factors related to low pain tolerance during the procedure would be anxiety, increased tonus of the anal sphincter, and the number of biopsies obtained during the procedure (2,9).

The contemporary protocols establish least 10 fragments as a minimum acceptable for prostate biopsy. In our preliminary study with twelve cores, however, 90% submitted to biopsy without any form of anesthesia reported moderate to unbearable pain (2). At that moment, the procedure with no anesthesia was the standard of care. On the initial years of the XXI century, the tendency to improve pain tolerance during the biopsy was documented by a survey that showed that 50% of United States urologists were using some type of analgesia by that time (13).

Today it is accepted that some type of analgesia should be applied to minimize patient discomfort. Determining which option was the most efficient and associated with the less morbidity was the reason for this randomized study.

The contemporary options for analgesia during prostate biopsy are intrarectal topical anesthesia, periprostatic blockade, oral or intrarectal analgesia and endovenous or inhalation anesthesia.

The use of topical anesthesia with intrarectal lidocaine gel in transrectal ultrasound-guided prostatic biopsy seems quite attractive in view of its advantages, such as simplicity, clinical safety, and low cost. However, the data in the literature are scarce and controversial concerning the real value of this method. Issa et al. noted a decrease of 52% to 2% in the complaints of moderate or severe pain using the same anesthetic method (14). Most randomized prospective studies did not find a statistically significant difference between the intrarectal application of 2% lidocaine gel and placebo (12).

Stirling et al. observed that, with respect to the relief of probe- related pain (as opposed to the puncture- related pain), application of lidocaine gel was more efficient than both placebo and periprostatic injection (15).

In our study, 70% complained of moderate to unbearable pain, without a statistical difference when compared to the control group.

After statistical analysis of the first 80 patients and evaluation of the Ethics Research Committee, topical anesthesia and the use of placebo were discontinued in our study.

Of the various methods, periprostatic blockade has been shown to be safe, easy to perform and highly effective (3-5).

In 1996, Nash et al. described the technique of the periprostatic anesthesia for the performance of transrectal ultrasound-guided prostatic biopsy in 64 patients (3).

Initial reports of the University of Miami showed that periprostatic blockade was better than the use of intrarectal lidocaine gel analgesia (16). After that, the application of periprostatic blockade to reduce pain in prostatic biopsy has been gaining more acceptance worldwide, specially in more extensive biopsies (14,17).

Most comparative studies show that periprostatic blockade promotes a significant reduction in pain intensity measured by objective methods when compared to either placebo or topical analgesia with lidocaine gel (14, 15, 18). On the other hand, in a prospective and randomized clinical trial, Mallick et al. did not confirm the superiority of lidocaine infiltration over lidocaine gel (19).

Of all comparative studies, only one challenged the validity of this approach. Wu et al. (20), comparing application of 5 mL of 1% lidocaine or normal sterile saline bilaterally at the extremities of the seminal vesicles in 40 randomized patients, and they did not find any difference in pain complaints between these 2 groups.

Although the addition of periprostatic injection brings the theoretical possibility of higher bleeding and infection risks, most papers that adopt periprostatic blockade report that the procedure is safe when compared to the placebo group (21).

Other attempts for reducing the pain related to prostate biopsy are the use of oral and intrarectal non- steroidal anti-inflammatory agents and opioids like tramadol alone or in combination with other analgesics modalities.

Diclofenac administered as a suppository resulted in significantly less pain than placebo when administered 1 h prior to the biopsy procedure (22) and the combination of lidocaine periprostatic blockade with Diclofenac suppository provides additional pain relief during and after prostatic biopsy (23).

Tramadol 1.5 mg/kg in 100 mL of saline as an intravenous infusion given 30 min prior to the biopsy procedure was compared to placebo and periprostatic nerve block in a randomized study (24,25). Tramadol was found to be superior to placebo and not statistically different from periprostatic block, although a visual analogue scale indicated slightly more pain.

Application of intravenous analgesia during transrectal biopsy has been poorly reported and no comparative study with periprostatic blockade has been described so far. Some physicians do not do this procedure at the office, because an adequate hospital and anesthesiology support is needed.

The study of Peters et al. (7) remains the only one to address the use of propofol for sedation during prostate biopsy. They found significantly reduced discomfort, especially for patients who need repeated prostatic biopsies. The authors also emphasized the need for a cost analysis; obviously, propofol anesthesia needed operating theatre conditions and an anesthesiologist.

However, some recent papers show that this modality is safe and can be performed in the office. Manikandan et al. showed that nitrous oxide inhalation and periprostatic lidocaine infiltration provide significant pain relief during transrectal guided biopsy of the prostate in the outpatient setting and the techniques are effective, safe and inexpensive, but lidocaine may be better tolerated than nitrous oxide (6).

In the present study, we utilized a schedule previously described in ambulatory procedures to minimize cardiorespiratory events (26). The choice of the midazolam and meperidine combination is justified, as it allows a sedating and relaxing effect on the muscle tonus (benzodiazepine), which is important for the probe-related pain component, in addition to their analgesic effect (opiate). Such combination has also the advantage of reducing the side effects related to each single drug. Many patients may also benefit from the amnesia occurring after the procedure.

We should point out that in the adoption of this scheme of intravenous anesthesia, we chose doses that did not present relevant risks of undesirable side effects (26). With the anesthetic support available, it is possible to use such drugs in higher doses, probably decreasing or even eliminating complaints of pain during the exam.

The majority of patients submitted to this low-dose sedation scheme reported a significant reduction of pain, when compared to the control group. In our series, we have not observed any ventilatory or hemodynamic side effect with the dosage used.

Another criterion to check on the efficiency of local anesthesia is the subjective impression of the patient confronted with the need to repeat the biopsy. Such criterion reinforces the concept of benefit achieved both by using the periprostatic blockade or intravenous sedation.

CONCLUSION

Periprostatic local anesthesia and low-dose sedation reduce the painful sensation in an effective and safe way, improving tolerance to the exam and acceptance of a possible repetition biopsy without additional morbidity. Low dose sedation can reduce the anal tonus and induces amnesia in some patients.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Hodge KK, McNeal JE, Terris MK, Stamey TA: Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol. 1989; 142: 71-4; discussion 74-5.

2. Machado MT, Aragao AJ, Rodrigues AO, Wroclawski ER: Periprostatic local anesthesia in transrectal ultrasound-guided prostate biopsy: is it possible to improve pain tolerance? Int Braz J Urol. 2002; 28: 323-9.
3. Nash PA, Bruce JE, Indudhara R, Shinohara K: Transrectal ultrasound guided prostatic nerve blockade eases systematic needle biopsy of the prostate. J Urol. 1996; 155: 607-9.
4. Soloway MS, Obek C: Periprostatic local anesthesia before ultrasound guided prostate biopsy. J Urol. 2000; 163: 172-3.
5. Autorino R, De Sio M, Di Lorenzo G, Damiano R, Perdona S, Cindolo L, D'Armiento M: How to decrease pain during transrectal ultrasound guided prostate biopsy: a look at the literature. J Urol. 2005; 174: 2091-7.
6. Manikandan R, Srirangam SJ, Brown SC, O'Reilly PH, Collins GN: Nitrous oxide vs periprostatic nerve block with 1% lidocaine during transrectal ultrasound guided biopsy of the prostate: a prospective, randomized, controlled trial. J Urol. 2003; 170: 1881-3; discussion 1883.
7. Peters JL, Thompson AC, McNicholas TA, Hines JE, Hanbury DC, Boustead GB: Increased patient satisfaction from transrectal ultrasonography and biopsy under sedation. BJU Int. 2001; 87: 827-30.
8. Aus G, Hermansson CG, Hugosson J, Pedersen KV: Transrectal ultrasound examination of the prostate: complications and acceptance by patients. Br J Urol. 1993; 71: 457-9.
9. Collins GN, Lloyd SN, Hehir M, McKelvie GB: Multiple transrectal ultrasound-guided prostatic biopsies—true morbidity and patient acceptance. Br J Urol. 1993; 71: 460-3.
10. Melzack R: The McGill Pain Questionnaire: major properties and scoring methods. Pain. 1975; 1: 277-99.
11. Rodrigues AO, Tobias-Machado M, Wroclawski ER: Prostate inervation and local anesthesia in prostate procedures. Rev. Hosp. Clin. São Paulo. 2002; vol. 57; nº 6.
12. Desgrandchamps F, Meria P, Irani J, Desgrippes A, Teillac P, Le Duc A: The rectal administration of lidocaine gel and tolerance of transrectal ultrasonography-guided biopsy of the prostate: a prospective randomized placebo-controlled study. BJU Int. 1999; 83: 1007-9.
13. Davis M, Sofer M, Kim SS, Soloway MS: The procedure of transrectal ultrasound guided biopsy of the prostate: a survey of patient preparation and biopsy technique. J Urol. 2002; 167: 566-70.
14. Issa MM: Lidocaine safe, effective for topical anesthesia in transrectal prostate biopsy. J Urol. 2000; 164:397-9.
15. Stirling BN, Shockley KF, Carothers GG, Maatman TJ: Comparison of local anesthesia techniques during transrectal ultrasound-guided biopsies. Urology. 2002; 60: 89-92.
16. Al Alavi AS, Soloway MS, Vaidya A, Lynne CM, Gheiler EL: Local anesthesia for ultrasound guided prostate biopsy: a prospective randomized trial comparing 2 methods. J Urol. 2001; 166: 1343-5.
17. Leibovici D, Zisman A, Siegel YI, Sella A, Kleinmann J, Lindner A: Local anesthesia for prostate biopsy by periprostatic lidocaine injection: a double-blind placebo controlled study. J Urol. 2002; 167: 563-5.
18. Taverna G, Maffezzini M, Benetti A, Seveso M, Giusti G, Graziotti P: A single injection of lidocaine as local anesthesia for ultrasound guided needle biopsy of the prostate. J Urol. 2002; 167: 222-3.
19. Mallick S, Humbert M, Braud F, Fofana M, Blanchet P: Local anesthesia before transrectal ultrasound guided prostate biopsy: comparison of 2 methods in a prospective, randomized clinical trial. J Urol. 2004; 171: 730-3.
20. Wu CL, Carter HB, Naqibuddin M, Fleisher LA: Effect of local anesthetics on patient recovery after transrectal biopsy. Urology. 2001; 57: 925-9.
21. Obek C, Onal B, Ozkan B, Onder AU, Yalcin V, Solok V: Is periprostatic local anesthesia for transrectal ultrasound guided prostate biopsy associated with increased infectious or hemorrhagic complications? A prospective randomized trial. J Urol. 2002; 168: 558-61.
22. Haq A, Patel HR, Habib MR, Donaldson PJ, Parry JR: Diclofenac suppository analgesia for transrectal ultrasound guided biopsies of the prostate: a double-blind, randomized controlled trial. J Urol. 2004; 171: 1489-91.
23. Ragavan N, Philip J, Balasubramanian SP, Desouza J, Marr C, Javle P: A randomized, controlled trial comparing lidocaine periprostatic nerve block, diclofenac suppository and both for transrectal ultrasound guided biopsy of prostate. J Urol. 2005; 174: 510-3.
24. Ozden E, Yaman O, Gogus C, Ozgencil E, Soygur T: The optimum doses of and injection locations for periprostatic nerve blockade for transrectal ultrasound

guided biopsy of the prostate: a prospective, randomized, placebo controlled study. J Urol. 2003; 170: 2319-22.
25. Obek C, Ozkan B, Tunc B, Can G, Yalcin V, Solok V: Comparison of 3 different methods of anesthesia before transrectal prostate biopsy: a prospective randomized trial. J Urol. 2004; 172: 502-5.
26. Sa Rego MM, Watcha MF, White PF: The changing role of monitored anesthesia care in the ambulatory setting. Anesth Analg. 1997; 85: 1020-36.

Accepted after revision:
February 28, 2006

Correspondence address:
Dr. Marcos Tobias-Machado
Rua Graúna, 104 / 131
São Paulo, SP, 04514-000, Brazil
E-mail: tobias-machado@uol.com.br

EDITORIAL COMMENT

The authors are to be congratulated for their article reporting interesting data from a prospective randomized study comparing three different ways of anesthesia in transrectal ultrasound (TRUS) guided prostate biopsy. They concluded that periprostatic nerve blockade (PNB) and low-dose sedation withy midazolam and meperidine are both safe and effective in this setting, whereas anesthetic gel instillation did not provide any benefit to the patients.

During the last 5 years, there has been a growing awareness on the need of adopting anesthesia in clinical practice when performing a TRUS guided prostate biopsy. As a proof of this phenomenon, there have been an increasing number of reports in this field during this period in the urological literature.

Although most of the morbidity associated with the procedure involves minor complications, patients perceive it as traumatic and worrisome. It is every urologist's experience that anxiety is common in men undergoing prostate biopsy and 2 important issues that should be considered are the age of the patients, that are more and more young, and the adopted biopsy protocols, that are more and more extensive in order to improve prostate cancer detection. In this respect, it has been determined that age had a significant independent effect on pain perception and younger patients had significantly more pain than older ones. Interestingly, the authors have been adopting (12 core scheme) an extensive prostate biopsy protocol, in line with the policy of most urology departments worldwide nowadays. On the other hand in most of the previous published reports, the number of cores obtained per patient ranged from 6 to 10.

Two main factors are usually responsible for pain during prostate biopsy: anal discomfort due to the ultrasound probe and insertion of needles through the prostate gland. In this report the authors provide a specific evaluation of these 2 main portions of the biopsy procedure. In addition, it is interesting to note that they did not find any difference during probe insertion and biopsy punctures when submitted to PNB. In our experience we found the patients suffering from probe insertion even after PNB, whereas they feel comfortable with the biopsy portion of the procedure. General anesthesia may overcome the pain issue during TRUS prostate biopsy, but it should be considered that it is not without risk and it

could have a significant impact on manpower and financial resources, since most of general anesthetics obviously require operation theatre conditions with increasing cost. In this respect the suggestion from the authors of the present report is interesting since the use of low dose sedation offers the possibility of an office procedure.

Different groups proposed different amounts of anesthetic medium and different injection sites for local anesthesia during prostate biopsy. Nash et al initially suggested bilateral injections at the junction of the base of the prostate and seminal vesicles. We found this technique to be safe, easy and effective. Soloway & Obek (reference 4 in the article) proposed 2 additional injections on each side, one beside the apex and one between the apex and the base. The technique adopted by the authors of this report consists of two injections for each lobe, one at the base, one at the apex. We are presently adopting one single injection per lobe at the apex level, as already suggested by others.

Interpreting the results in terms of pain and discomfort during TRUS guided biopsy remains subjective and there are no standardized criteria to define whether a given procedure is well tolerated or not. Pain is a complex perceptual experience that remains difficult to quantify. Different methods have been described for this purpose and this fact represents a bias that should be considered when analyzing the outcome from the different experiences. In the last decades the VAS has proven to be satisfactory for the subjective measurement of pain intensity. It is independent of language after instruction, provides a sensitive measure and enables statistical comparison. In some cases, besides the VAS, patients were given specific questionnaire to be completed. The authors suggested using a grading scale correlating numbers, colors and pain intensity. This option took into account the known difficulty of pain evaluation, owing the subjectivity of the symptoms and the intellectual level of some patients.

PNB requires 1 or extra needle punctures and it can be expected that these extra punctures may increase complications. It has been showed that increasing the number of injections had no effect on hemorrhagic complications. The authors did not find any significant complications after either PNB or sedation. Also in our experience the rate of complications is more related to the number of cores taken than the injection of anesthetics.

The theoretical concern of increased scarring from injection in the neurovascular bundles has not been reported to make nerve-sparing prostatectomies more difficult. This remains an open issue since reports specifically addressing this issue have not been published yet.

All urologists should be urged to introduce anesthesia in their clinical practice as a routine part of the procedure, whatever the patient characteristics and biopsy scheme. Among the various methods, PNB has shown to be safe, easy to perform, highly effective. It can be considered the gold standard at the moment, even if the optimal technique remains to be established.

Dr. Rocco Damiano
Magna Graecia University
Catanzaro, Italy
E-mail: damiano@unicz.it

Dr. Ricardo Autorino
Second University, Naples, Italy

E. P. Zukovski
Consultant Radiologist, PR, Brazil

Clinical Urology
International Braz J Urol Vol. 32 (2): 181-186, March - April, 2006

Effect of Allopurinol in Chronic Nonbacterial Prostatitis: A Double Blind Randomized Clinical Trial

Amir M. Ziaee, Hamed Akhavizadegan, Mojgan Karbakhsh

Labbafinejad Hospital, Urology Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, and Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Introduction: The exact mechanism of chronic nonbacterial prostatitis has not been yet elucidated and the outcome with the current management is dismal. In this trial, we studied the effect of allopurinol in the treatment of this disease.
Materials and Methods: In this randomized double blind controlled trial, a calculated sample size of 56 were grouped into "intervention group" who received allopurinol (100 mg tds for 3 months) with ofloxacin (200 mg tds) for 3 weeks (n = 29) and "control group" who received placebo tablets with ofloxacin (n = 27). Patients' scores based on the National Institute of Health Chronic Prostatitis Symptom Score were recorded before therapy and then every month during the study. A four-glass study was performed before intervention and after 3 months.
Results: The 2 groups were similar regarding outcome variables. In the first month of study, a significant but similar improvement in symptom scores was observed in both groups. Microscopic examination of prostate massage and post-massage samples were also similar in both groups. No side effects due to allopurinol were observed in patients.
Conclusion: We did not find any advantage for allopurinol in the management of chronic prostatitis versus placebo in patients receiving routine antibacterial treatment.

Key words*: allopurinol; chronic nonbacterial prostatitis; urine reflux*
Int Braz J Urol. 2006; 32: 181-6

INTRODUCTION

Chronic nonbacterial prostatitis / chronic pelvic pain syndrome (CP/CPPS) is a common reason for urologic visits (1). Despite significant negative impact on patient quality of life (2), the management of the disease has been dismal (3). Because of the heterogeneous nature of this disease, many types of single agents (4) and multimodal therapies (5) have been tried but not proved to be effective. Persson and colleagues hypothesized the role of urate reflux from urine to the prostate in the pathophysiology of the disease for the first time (6) and recommended allopurinol for its treatment in a randomized clinical trial (7). This therapy has not been widely accepted by other urologists because of low response rate reported by others (8). Now in various papers, allopurinol has appeared in the list of potential treatment modalities of chronic prostatitis (9-11). Nevertheless, according to a Cochrane review, provided data are not convincing that allopurinol resulted in the relief of symptoms (12). No other studies have assessed this therapeutic effect. In this study we evaluated the improving effect of allopurinol on clinical signs and symptoms of nonbacterial prostatitis.

MATERIALS AND METHODS

This was a double blind randomized controlled trial. To calculate the sample size, we assumed an alpha error of 0.05, a beta error of 0.2 and the mean scores provided by Persson et al. study (7), the only article similar to ours. In that trial, the mean symptom score between days 45-135 was -1.08 (SD = 1.29) for the 25 men in the allopurinol group, compared to -0.21 (SD = 0.97) for the 14 men in the control group. When the formula of sample size estimation for comparison of 2 means was applied, it was established that the sample size had to be 27 patients per group. Thus, we randomized 56 cases diagnosed with CP/CPPS into 2 groups: intervention (n = 29) and control (n = 27). The patients were recruited from September 2002 to September 2004. All patients were followed to the end of the study (no loss to follow-up). According to the prevailing evidence (3,13-15), the following components were used as the inclusion criteria in this study.

Inclusion criteria - Pain in penis, perineal region, supra pubic, testis and/or pelvis after ejaculation. Voiding symptoms such as dysuria, frequency and sense of incomplete urination. Minimum duration of these symptoms for inclusion in the study was 1 year and minimum total symptom score 14 (moderate severity of symptom). We included only those 20 to 40 years old in order to minimize the effect of BPH on symptom score. A normal abdominal palpation was necessary for inclusion. A classical 4 glass study was performed for each patient which must have been typical for CP/CPPS for being included (4 negative cultures and inactive at least for the first 2 specimens) (1).

Exclusion criteria - No past medical history for documented urinary tract infection (positive urine culture, symptoms suggesting acute bacterial prostatitis, upper urinary tract infection and urinary tract tuberculosis), sexually transmitted disease (urethral discharge, genital ulcer and epididymo-orchitis), urethral stricture (pelvic fracture, urethral bleeding, urethral instrumentation other than diagnostic cystoscopy and urethral catheterization), neurological disease (vertebral column disease, trauma or surgery, disease affecting nervous system such as multiple sclerosis, cerebrovascular accident), drugs which mimic these symptoms (for example anticholinergics and psychotropics), urinary system disease (tumors, stones and interstitial cystitis diagnosed by cystoscopy or biopsy) and genitourinary system surgery (bladder, kidney, ureter, vasectomy, hernia, varicocelectomy, etc.).

No evidence of neurological disease (gait disturbance, abnormal perineal sensation or anal sphincter tone - a mildly spastic sphincter was considered normal, and spina bifida), genital disease (ulcer, discharge or scar), prostate nodules.

Regarding paraclinics and imaging, normal urine analysis and culture were mandatory. Cases with hematuria or pyuria were excluded from the study. Normal ultrasonography of urinary tract was another essential para-clinical index (no stones, diverticula, masses, abnormally thick bladder wall or post-voiding residue above 50 milliliters).

All the included patients were offered information regarding the explorative nature of the study and consented by written agreement. They were interviewed before any medical interventions and then monthly for 3 months using the National Institute of Health (NIH) prostatitis symptom index (13) translated into Farsi. Translation and back translation was made by 2 of the authors; one of whom did the translation and the other who did not know the original English text did the back translation. The final translation was fixed by consensus of all authors and was ready to the patients to facilitate communication of symptoms and improve response rate.

The intervention group received allopurinol 100 mg three-times-daily (tds) for 3 months in addition to ofloxacin for the 3 first weeks and the control group received placebo tablets (manufactured exactly similar to the color and shape of allopurinol tablets for the purpose of this trial) and ofloxacin. The rationale for ofloxacin usage was being the recommended drug for chronic nonbacterial prostatitis management, covering culture-negative germs like clamydia (3) and the dosage (200 mg tds instead of 300 mg bid) was chosen to improve compliance (as allopurinol/placebo were also prescribed tds) (16).

Pain score, urinary symptom score, quality of life score and total symptom score (the primary

major outcome) were recorded four times for each patient: once before treatment and three times afterwards in one-month intervals. In the case of patients' participation, the four-glass test was repeated at the end of the trial. The patients were also requested a 24-hour urine collection for creatinine and uric acid before and after the treatment. Age, duration of current disease, history of alpha-blocker intake and its response, four glass results and symptom index were recorded for patients.

Scores numerated from baseline through 3 (e.g. total score baseline, total score 1) refer to scores before intervention (0) and at the corresponding months of drug administration.

In each visit, patients were asked about any side effects (jaundice, pruritus, rash, and edema).

General Linear Model (repeated measures) in SPSS 11.5 was used for statistical analysis. P = 0.05 was considered as the level of statistical significance.

RESULTS

Mean and standard deviation of age was 33.39 ± 6.2. Comparison of underlying variables between 2 groups before intervention showed no statistical differences (Table-1).

No significant differences between the 2 treatment groups on the study scores were observed ("no between-group effect") (Table-2). Nevertheless, significant differences were detected at the end of the first month "within" each group ($P_{pain\ score} = 0.001$, $P_{urinary\ score} = 0.05$, $P_{quality\ of\ life\ score} \leq 0.001$ and $P_{total\ score} \leq 0.001$). Therefore, the symptom scores decreased nearly 30 percent in the first month of study in both groups with no significant changes following (Figure-1).

The white blood cells content in 4-glass test and 24-hour urine collection for uric acid showed no significant differences, neither within nor between the 2 treatment groups. No side effects of allopurinol were detected in intervention group.

COMMENTS

Only one small trial of allopurinol for treatment of chronic prostatitis has shown improvements in patient-reported symptoms, investigator-graded prostate pain and biochemical parameters to date (7); but no other evidence exists to support it (9). In that very research (7), 54 patients (with 39 patients completing the study) were randomized into 2 groups (placebo and allopurinol) with significant improvement in the intervention group.

Table 1 – *Comparison of underlying variables between 2 groups (intervention and control) before treatment.*

Variable/Group	Intervention Group	Control Group	p Value
Age (mean ± SD)	33.28 ± 6.4	33.52 ± 6.15	0.89
History of alpha-blocker usage (%)	55.2	63	0.55
Good response to alpha-blocker (%)	00	01.8	0.31
> 10 WBC/HPF in EPS (%)	35.7	26.9	0.49
> 10 WBC/HPF in VB3 (%)	21.4	26.9	0.64
Pain score (mean ± SD)	11.48 ± 2.87	10.37 ± 4.61	0.28
Voiding symptom score (mean ± SD)	06.69 ± 3.2	05.70 ± 3.9	0.3
Quality of life score (mean ± SD)	08.10 ± 2.24	8.370 ± 0.2	0.64
Pain plus voiding score (mean ± SD)	18.17 ± 4.38	16.70 ± 5.45	0.27
Total score (mean ± SD)	26.28 ± 5.5	25.07 ± 6.53	0.46

WBC = white blood cells; HPF = high power field.

Table 2 *– Mean and standard deviation of symptom scores in the 2 study groups.*

Scores (mean ± SD)	Group	Time Interval				p Value
		Baseline	Month 1	Month 2	Month 3	
Pain symptom score	allopurinol	12.04 ± 2.66	8.66 ± 4.66	6.96 ± 4.38	7.62 ± 4.37	0.65
	placebo	9.65 ± 4.57	8.17 ± 4.46	7.82 ± 5.04	7.73 ± 4.25	
Urinary symptom score	allopurinol	6.96 ± 3.34	4.46 ± 3.61	5.31 ± 7.80	4.16 ± 2.82	0.142
	placebo	5.61 ± 3.83	3.56 ± 3.36	3.52 ± 3.34	3.39 ± 3.07	
Quality of life symptom score	allopurinol	8.33 ± 2.16	5.41 ± 2.65	5.41 ± 2.6	5.21 ± 2.84	0.42
	placebo	8.43 ± 1.97	6 ± 2.28	6 ± 2.95	65.87 ± 2.75	
Total symptom score	allopurinol	27.33 ± 5.21	18.54 ± 9.09	16.29 ± 7.50	17 ± 7.76	0.85
	placebo	24.43 ± 6.46	17.95 ± 7.6	18.13 ± 9.61	17.21 ± 8.5	

**p value of between group effects.*

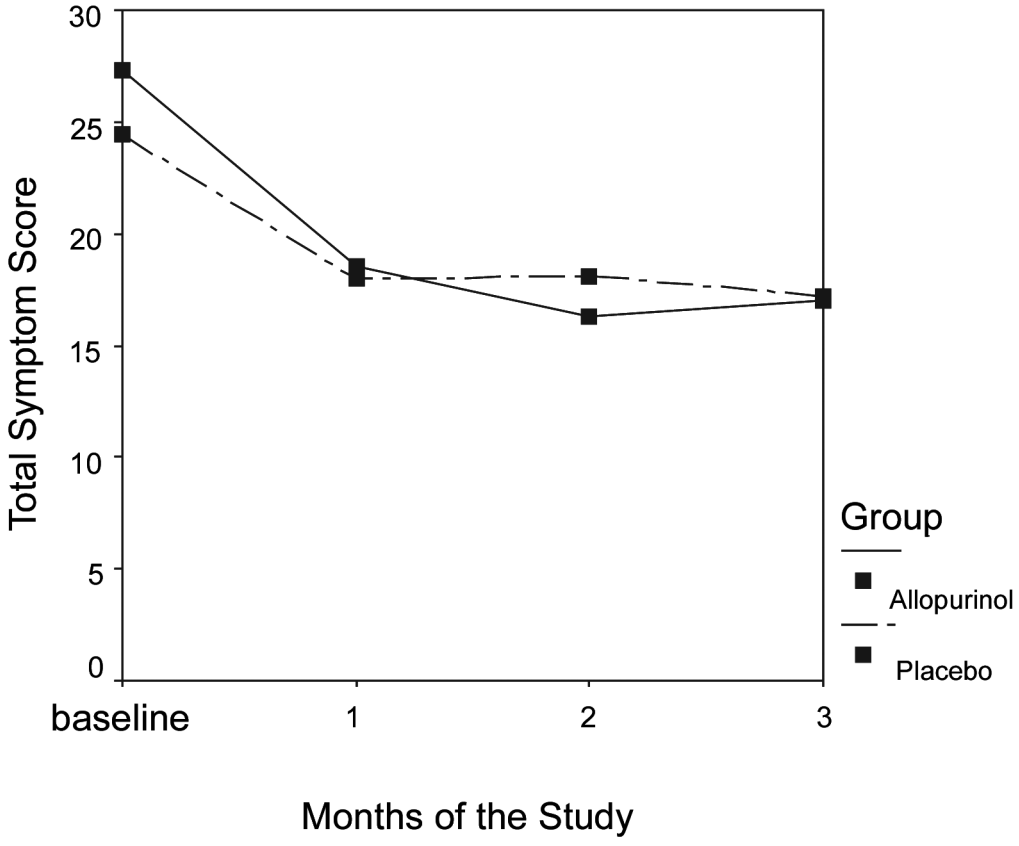


Figure 1 – *Mean of total symptom score at different months of the study in the 2 groups.*

Our study was designed in line with the CP/CPPS clinical trial reported by the National Institutes of Health Chronic Prostatitis Collaborative Research Network (13). The NIH/ symptom score (17), which is a valid questionnaire (18-21) for CP/CPPS, has been used for scoring the prostatitis symptoms. Persson and colleagues (7), using their own questionnaire, observed the peak ameliorative effect of allopurinol after three months. The three-month period for follow-up was decided on this basis in our trial.

In this study, we did not find any differences between "allopurinol and ofloxacin" and "placebo and ofloxacin" in treating CP/CPPS. In the first month of follow up, symptoms improved significantly in both groups. Nevertheless, no further improvement was observed in the intervention group in comparison with the control groups. The improvement of all symptom indices in the first month might be attributed to initial placebo effect or elimination of culture-negative germs, with the latter hypothesis being rather farfetched: in that case, we have to consider "chronic bacterial prostatitis" as the main etiology of our patients' symptoms, an otherwise uncommon condition (22).

Persson's paper was the only study reporting the effect of allopurinol on CP/CPPS. In his study, there were some methodological limitations. Some patients were not in the active phase of disease, some had positive cultures, some were lost in follow up, white blood cells in 4 glass test was not measured directly and some of the symptom scores and P value were not reported (8). Because of these shortcomings and lack of any other supporting studies, it has been difficult to verify the effect of allopurinol in chronic nonbacterial prostatitis (12). In this study we tried to overcome these methodological shortcomings. Nevertheless, we did not find any preference for allopurinol to placebo in CP/CPPS management.

Our study has some limitations: first, the possibility of selection bias: although according to the related literature, urine analysis and culture, ultra-sonography and four-glass test are considered enough to confirm the diagnosis of chronic nonbacterial prostatitis (3,14,15), it is still probable that some patients with other diseases - mimicking chronic nonbacterial prostatitis symptoms - have been included in our study (16). Second, the low power of the study due to low number of patients recruited, according to the calculated sample size. Nevertheless, the probability that a significant difference really exists is very low considering the very similar results in the two groups. Third, antibiotic usage in both groups, which is generally recommended in cases of chronic prostatitis, may make it difficult to interpret the first-month improvement in patients' symptoms.

CONCLUSION

Our study showed that allopurinol does not have any ameliorative effect on chronic nonbacterial prostatitis regarding clinical symptoms or improvement of quality of life in comparison with placebo. This disease or syndrome has a collection of symptoms with unknown origins. These symptoms may have diverse etiologies and thus a small subgroup may benefit from allopurinol but we do not recommend the routine use of allopurinol for treatment of CP/CPPS.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Batstone GR, Doble A: Chronic prostatitis. Curr Opin Urol. 2003; 13: 23-9. Review. Erratum in: Curr Opin Urol. 2003; 13: 177. Batstone D [corrected to Batstone G Richard D].
2. Turner JA, Ciol MA, Von Korff M, Berger R: Prognosis of patients with new prostatitis/pelvic pain syndrome episodes. J Urol. 2004; 172: 538-41.
3. Nickel JC, Downey J, Ardern D, Clark J, Nickel K: Failure of a monotherapy strategy for difficult chronic prostatitis/chronic pelvic pain syndrome. J Urol. 2004; 172: 551-4.
4. Krieger JN: The problem with prostatitis. What do we know? What do we need to know? J Urol. 2004; 172: 432-3.
5. Shoskes DA, Hakim L, Ghoniem G, Jackson CL: Long-term results of multimodal therapy for chronic

prostatitis/chronic pelvic pain syndrome. J Urol. 2003; 169: 1406-10.
6. Persson BE, Ronquist G: Evidence for a mechanistic association between nonbacterial prostatitis and levels of urate and creatinine in expressed prostatic secretion. J Urol. 1996; 155: 958-60.
7. Persson BE, Ronquist G, Ekblom M: Ameliorative effect of allopurinol on nonbacterial prostatitis: a parallel double-blind controlled study. J Urol. 1996; 155: 961-4.
8. Nickel JC, Siemens DR, Lundie MJ: Re: Ameliorative effect of allopurinol on nonbacterial prostatitis: a parallel double-blind controlled study. J Urol. 1997; 157: 628-9.
9. Stevermer JJ, Easley SK: Treatment of prostatitis. Am Fam Physician. 2000; 61: 3015-22, 3025-6. Erratum in: Am Fam Physician 2001; 63: 2129.
10. Naber KG, Weidner W: Chronic prostatitis-an infectious disease? J Antimicrob Chemother. 2000; 46: 157-61.
11. Doble A: An evidence-based approach to the treatment of prostatitis: is it possible? Curr Urol Rep. 2000; 1: 142-7.
12. McNaughton CO, Wilt T: Allopurinol for chronic prostatitis. Cochrane Database Syst Rev. 2002; 4: CD001041.
13. Propert KJ, Alexander RB, Nickel JC, Kusek JW, Litwin MS, Landis JR, et al.: Design of a multicenter randomized clinical trial for chronic prostatitis/chronic pelvic pain syndrome. Urology. 2002; 59: 870-6.
14. Kaplan SA, Volpe MA, Te AE. A Prospective, 1-Year Trial Using Saw Palmetto Versus Finasteride in the Treatment of Category III Prostatitis/Chronic Pelvic Pain Syndrome. J Urol. 2004; 171: 284-8.
15. Nickel JC, Downey J, Pontari MA, Shoskes DA, Zeitlin SI: A randomized placebo-controlled multicentre study to evaluate the safety and efficacy of finasteride for male chronic pelvic pain syndrome (category IIIA chronic nonbacterial prostatitis). BJU Int. 2004; 93: 991-5.
16. McNaughton Collins M, MacDonald R, Wilt TJ: Diagnosis and treatment of chronic abacterial prostatitis: a systematic review. Ann Intern Med. 2000; 133: 367-81.
17. Litwin MS, McNaughton-Collins M, Fowler FJ Jr, Nickel JC, Calhoun EA, Pontari MA, et al.: The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol. 1999; 162: 369-75.
18. Turner JA, Ciol MA, Von Korff M, Berger R: Validity and responsiveness of the national institutes of health chronic prostatitis symptom index. J Urol. 2003; 169: 580-3.
19. Collins MM, O'Leary MP, Calhoun EA, Pontari MA, Adler A, Eremenco S, et al.: The Spanish National Institutes of Health-Chronic Prostatitis Symptom Index: translation and linguistic validation. J Urol. 2001; 166: 1800-3.
20. Leskinen MJ, Mehik A, Sarpola A, Tammela TL, Jarvelin MR: The Finnish version of The National Institutes Of Health Chronic Prostatitis Symptom Index correlates well with the visual pain scale: translation and results of a modified linguistic validation study. BJU Int. 2003; 92: 251-6.
21. Nickel JC: Prostatitis: lessons from the 20th century. BJU Int. 2000; 85: 179-85.
22. Usupbaev AC, Hakimhodjaev ZS, Kim AS. The new diagnostic approaches in assessment of abacterial forms (category III) of the chronic prostatitis. BJU Int September 2002: Vol 90; Suppl 2, pp. 226-7.

Accepted after revision:
October 10, 2005

Correspondence address:
Dr. Amir Mohsen Ziaee
Shahid Dr. Labbafinegad Hospital
9th Boostan Street, Pasdaran Avenue, Tehran, Iran
Fax: + 98 21 254-9088
E-mail: ziaee@hotmail.com

Case Report
International Braz J Urol Vol. 32 (2): 187-189, March - April, 2006

Cystic Renal Cell Carcinoma Arising From Multilocular Cystic Nephroma of the Same Kidney

Ahmad M. Omar, Altaf Q. Khattak, John A. Lee

Departments of Urology and Histopathology, Rotherham General Hospital United Kingdom, and Hull York Medical School, United Kingdom

ABSTRACT

Multilocular cystic nephroma is an uncommon benign entity grouped among the cystic non-genetic diseases. It is characterized by variable-sized, non-communicating cysts separated by irregular thin walled septa. Though multilocular cystic nephroma is usually considered a benign lesion, malignant changes in the cysts should not be overlooked.

Key words: *kidney; cyst; renal cell carcinoma*
Int Braz J Urol. 2006; 32: 187-9

INTRODUCTION

The kidneys are prone to a variety of cystic disorders that includes developmental, acquired, and neoplastic lesions. However, the synchronous occurrence of two different renal tumors in the same kidney is a rare event. Here we report a case of cystic renal cell carcinoma arising in a multilocular cystic nephroma in a 65-year-old woman.

CASE REPORT

A 65-year-old white woman presented with a 10-month history of weight loss and malaise. There was no history of urinary or bowel symptoms. A mass was palpated in the right loin. Urine analysis was normal and urine cytology was negative for malignancy. Full blood count, liver function tests and renal function tests were all normal. An ultrasound scan showed a large complex mass arising from the lower pole of the right kidney. CT scanning displayed a huge multilocular heterogeneous mass in the lower pole of the right kidney (Figure-1). The differential diagnosis of a malignant versus a benign lesion was not possible with imaging, and a right radical nephrectomy was performed.

On pathology, a large multi-loculated cyst with occasional more solid areas replaced the kidney. The lesion had an intact fibrous capsule with no involvement of the peri-renal tissues. Microscopically, the cysts were thin walled and epithelial lined, with varying amounts of intervening cellular stroma containing numerous small tubular cysts and focal smooth muscle (Figure-2). The appearances were those of a multilocular cystic nephroma (Figure-3). However, in some of the variegated and thickened areas noted macroscopically, the typical clear cells of cystic renal cell carcinoma were found (Figure-4). The renal cell carcinoma did not breach the capsule or invade adjacent renal tissues.

COMMENTS

The etiology of multilocular cystic nephroma (MCN) has been the subject of controversy for a long period of time. However, many currently believe that MCN is a benign neoplasm and lies at the benign end of a continuum that includes the cystic partially differentiated nephroblastoma (CPDN) variants of Wilms' tumor (1,2).

There is a bimodal age distribution. Under the age of 5 years, MCN occurs most frequently in males, whereas the adult group has a female predominance between the ages of 40 and 60. The most common presenting symptoms are a painless abdominal mass, abdominal or flank pain, and occasionally hematuria (2).

Several authors have reported on the difficulty of differentiating between MCN and multilocular cystic renal cell carcinoma (MLCC). However, definitive diagnosis is always histological.

Renal cell carcinoma may occasionally arise in a variety of longstanding cystic diseases of the kidney, including the cysts of multilocular cystic nephroma. However, most of the reported malignancies in multilocular renal cysts have been clear cell carcinomas.

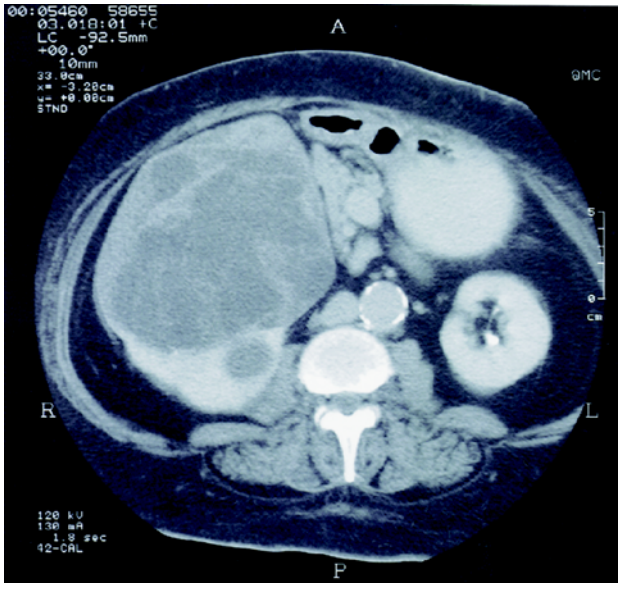


Figure 1 – *Contrast-enhanced CT scan of the abdomen showing the large right-sided multiseptated renal mass.*

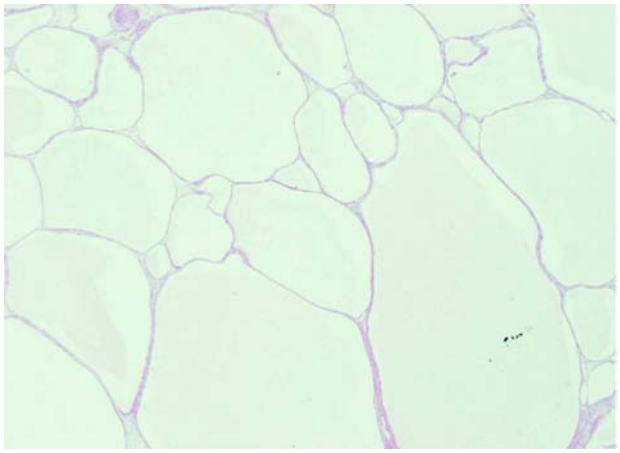


Figure 2 – *Photomicrograph showing the multiple thin walled cysts, with varying amount of intervening stroma (HE, X20).*

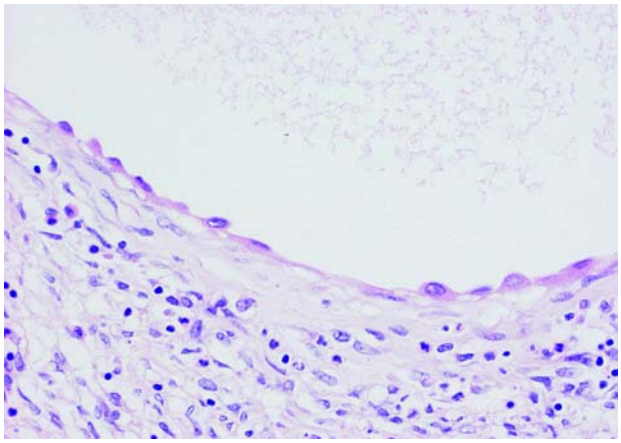


Figure 3 – *Photomicrograph showing a cyst lining by the flattened epithelial cells with hobnail appearance (HE, X200).*

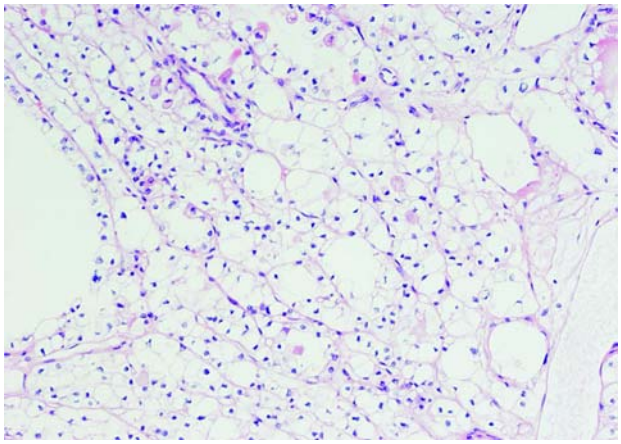


Figure 4 – *Photomicrograph showing the neoplastic clear cells lining the wall of a cyst (HE, X250).*

The prognosis for CRCC is excellent. A recent study of 21 patients from Japan reported that after surgery, 5-year and 10-year disease free specific survival for these patients were both 100% (3). Our patient remains free of recurrence with 4 years follow-up.

In summary, a multilocular renal cyst is usually considered a benign lesion, but malignant changes in the cyst can occur, indicating that thorough sampling should be undertaken for histology. However, the prognosis is excellent and most patients are likely to achieve long-term survival.

CONFLICT OF INTEREST

None declared.

Accepted after revision:
September 30, 2005

Correspondence address:
Dr. Ahmad M. Omar
Department of Urology
Rotherham General Hospital
Rotherham, S60 2UD, South Yorkshire
United Kingdom
E-mail: amomar70@hotmail.com

REFERENCES

1. Joshi VV, Beckwith JB: Multilocular cyst of the kidney (cystic nephroma) and cystic, partially differentiated nephroblastoma. Terminology and criteria for diagnosis. Cancer. 1989; 64: 466-79.
2. Madewell JE, Goldman SM, Davis CJ Jr, Hartman DS, Feigin DS, Lichtenstein JE: Multilocular cystic nephroma: a radiographic-pathologic correlation of 58 patients. Radiology. 1983; 146: 309-21
3. Koga S, Nishikido M, Hayashi T, Matsuya F, Saito Y, Kanetake H: Outcome of surgery in cystic renal cell carcinoma. Urology. 2000; 56: 67-70.

EDITORIAL COMMENT

Epithelial hyperplasia evolving to neoplasia is common to several forms of human renal cystic disease, both congenital and acquired. Most frequently occurs in von Hippel-Lindau disease, a dominantly inherited syndrome of cerebellar and retinal hemangioblastomas, pancreatic, epididimal and renal cysts and tumors. Tumors also occur in acquired renal cystic disease in end-stage kidneys especially those of patients on long-term hemodialysis, in the dominantly inherited disorder tuberous sclerosis complex and, less frequently, in the adult polycystic renal disease. The arising of cystic renal cell carcinoma from multilocular cystic nephroma is a very controversial condition. The present case is worth reporting because the multilocular cystic nephroma is well documented. Thin septa of either fibrous tissue or resembling ovarian stroma are present and covered by flattened or low cuboidal epithelium with small amounts of cytoplasm occasionally with hobnail appearance. However, this cystic lesion may be coincidental to the renal cell carcinoma. Many other cases should be reported in order to consider cystic multilocular nephroma a predisposing lesion to kidney neoplasias.

Dr. Athanase Billis
Full-Professor of Pathology
State University of Campinas, Unicamp
Campinas, São Paulo, Brazil
E-mail: athanase@fcm.unicamp.br

Case Report
International Braz J Urol Vol. 32 (2): 190-192, March - April, 2006

Renal Lymphoma. Atypical Presentation of a Renal Tumor

Francualdo Barreto, Marcos F. Dall'Oglio, Miguel Srougi

Department of Urology, Federal University of Sao Paulo (UNIFESP), Paulista School of Medicine, Sao Paulo, Brazil

ABSTRACT

Primary renal lymphoma is a rare lesion that represents less than 1% of the kidney's lesions. The authors discuss the case of a 67-year-old woman with a renal mass identified 7 years after treatment of a non-Hodgkin's lymphoma, and analyze clinical and prognostic aspects of renal lymphomas. Radiological findings in this case showed an uncommon presentation of the renal lymphomatous lesion which served as a warning that tumors might appear during follow-up as atypical and uncommon lesions.

***Key words**: kidney neoplasms; nephrectomy; lymphoma*
Int Braz J Urol. 2006; 32: 190-2

INTRODUCTION

A primary renal lymphoma is a rare lesion that represents less than 1% of the lesions in this organ (1). Renal lymphoma has an insidious clinical presentation that occurs late in the course of the disease (2,3). It can present in many ways, however the most common are primary tumors presenting single or multiple nodules, or that involve the kidney, either in a hematogenic dissemination form or through a contiguous retroperineal disease (2).

The authors discuss the case of a 67-year-old patient presenting a solitary renal mass 7 years after the chemotherapy and radiotherapy treatment of a non-Hodgkin's lymphoma.

CASE REPORT

A 67-year-old female asymptomatic patient with no palpable lymph nodes presented a right renal mass (Figure-1) in an abdomen computerized tomography (CT) in a routine check up for a non-Hodgkin's lymphoma that had been diagnosed and treated with chemotherapy and radiotherapy 7 years earlier.

The patient underwent a radical right nephrectomy and the macroscopic exam revealed an expansion of fat caused by a homogeneous, yellowish tumor infiltration. The microscopic exam revealed a centrofollicular lymphoma, follicular grade I, diffusely infiltrating the renal interstitium. The immunohistochemical analysis demonstrated a CD 20 positivity, characterizing a lymphoma originating in lymphocytes B (Figure-2). This finding led to adjuvant radiotherapy and the patient is now with a 16-month follow-up.

COMMENTS

Among cases of renal lymphoma, between 37% and 47% occur due to dissemination of an ad-

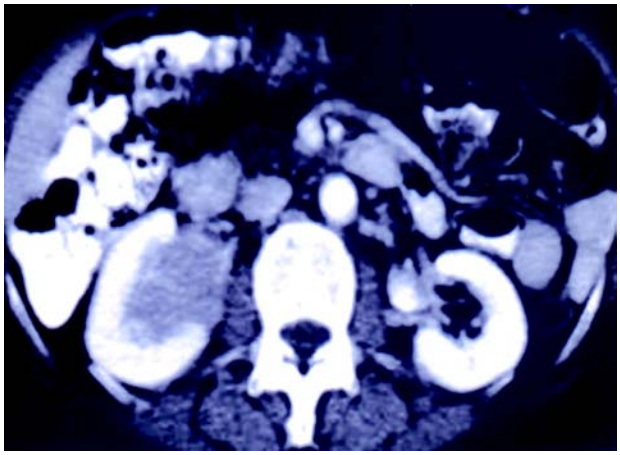


Figure 1 – *A four-centimeter solid and intra-sinusal right renal mass with contrast enhancement.*

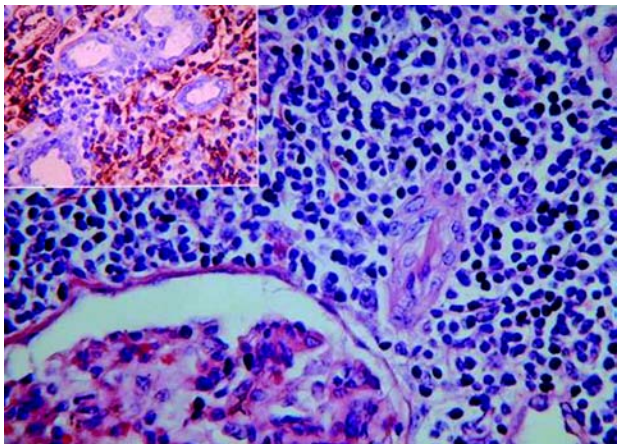


Figure 2 – *Centrofollicular lymphoma, follicular grade I diffusely infiltrating the renal interstitium (HE). Insert: Immunohistochemical study demonstrating the CD20 expression, characterizing a cell B origing lymphoma.*

vanced systemic disease (2), while 0.1% are due to primary involvement of the kidney (1). The term, primary renal lymphoma, can be used either when the initial manifestation involves the kidney or the lesion is limited to it (3).

Renal lymphoma usually is of small cells (Burkitt´s), or less frequently of lymphocytes B (1). Prognosis of these cases is not well established, but is typically defined using the criteria of the Working Formulation, Ann Arbor Stage and International Prognostic Index (3). The disease has the same prevalence in both sexes and is predominant in patients with a mean age of 66 years (3). The symptoms observed during the later stages are lumbalgia, hematuria and fever (3). However, in the series studied by Dimopoulos et al., all 6 patients presented symptoms related to the involvement of the urinary tract and the absence of peripheral palpable lymph nodes (3). Even with chemotherapy, only 2 patients had complete remission of the disease. The patients with unfavorable prognostic factors as defined by the International Prognostic Index presented poor results with chemotherapy treatment (3), which is based on cyclofosfamide, doxorubicin, vincristine and prednisone.

Lesions can be solitary masses (10-20%) or multiple masses (60%). They are generally bilateral and present extension by contiguity (25%-30%), diffuse infiltration (20%) or perirenal involvement 10% (2). Radiological findings frequently indicate renal involvement with multiple nodules (60%) and help in clarifying the diagnosis when considered along with previous family history. Renal lymphoma generally is presented as a bilateral nodular infiltration with a diffuse kidney increase and infiltration of the renal parenchyma by a diffuse invasion of the retroperitoneum (3). Solitary unilateral renal mass, perirenal mass with distortion of the renal architecture in the CT scan and absence of lymph node enlargements are more suggestive of renal cell carcinomas (3), however the presence of solid masses can require a biopsy to rule out other pathologies (2).

Radiological findings in this case showed an uncommon presentation of the renal lymphomatous lesion which served as a warning that tumors might appear during follow-up as atypical and uncommon lesions.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Stallone G, Infante B, Manno C, Campobasso N, Pannarale G, Schena FP: Primary renal lymphoma does

exist: case report and review of the literature. J Nephrol. 2000; 13: 367-72.
2. Urban BA, Fishman EK: Renal lymphoma: CT patterns with emphasis on helical CT. Radiographics. 2000; 20: 197-212.
3. Dimopoulos MA, Moulopoulos LA, Costantinides C, Deliveliotis C, Pantazopoulos D, Dimopoulos C: Primary renal lymphoma: a clinical and radiological study. J Urol. 1996; 155: 1865-7.

Accepted after revision:
August 31, 2005

Correspondence address:
Dr. Marcos F Dall'Oglio
Rua Manoel da Nóbrega, 853 / 22
São Paulo, SP, 04001-084, Brazil
Fax: + 55 11 3885-0658
E-mail: marcosdalloglioouro@terra.com.br

Case Report
International Braz J Urol Vol. 32 (2): 193-195, March - April, 2006

Retroperitoneal Migration of a Self-Inflicted Ballpoint Pen via the Urethra

Jose Cury, Rafael F. Coelho, Miguel Srougi

Division of Urology, School of Medicine, University of Sao Paulo, USP, Sao Paulo, SP, Brazil

ABSTRACT

Numerous accounts documenting the introduction of foreign bodies into the urinary bladder have been reported. These foreign bodies are typically self-inserted via urethral but migration from adjacent organs by an ulcerative process and penetrating injuries are also reported. However, "contrary" migration of a self-inflicted vesical foreign body to the retroperitoneum was not previously reported in literature. We report here a case of a ballpoint pen self-inserted via urethral by a female patient, which was identified in retroperitoneal position years later.

***Key words**: urethra; bladder; foreign-body migration; retroperitoneum; masturbation*
Int Braz J Urol. 2006; 32: 193-5

INTRODUCTION

Numerous accounts documenting the introduction of foreign bodies into the genitourinary tract have been reported (1). Most cases are associated with psychiatric disorders, intoxication, and autoerotic stimulation or to get relief of urinary complaints (2). Vesical foreign bodies are typically self-inserted via urethral but migration from adjacent organs by an ulcerative process and penetrating injuries are also reported (1). However, "contrary" migration of a self-inflicted vesical foreign body to the retroperitoneum was not previously reported in literature. We report here a case of a ballpoint pen self-inserted via urethral by a female patient, which was identified in retroperitoneal position years later.

CASE REPORT

A 38-year-old patient presented to our emergency service with complaint of left iliac fossa pain that had lasted for 12 months and worsened in the last month. The pain was continuous, of light to moderate intensity and was not relieved with common analgesics. The patient also complained of recurrent irritative urinary symptoms, such as dysuria and suprapubic pain, compatible with urinary tract infections. She referred no previous sexual relationships. Physical examination revealed evident pain at palpation of left iliac fossa without peritoneal signs. Genital examination was normal and hymen was not ruptured. Laboratorial findings were normal. A plain abdominal x-ray revealed a radiopaque foreign body in the left iliac fossa compatible with a pen tip (Figure-1). Upon further interrogation, the patient referred to autoerotic stimulation with ballpoint pen via the urethra for years. In an undetermined date, the ballpoint pen was lost inside the urethra and migrated probably to the bladder. Under general anesthesia, the patient was submitted to a cystoscopy but no pen, calculus or lesions were found. We opted to perform an exploratory laparotomy through a left Judd-Gibson incision. We founded a rounded fibrous capsule con-

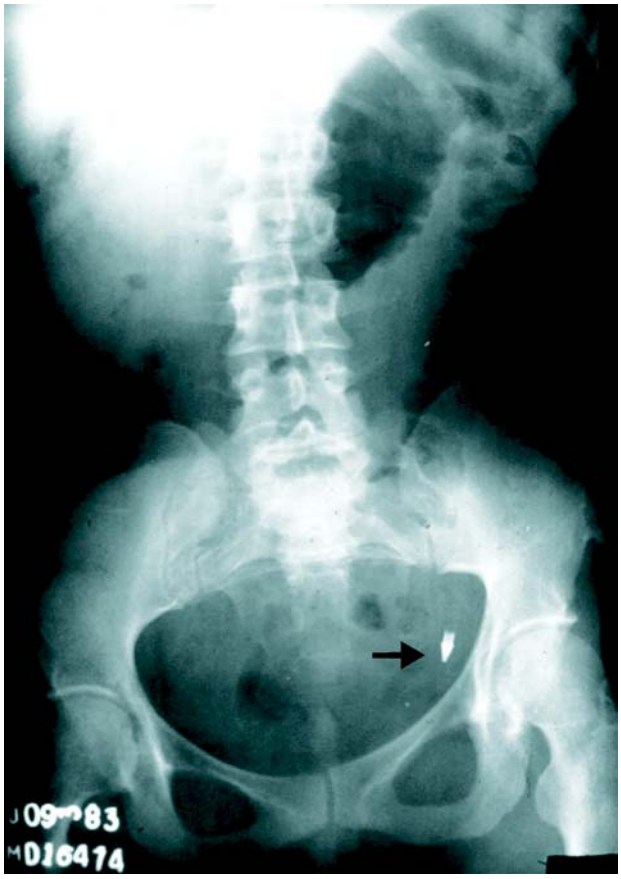


Figure 1 – *Abdominal X-ray revealed a radiopaque foreign body (white arrow) in left inferior quadrant compatible with a pen tip.*

taining the ballpoint pen in the retroperitoneum adjacent to the bladder. The fibrous capsule and the pen were complete excised (Figure-2). Postoperatory was uneventful.

COMMENTS

Foreign bodies inserted in the urogenital tract represent a urological challenge that often requires prompt intervention (1). The most common reason for such behavior is sexual or erotic in nature, just as in our case patient. Psychiatric disturbances such as borderline personality disorder or schizophrenia may also be present. Patients tend to take time before seeking treatment, usually not before symptoms show up. X-rays are usually enough to diagnose such condi-

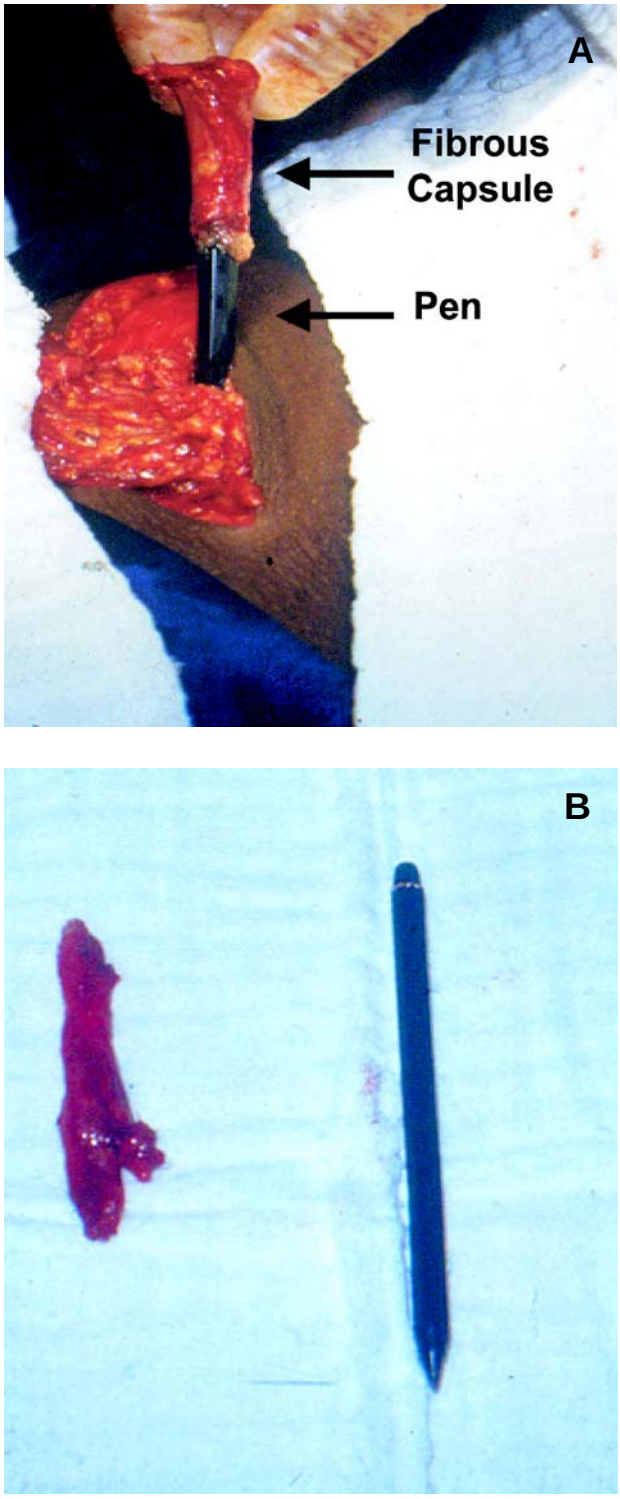


Figure 2 – *A) Exteriorization of the pen and fibrous capsule through a left Judd-Gibson incision. B) In detail, the pen and the fibrous capsule excised.*

tions (2). The urethra is the main entrance of foreign bodies in the genitourinary tract and a variety of urethral foreign bodies have been reported in the literature including pencils, electric cable, thermometer, glass rod, toothbrush, candle, serum set, balloon and hairpin among others (1). Vesical foreign bodies are also typically propelled into the bladder and pushed further into the urethra. However, a large number of cases are reported in which various types of foreign bodies migrate into the bladder by an ulcerative process from different organs adjacent to the bladder (1, 2). Chicken and fish bones, pins and needles, pencil, thermometer, toothpicks were reported perforating the bladder via gastrointestinal tract. Other foreign bodies that perforate the bladder via vagina are mostly a result of masturbation injuries (1). A case of retroperitoneal foreign body localized after the eroded vaginal wall was also reported (3). However, to our knowledge, this is the first case report of retroperitoneal migration of foreign bodies inflicted via the urethra in the English language. The patient clearly refers to the introduction of the pen in the urethra, not in the vagina, and the integrity of the hymen corroborates this affirmation. Moreover, she refers to recurrent urinary tract infections after the pen introduction. We believe that the pen migrated to the bladder and retroperitoneum through an ulcerative process.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. van Ophoven A, deKernion JB: Clinical management of foreign bodies of the genitourinary tract. J Urol. 2000; 164: 274-87.
2. Pal DK, Bag AK: Intravesical wire as foreign body in urinary bladder. Int Braz J Urol. 2005; 31: 472-4.
3. O'Hanlan KA, Westphal LM: First report of a vaginal foreign body perforating into the retroperitoneum. Am J Obstet Gynecol. 1995; 173: 962-4.

Accepted after revision:
February 28, 2006

Correspondence address:
Dr. José Cury
Rua Canada, 541
Sao Paulo, SP, 01436-000, Brazil
E-mail: jc_uro@osite.com.br

Surgical Technique
International Braz J Urol Vol. 32 (2): 196-201, March - April, 2006

Refining the Laparoscopic Retroperitoneal Lymph Node Dissection for Testicular Cancer

Frederico R. Romero, Andrew Wagner, Fabio A. Brito, Michael Muntener, Guilherme C. Lima, Louis R. Kavoussi

James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA

ABSTRACT

Since its initial description, the laparoscopic retroperitoneal lymph node dissection has evolved considerably, from a purely diagnostic tool performed to stage germ cell testicular cancer to a therapeutic operation that fully duplicates the open technique. Herein, we describe the current technique employed at our institution, along with illustrations of all surgical steps, and delineate the refinements of the technique over time.

***Key words**: testicular neoplasms; lymph node excision; laparoscopy; diagnostic techniques, surgical*
Int Braz J Urol. 2006; 32: 196-201

INTRODUCTION

Retroperitoneal lymph node dissection (RPLND) has been used for diagnosis and treatment of clinical stage I and II nonseminomatous germ cell tumors (NSGCT), and as a salvage therapy for bulky metastatic germ cell testicular tumors following cisplatin-based chemotherapy.

Since the first description of open RPLND in 1902 (1), the surgical technique has undergone several modifications in an effort to decrease morbidity and enhance oncological efficacy (2). The laparoscopic RPLND (L-RPLND) has similarly evolved. Initially used purely as a diagnostic tool, L-RPLND, when properly performed, has developed into a therapeutic operation that strictly adheres to established oncologic principles and fully duplicates the open technique (3).

The objective of the present article is to illustrate in detail the laparoscopic technique employed at our institution, outlining the refinements of L-RPLND over time.

SURGICAL TECHNIQUE

After the induction with general endotracheal anesthesia, a nasogastric tube and Foley catheter are inserted. Patients are placed in a modified flank-up position using a jelly role to slightly elevate the ipsilateral side. They are then taped securely to the operating room table across the chest, hips, and legs. This allows the surgeon to role the patient into a completely lateral position during the procedure if necessary. Abdomen and flank are prepped and draped in a sterile fashion.

Pneumoperitoneum is achieved in the standard manner. Four equidistant 10/12 mm laparoscopic ports are positioned in the midline beginning 2 to 4

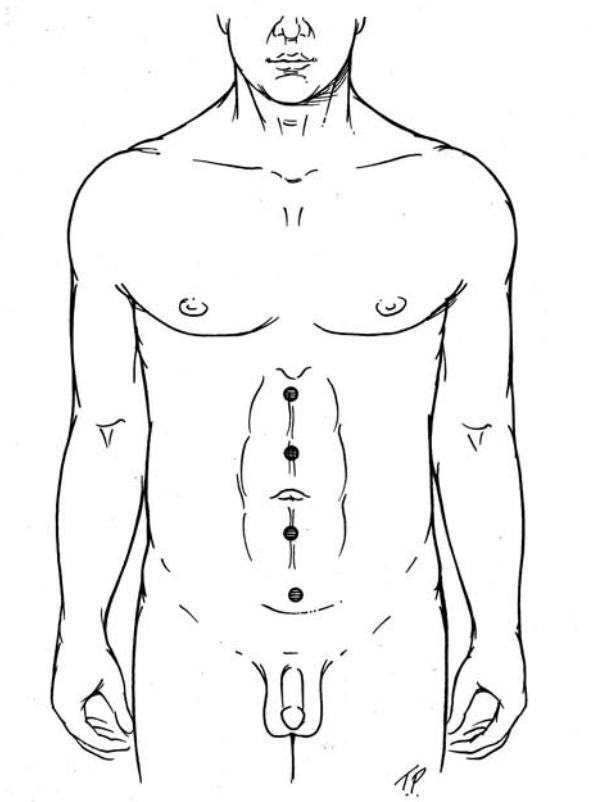


Figure 1 – *Port site placement during laparoscopic retroperitoneal lymph node dissection.*

cm below the xiphoid process (Figure-1). All ports are placed under direct vision and sutured to the skin with 2-0 silk sutures to avoid inadvertent removal during the procedure.

To begin the dissection on either side, the colon is reflected medially by incising the line of Toldt. Care is taken not to damage the delicate mesenteric vasculature. The spermatic vessels are first identified, then dissected free of surrounding tissues distally toward the internal inguinal ring (Figure-2). At the area of the internal ring, sharp and blunt dissection is necessary, often using monopolar cautery, to liberate the most distal aspect of the vessels, along with the non-absorbable stitch from the previous radical inguinal orchiectomy. Great care is necessary to avoid injury to the adjacent iliac vessels during this dissection. The spermatic vessels, along with all contiguous lymphatic tissue, are sharply dissected and brought up to their origin (renal hilum on the left, and inferior vena cava on the right), where they are clipped and transected.

The removal of the retroperitoneal lymph node packets is performed in a modified template fashion. The borders of our dissection are shown in Figure-3. Dissection over the aorta is halted at the level of the inferior mesenteric artery to avoid damaging the hy-

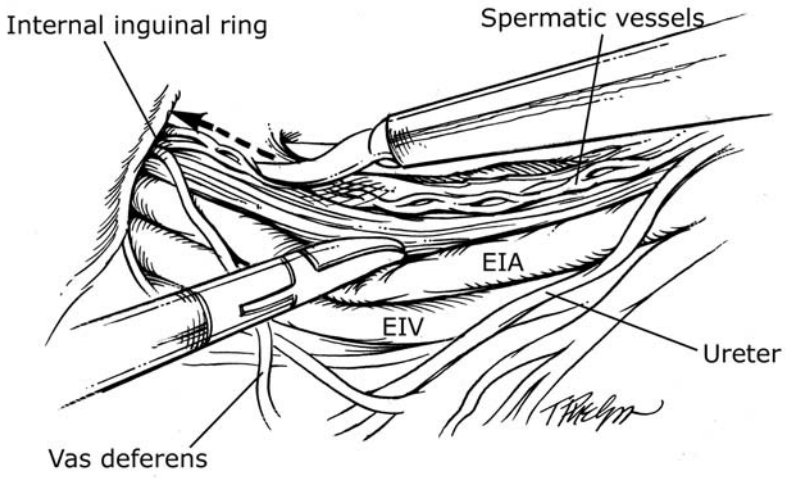


Figure 2 – *The spermatic vessels are dissected distally in the direction of the internal inguinal ring (arrow – dotted line). Observe the close relationship with the iliac vessels, which must be identified to avoid inadvertent injury (EIA = external iliac artery; EIV = external iliac vein).*

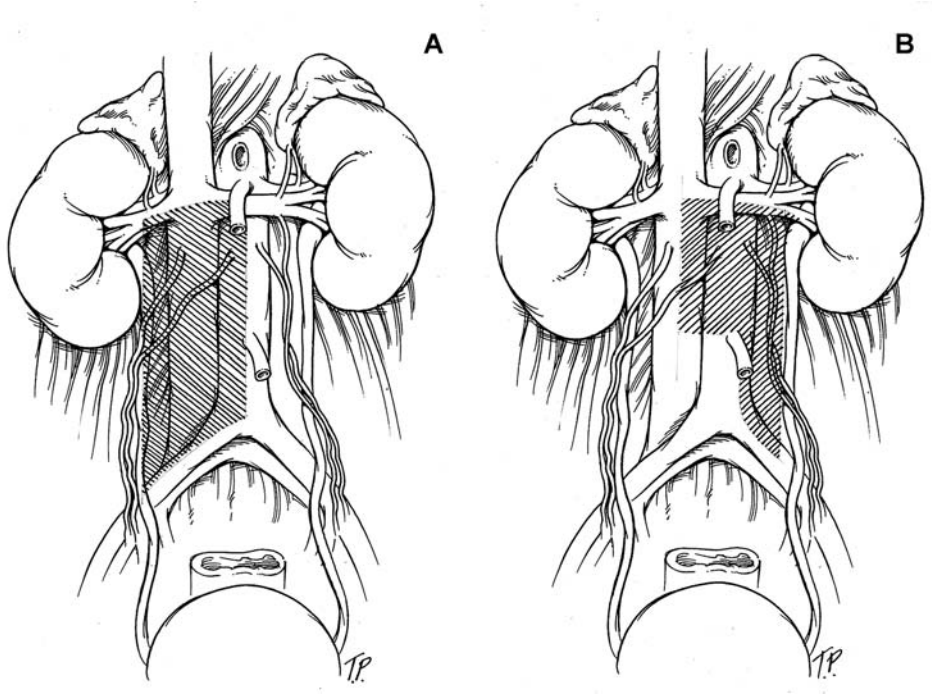


Figure 3 – *A) Template dissection limits for right-sided tumors consist of ureter (lateral), midpoint of aorta (medial), bifurcation of iliac vessels (inferior), and renal hilum (superior). B) Template dissection limits for left-sided tumors consist of ureter (lateral), midpoint of vena cava (medial), bifurcation of iliac vessels (distal), and renal hilum (superior).*

pogastric plexus of nerves, which can result in impaired ejaculation. A right-sided dissection necessitates complete mobilization of the duodenum and head of pancreas medially using sharp dissection and the strict avoidance of thermal energy (Kocher maneuver). This will expose the inferior vena cava (IVC) and aorta (Ao).

Both right and left dissections generally proceed in a similar fashion. First, a split/roll technique is used to gather all precaval/preaortic and lateral lymphatic tissues up to the renal hilum, exposing the renal vein and renal artery (Figure-4). The lateral nodal tissues are lifted and separated from the underlying

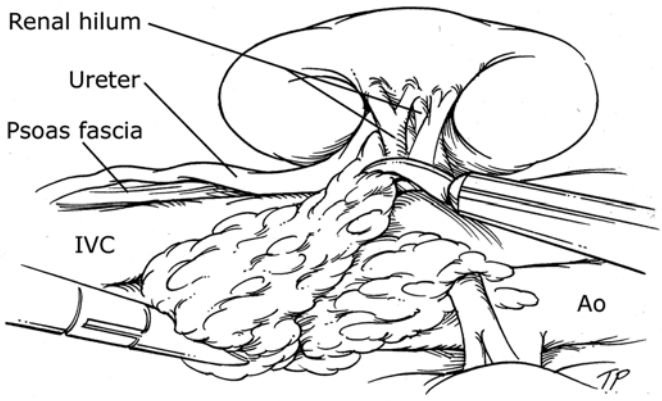


Figure 4 – *The tissues overlying the great vessels are gently dissected using blunt and sharp dissection. The dissection is carried superiorly to the renal hilum, and laterally to the ureter, revealing the underlying psoas fascia. IVC = inferior vena cava, Ao = aorta.*

psoas fascia. The interaortocaval tissue is then dissected. An atraumatic grasper is used to gain additional exposure to this area by lifting the vena cava and aorta, allowing the nodal packet to be gently teased off the surface of the great vessels (Figure-5). We liberally use 5 and 10 mm titanium clips to secure vasculature and lymph structures. Finally, retrocaval/retroaortic dissection is performed to remove the only remaining lymphatic tissue, again taking care to clip all lymphatic channels and lumbar vessels encountered (Figure-6). The sympathetic chains are identified and carefully dissected free (Figure-7).

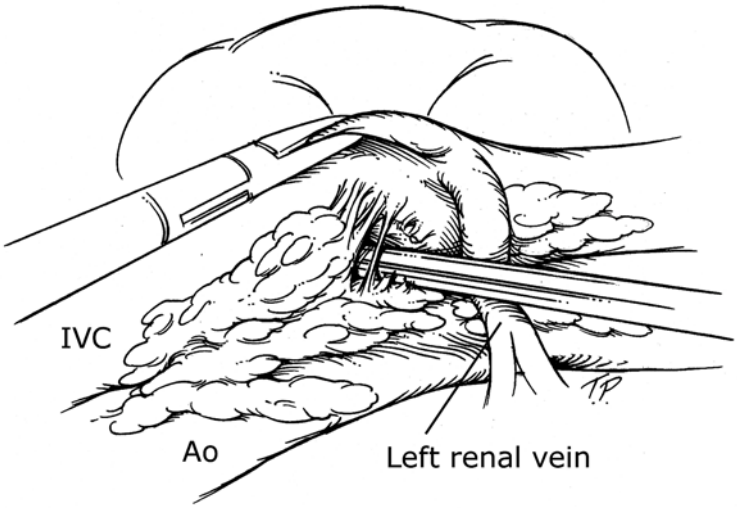


Figure 5 – *Interaortocaval dissection is performed with meticulous ligation of all lumbar and lymphatic vessels encountered. The right renal artery and left renal vein are always identified during the superior portion of this dissection and should not be confounded with lumbar vessels. IVC = inferior vena cava, Ao= aorta.*

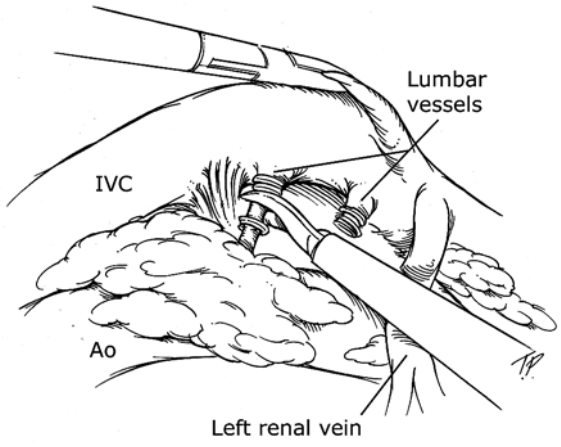


Figure 6 – *Retrocaval dissection is facilitated by rolling and retracting the vena cava with an atraumatic grasper, to allow access to the retrocaval space. All lymphatic and lumbar vessels encountered are carefully ligated and divided. IVC = inferior vena cava, Ao = aorta.*

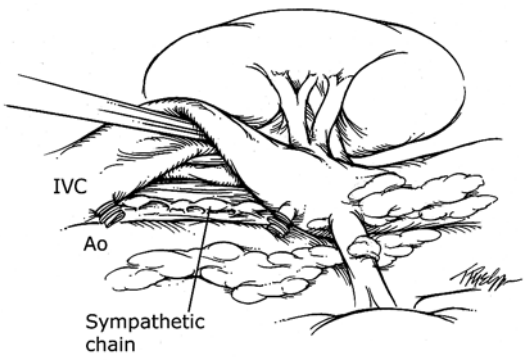


Figure 7 – *At the end of the dissection, we can observe that all lymph node tissues inside the template limits have been removed, with preservation of the sympathetic chains along the posterolateral aspect of the great vessels. IVC = inferior vena cava, Ao = aorta.*

Meticulous lymphatic ligation minimizes the risk of postoperative lymphocele. Venous bleeding is often encountered and should first be controlled using direct pressure. A laparoscopic laparotomy pad (standard pad cut into a 3 cm wide strip for insertion through the trocar) is frequently used for this purpose and most venous bleeding will stop with several minutes of continuous pressure. To gain control of arterial bleeding, especially that from the aorta, we resort to using clips, bipolar cautery, or if the bleeding is directly from the aorta, intracorporeal suturing using 3-0 monofilament, nonabsorbable suture.

Retroperitoneal lymph nodes and spermatic cord are placed into a 10 cm specimen bag, removed from the abdomen, and sent for pathologic analysis. At the end of the procedure, intraabdominal pressure is lowered to 5 mm Hg to evaluate active bleeding. Port sites are closed endoscopically under direct vision using 0-polyglactin suture.

COMMENTS

We have been performing L-RPLND for testicular cancer since 1992 at our institution. Originally, the procedure was used in a diagnostic fashion to provide pathologic staging information for clinical Stage I NSGCT. In 1999, we retrospectively reviewed our first 29 patients undergoing L-RPLND for clinical Stage I NSGCT. We demonstrated that the procedure provided useful pathologic information with minimal short and long-term morbidity. This data supported the notion that L-RPLND was a feasible, minimally invasive surgical alternative to observation or open RPLND (4). With time and additional laparoscopic experience, we began to perform L-RPLND on post-chemotherapy patients who required resection of residual retroperitoneal masses. In 2002, we reported the results of 7 such patients. Again, L-RPLND was considered feasible in this situation, though extremely challenging due to the chemotherapy-induced retroperitoneal fibrosis (5).

After our initial experience, it was apparent that we could perform a dissection that mirrored that of the open procedure. Therefore, our objectives for L-RPLND evolved from a diagnostic to a therapeutic intervention, although because approximately 50% of pathologic stage II patients relapse (6), we continue to use 2 cycles of chemotherapy when positive nodes are discovered. In 2003, we evaluated the long-term oncologic efficacy of our patients. There were no abdominal recurrences, however 1 of 15 (6.6%) patients with pathologic stage I disease had biochemical recurrence with a median follow-up of 5.8 years. Though our numbers were relatively small we concluded that cancer control appeared similar, and L-RPLND offered minimal morbidity compared with the open procedure (7).

As of May 2005, we have performed a total of 92 L-RPLND for testicular cancer. Seventy-six (82.6%) patients underwent the complete template dissection as described above, and sixteen (17.4%) patients underwent an abbreviated dissection due to positive lymph nodes found on frozen section. Median age was 30.5 years-old (range 15 to 45). Seventy-seven (83.7%) patients underwent L-RPLND for clinical stage I or II NSGCT of the testis, and 15 (16.3%) for residual retroperitoneal mass following chemotherapy. Right and left-sided modified unilateral template dissection were performed in 49 (53.3%) and 40 (43.5%) patients, respectively. Three (3.2%) patients underwent bilateral dissection. Intraoperative complications occurred in 10 (10.8%) patients: cavotomy (5.4%), injury to the renal hilum (3.1%), transection of the external iliac artery (1%), and gallbladder lesion (1%). Open conversion rate was 5.4%. The median estimate blood loss was 300 mL (range 50 to 4500), and median length of hospital stay was 2 days (range 1 to 71).

After the establishment and refinement of L-RPLND by experienced laparoscopists throughout the world (8-10), appropriate changes in the procedure, namely resection of retrocaval and retroaortic tissue and preservation of the sympathetic chains, have allowed the procedure to truly mimic its open counterpart. This has allowed L-RPLND to become an oncologically sound treatment option for men with germ cell testicular tumors. Early and mid-term results of L-RPLND parallel those of the open technique, and moreover, provide the patients with the inherent benefits of a laparoscopic approach (decreases in postoperative pain, scarring, and conva-

lescence). It remains to be seen, however, if this procedure will become commonplace as it requires advanced laparoscopic skill and patience. Furthermore, with improvements in chemotherapeutic regimens, RPLND may be less commonly indicated in the future. A prospective randomized trial comparing the morbidity and oncologic outcomes of laparoscopic and open RPLND would be the ideal method of fully evaluating the L-RPLND in this setting.

ACKNOWLEDGEMENT

Timothy Phelps, MS, FAMI (Department of Arts as Applied to Medicine, Johns Hopkins University) made the illustrations.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Roberts JB: Excision of lumbar lymphatic nodes and spermatic vein in malignant diseases of the testicle. Ann Surg. 1902; 36: 539-49.
2. Donohue JP: Evolution of retroperitoneal lymphadenectomy (RPLND) in the management of nonseminomatous testicular cancer (NSGCT). Urol Oncol. 2003; 21: 129-32.
3. Allaf ME, Bhayani SB, Link RE, Schaeffer EM, Varkarakis JM, Shadpour P, et al.: Laparoscopic retroperitoneal lymph node dissection: duplication of open technique. Urology. 2005; 65: 575-7.
4. Nelson JE, Chen RN, Bishoff JT, Oh WK, Kantoff PW, Donehower RC, et al.: Laparoscopic retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell testicular tumors. Urology. 1999; 54: 1064-7.
5. Palese MA, Su LM, Kavoussi LR: Laparoscopic retroperitoneal lymph node dissection after chemotherapy. Urology. 2002; 60: 130-4.
6. Williams SD, Stablein DM, Einhorn LH, Muggia FM, Weiss RB, Donohue JP, et al.: Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. N Engl J Med. 1987; 317: 1433-8.
7. Bhayani SB, Ong A, Oh WK, Kantoff PW, Kavoussi LR: Laparoscopic retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell testicular cancer: a long-term update. Urology. 2003; 62: 324-7.
8. Peschel R, Gettman MT, Neururer R, Hobisch A, Bartsch G: Laparoscopic retroperitoneal lymph node dissection: description of the nerve-sparing technique. Urology. 2002; 60: 339-43; discussion 343.
9. Albqami N, Janetschek G: Laparoscopic retroperitoneal lymph-node dissection in the management of clinical stage I and II testicular cancer. J Endourol. 2005; 19: 683-92; discussion 692.
10. Mariano MB, Tefilli MV: Laparoscopic retroperitoneal lymphadenectomy after chemotherapy for stage IIB testicular tumors. Int Braz J Urol. 2001; 27: 527-34.

Accepted after revision:
October 10, 2005

Correspondence address:
Dr. Frederico R. Romero
600 North Wolfe Street Suite 161
Jefferson Street Bldg.
Baltimore, MD, 21287-8915, USA
Fax: + 1 410-502-7711
E-mail: fredromero@terra.com.br

International Braz J Urol Vol. 32 (2): 202-207, March - April, 2006

Ectopic Adrenal Tissue in the Spermatic Cord in Pediatric Patients: Surgical Implications

Roberto Mendez, Manuel G. Tellado, Ivan Somoza, Jorge Liras, A. Sanchez-Abuin, Ernesto Pais, Diego Vela

Pediatric Urology, Department of Pediatric Surgery, Children's Hospital Teresa Herrera, Complexo Hospitalario Juan Canalejo, A Coruna, Spain

ABSTRACT

Objective: To study the incidence and relevance of ectopic adrenal tissue in pediatric patients who underwent groin surgical explorations.
Materials and Methods: We studied 1120 patients with groin surgical explorations during a period of 8 consecutive years. Patients' clinical data and histological findings were analyzed.
Results: We found ectopic adrenal tissue in 13 patients in 1120 groin surgical exploration (1.16%). Of the 13 cases, 5 were diagnosed as having undescended testes, 6 inguinal hernia and 2 communicating hydrocele. Median age at diagnosis was 5.6 years. Histological sections showed adrenal cortical tissue with no medulla present.
Conclusion: Based on the clinical implications of those adrenal rests it is mandatory the removal of this ectopic tissue whenever encountered during surgical interventions in the groin region in children.

***Key words**: adrenal glands; aberrant tissue; spermatic cord; child*
Int Braz J Urol. 2006; 32: 202-7

INTRODUCTION

Ectopic adrenal tissue along the spermatic cord is a rare diagnosis in childhood. Since Morgagni´s first description in 1740, only 95 additional cases have been reported in the available English literature, most of them in pediatric patients. Overall incidence in different studies varies from 1% to 9.3% of the patients who underwent groin surgical explorations (Table-1). Adrenal cortex rests may undergo hyperplasia in patients with increased adrenocorticotropic hormone (ACTH) production and potentially malignant neoplasm.

We report thirteen cases of accessory adrenal located in the spermatic cord. The clinical and surgical implications of this uncommon anomaly are discussed and a through review of the literature is made.

MATERIAL AND METHODS

From April 1997 to March 2005, we studied 1120 pediatric patients under 14 years of age, who underwent surgical groin exploration for undescended testes, communicating hydrocele or inguinal hernia. We reviewed the clinical charts of patients encoded as having ectopic adrenal in the database of our department.

The surgical operation for inguinal hernia, communicating hydrocele and cryptorchidism were

carried out using standard procedure opening the external oblique fascia and dissecting the spermatic cord elements. No surgical efforts of more aggressive cranial dissection of the spermatic cord were made.

Data about operation performed, age, gender and pathological characteristics of the nodules were recorded. All the pathological tissue founded along the spermatic cord were analyzed by the pathology department of our hospital and confirmed as ectopic adrenal cortical rests using the hematoxylin-eosin stain.

Data were registered using Microsoft Excel® database and analyzed using SPSS® 11.0 software. The chi-squared statistical test was used for comparison of incidence between diagnostic groups with p value < 0.001.

RESULTS

We found ectopic adrenal tissue in 13 patients of 1120 groin surgical exploration (1.16%). All the cases were boys with none detected in girls. No cases of bilateral nodules were demonstrated in patients submitted for bilateral procedures. Of the 13 cases, 5 were diagnosed as having undescended testes, 6 inguinal hernia and 2 communicating hydrocele. Median age at diagnosis was 5.6 years (range 2 to 10 years). There was no statistically significant difference concerning the incidence in the diagnostic groups studied (p = 0.37).

All the nodules were located along the spermatic cord in proximity to the deep inguinal ring embedded in the cremasteric fibers near the deferens. The appearance of the ectopic adrenal tissue was similar in all the patients: a small in size (< 3 mm) bright yellowish soft nodule clearly different in color and consistency from the fat (Figure-1).

Histological sections of the excised nodules showed adrenal cortical tissue consisting of three layers of adrenal cortex (glomerulosa, fasciculata and reticularis) with no medullary tissue present (Figure-2). Two cases of focal calcifications were observed (Figure-3).

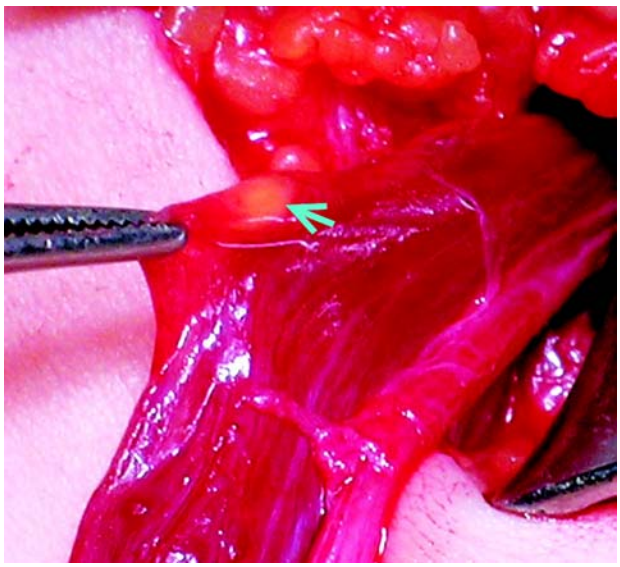


Figure 1 – *Intraoperative photograph during orchidopexy for criptorchidism. Arrow and forceps tip marks the well-defined yellow nodule.*

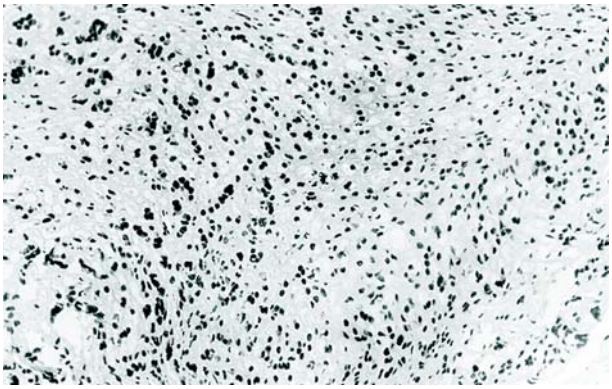


Figure 2 – *Histologic section with lipid rich cortical cells clearly seen with no medullary tissue (HE, X150).*

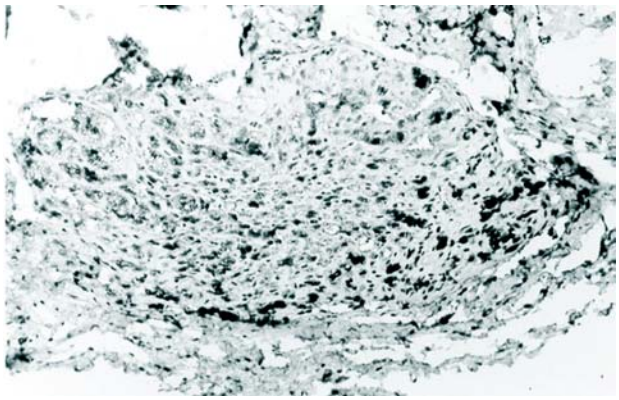


Figure 3 – *Histologic section showing encapsulated adrenal cortical tissue with focal calcification (HE, X50).*

COMMENTS

Aberrant adrenal tissue is not a rare finding near the adrenal gland proper but the occurrence of ectopic adrenal tissue in structures around the spermatic cord and testis is rather rare. In 1740, Morgagni first described yellowish nodules resembling adrenal tissue adjacent to the main glands (1). Since then, several accounts have been published locating ectopic adrenal tissue in various sites, most frequently in relation to the kidney, but less than 100 cases have been reported near the genital structures (Table-1). Of these, approximately 80 cases have been described in male genital structures in childhood (2-34). Instead this low rate of incidence, probably this entity is more frequent than we thought before, and likely many cases like these have not been reported. The lower incidence in girls is not easy to explain but may reflect differences in underlying diagnosis (29).

Table 1 – *Cases of adrenal rests in the structures around the testis reported in the available literature.*

Authors and Year	Cases Reported	Location	Gender	Mean Age
McLennan (1919) (2)	6 pediatric cases	Hernial sacs	4 M, 2 F	No data
Gualtieri & Segal (1949) (19)	1 adult case	Spermatic cord	Male	No data
Dahl & Bahn (1962) (3)	11 cases in infants	Paratestis	Males	Infants
Schechter (1968) (1)	1 adult case	Inguinal	Male	No data
Mininberg & Dattwyler (1973) (4)	1 case in a child	Inguinal	Male	Newborn
Feldman et al. (1975) (5)	1 pediatric case	Spermatic cord	Male	10 y
Gutowski & Gray (1979) (23)	5 adult cases	Inguinal	Males	No data
Anderson & McLean (1980) (13)	1 adult case	Inguinal	Male	53 y
Mares et al. (1980) (6)	12 pediatric cases	Spermatic cord	Males	No data
Lodeville et al. (1981) (20)	1 adult case	Genital	Males	No data
Landry (1982) (25)	1 adult case	Paratesticular	Male	30 y
Lambrecht & Kortmann (1983) (28)	1 pediatric case	Inguinal	Male	7 y
Brunning (1984) (22)	1 pediatric case	Spermatic cord	Male	5 y
Czaplick et al. (1985) (13)	2 adult cases	Inguinal	Males	18 y
Wolloch et al. (1986) (7)	1 case in a child	Spermatic cord	Male	9 y
Delmas & Dauge (1986) (17)	2 adult cases	Spermatic cord	Males	28 y
Ferro et al. (1988) (8)	13 pediatric cases	Inguinal	Males	No data
Vestita et al. (1989) (9)	1 case in a child	Spermatic cord	Male	5 y
Miersch et al. (1989) (27)	1 adult case	Spermatic cord	Male	40 y
Benvenuti et al. (1991) (18)	1 adult case	Perideferential	Male	21 y
Roggia et al. (1991) (10)	1 pediatric case	Perideferential	Male	11 y
Litovka et al. (1991) (11)	1 case in a child	Spermatic cord	Male	3 y
Habuchi et al. (1992) (12)	1 pediatric case	Spermatic cord	Male	6 y
Roca et al. (1993) (26)	6 adult cases	Spermatic cord	Males	No data
Okur et al. (1995) (33)	9 pediatric cases	Spermatic cord	Males	3.2 y
Basar et al. (1997) (24)	1 adult case	Near testis	Male	No data
Ventura et al. (1998) (32)	1 adult case	Spermatic cord	Male	42 y
Savas et al. (2001) (31)	11 pediatric cases	Inguinal region	8 M, 3 F	No data
Oguzkurt et al. (2002) (30)	4 pediatric cases	Hernial sacs	3 M, 1 F	No data
Mari et al. (2004) (34)	1 adult case	Spermatic cord	Male	40 y
Sullivan et al. (2005) (29)	29 pediatric cases	Spermatic cord	Males	No data
Actual Report (2005)	13 pediatric cases	Spermatic cord	Males	5.6 y

Embriologically the adrenal develops from 2 primordia: the cortex arises from the mesoderm and the medulla from ectoderm of the neural crest. The primitive cortex is formed during the 4th and 5th weeks from mesothelial cells formed between the mesentery root and the developing gonad that proliferate, separate and condense in the mesenchyma of the dorsal abdominal wall. Another group of cells from the same area is added to this later to form the definitive cortex. Cells from the neural crest invade the primitive cortex to form the medulla. Encapsulation of the medulla occurs late in fetal development (7,10,13). It is generally accepted that these adrenal rests were due to mechanical separation and displacement of portions of cortical tissue during migration and descent of the sex glands in the male embryonic development. They also may have a multiple primordial origin from pluripotent cells in the original locations (13,14). Some heterotopic tissue remains in the area of the adrenal gland near the kidney, but others may migrate with the genitalia descent to the pelvis and scrotum. Some authors estimated that these rests may be present in 50% of newborns but most of them become atrophic by adult life (1,15). Other organs in which an accessory adrenal has been found are the colon, pancreas, retroperitoneum, liver, broad ligament and celiac plexus (7,16).

The pathologic appearance of this tissue is characteristic. The findings consisted of a thin yellowish nodule 1 to 5 mm in diameter embedded in cremasteric fibers (13). Adrenal rests situated far from the original gland are composed entirely of cortical adrenal tissue with no evidence of medullary cells found in these rests, but the more proximal may contain medulla. Usually a capsule of connective tissue with small blood vessels can be seen surrounding these nodules (3). Of the three cortical layers, predominate the fasciculata and glomerulosa. The reticularis layer is usually seen only in older children (6).

Most cases of ectopic adrenal tissue in spermatic cord have been found incidentally during surgical procedures (like herniotomy, orchiopexy, etc) in the inguinoscrotal region (17,18). Examples of heterotopic tissues in autopsies have been reported in adults and children usually underneath the capsule of the kidney (1-3,6,16).

The clinical implications of those rests are essential in the surgical approach of the patients. Some authors cite a compensatory functional hypertrophy of these tissues in rats and human beings in which both adrenals were extirpated (1,6). In patients who have undergone bilateral adrenalectomy due to pathologic ACTH production, compensatory hyperplasia of the ectopic adrenal tissue may be responsible for the recurrence of the disease (7,10). Another clinical aspect is the possibility of formation and development of malignant diseases in the ectopic adrenal cells (13,19-21,34). Although the occurrence of neoplasm in ectopic adrenal nodules is far from common, pheochromocytoma, Leydig cell's tumor and adrenal adenoma has been reported (21,29,35).

Based on these facts, we think that removal of ectopic adrenal tissue in the spermatic cord would be warranted whenever encountered during surgical operations in inguinal region. It is very easy to excise the adrenocortical ectopic tissue during the groin surgery; however, meticulous dissection of the spermatic cord should not be performed in order to avoid the damage of the spermatic vessels and deferens. The nodule is usually embedded in the cremasteric fibers of the spermatic cord, very close to the deferens and attached to the hernia sac and it is very simple to have it dissected free without vascular injury. The lesion of the deferens has not been reported in the literature. In agreement with others authors, we consider that it is also important for urologist to keep in mind the possibility that a nodule around the spermatic cord may be ectopic adrenal tissue. It is reasonable to excise this nodule without jeopardizing the viability of the spermatic cord structures.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Schechter DC: Aberrant adrenal tissue. Ann Surg. 1968; 167: 421-6.

2. McLennan A: On the presence of adrenal rests in the walls of hernial sacs. Surg Gynec Obst. 1919; 29: 387.
3. Dahl EV, Bahn RC: Aberrant adrenal cortical tissue near the testis in human infants. Am J Pathol. 1962; 40: 587-598.
4. Mininberg DT, Dattwyler B: Ectopic adrenal tumor presenting as torsion of the spermatic cord in a newborn infant. J Urol. 1973; 109: 1037-8.
5. Feldman AE, Rosenthal RS, Shaw JL: Aberrant adrenal tissue: an incidental finding during orchiopexy. J Urol. 1975; 113: 706-8.
6. Mares AJ, Shkolnik A, Sacks M, Feuchtwanger MM: Aberrant (ectopic) adrenocortical tissue along the spermatic cord. J Pediatr Surg. 1980; 15: 289-92.
7. Wolloch Y, Ziv Y, Dintsman M: Accessory adrenal: an incidental finding during orchiopexy. Panminerva Med. 1986; 28: 47-9.
8. Ferro F, Bosman C, Caterino S et al. Ectopia corticosurrenale nel cordone spermatico: Solo una curiositá anatomica? Acta Urol Ital. 1988; 5: 415-7.
9. Vestita G, Veneziani P, Manghisi D, Scavelli V, Sorino F, Gabrieli G, et al.: A rare occurrence of adrenal ectopy im the spermatic cord. A short clinical note. G Chir. 1989; 10: 499-500.
10. Roggia A, Marandola P, Broggini P, Bono P, de Francesco O, Rovati L: Ectopic adrenal cortex tissue in the spermatic cord: clinico-surgical implications. Arch Esp Urol. 1991; 44: 1165-6.
11. Litovka VK, Zhurilo IP, Khudiakov AE: Atopic adrenal tissue in the testicle of a small child with cryptorchism. Khirurgiia (Mosk). 1991; 8: 164.
12. Habuchi T, Mizutani Y, Miyakawa M: Ectopic aberrant adrenals with epididymal abnormality. Urology. 1992; 39: 251-3.
13. Anderson JR, Ross AH: Ectopic adrenal tissue in adults. Postgrad Med J. 1980; 56: 806-8.
14. O´Crowley CR, Martland HS: Adrenal heterotopia rests and so-called Grawitz tumors. J Urol. 1943; 50: 756-68.
15. Czaplicki M, Bablok L, Kuzaka B, Janczewski Z: Heterotopic adrenal tissue. Int Urol Nephrol. 1985; 17: 177-81.
16. Nelson AA: Accessory adrenal cortical tissue. Arch Pathol 1939; 27: 955-9.
17. Delmas V, Dauge MC: Accessory adrenals in the spermatic cord. Apropos of 2 cases. Ann Urol (Paris). 1986; 20: 261-4.
18. Benvenuti S, Sepich CA, Cecchi M, Castagna M, Viacava P, Fiorentini L: Peri-deferential ectopic adrenal gland. Apropos of a case. J Urol (Paris). 1991; 97: 107-8.
19. Gualtieri T, Segal AD: Case of adrenal type tumor of spermatic cord. J Urol. 1949; 61: 949-5.
20. Lodeville D, Zaroli A, Lampertico P: Adenomatoid tumor of the male genital tract: report of three cases, one associated with adrenal cortical rest. Pathologica. 1981; 73: 629-37.
21. Vela Navarrete R, Barat A, Berrocal A, Lopez de Alda A, Quezada F: Testicular adrenal rests tumor: a difficult diagnosis. Actas Urol Esp. 1990; 14: 146-8.
22. Bruning H, Kootstra G, Walther FJ, Arends JW: Ectopic adrenocortical tissue along the spermatic cord. Z Kinderchir. 1984; 39: 269-70.
23. Gutowski WT 3rd, Gray G Jr: Ectopic adrenal in inguinal hernia sacs. J Urol. 1979; 121: 353-4.
24. Basar M, Erdogan S, Aydoganli L, Basar H, Kulacoglu S, Akalin Z: Aberrant adrenal cortical tissue adjacent to immature testis. Arch Ital Urol Androl. 1997; 69: 141-2.
25. Landry GS: Case for diagnosis: ectopic adrenal tissue in testicular adnexa. Mil Med. 1982; 147: 679-80.
26. Roca Suarez A, Alvarez Ossorio JL, Del Toro Bacerra JA, Maximiano Vasquez R, Gordon Laporte R: Adrenal ectopia in the spermatic cord. Actas Urol Esp. 1993; 17: 584-7.
27. Miersch WD, Vogel J, Molitor D, Winter P: Ectopic adrenal cortex tissue. Z Urol Nephrol. 1989; 82: 487-90.
28. Lambrecht W, Kortmann KB: Incidence and significance of accessory adrenal tissue in the inguinal region in childhood. Chirurg. 1983; 54: 39-41.
29. Sullivan JG, Gohel M, Kinder RB: Ectopic adrenocortical tissue found at groin exploration in children: incidence in relation to diagnosis, age and sex. BJU Int. 2005; 95: 407-10.
30. Oguzkurt P, Oz S, Kayaselcuk F: Ectopic adrenal tissue: an incidental finding during inguinoscrotal operations in children. Hernia. 2002; 6: 62-3.
31. Savas C, Candir O, Bezir M, Cakmak M: Ectopic adrenocortical nodules along the spermatic cord of children. Int Urol Nephrol. 2001; 32: 681-5.
32. Ventura L, Leocata P, Hind A, Greco I, Ventura T: Ectopic adrenal tissue in the spermatic cord. Case report and review of the literature. Arch Ital Urol Androl. 1998; 70: 15-8.
33. Okur H, Kucukaydin M, Kazez A, Kontas O: Ectopic adrenal tissue in the inguinal region in children. Pediatr Pathol Lab Med. 1995; 15: 763-7.
34. Mari M, Cagnazzi E, Bollito E, Bellina M: Ectopic adrenal cortex tissue in the spermatic cord in association with testicular cancer. Urol Int. 2004; 73: 191-2.

35. Abe T, Matsuda H, Shindo J, Nonomura K, Koyanagi T: Ectopic pheochromocytoma arising in the spermatic cord 5 years after removal of bilateral carotid body tumors and adrenal pheochromocytomas. Int J Urol. 2000; 7: 110-1.

Accepted after revision:
January 11, 2006

Correspondence address:
Dr. Roberto Méndez
Department of Paediatric Surgery
Complexo Hospitalario Universitario de Santiago
Avda. Choupana s/n.
15706 Santiago de Compostela, Spain
E-mail: roberto.mendez.gallart@sergas.es

EDITORIAL COMMENT

Heterotopic or ectopic adrenal cortical tissue (EACT) are found in the upper abdomen or anywhere along the path of descent of the gonads. The locations where EACT can be found are: celiac axis area (32%); broad ligament (23%); adnexa of the testes (7.5%); kidney (subcapsular upper pole) (0.1%-6%) and spermatic cord (3.8%-9.3%) (1,2). These anatomic locations can be explained on an embryologic basis given the close spatial relationship between the developing kidneys and adrenal glands. There are even bizarre anatomic sites where one can find these EACT, such as: placenta, liver, lung and intracranial cavity (1). Usually these adrenal rests are found incidentally during inguinal operations and present macroscopically as bright yellow small nodules (1-5mm in diameter) and microscopically as lipid rich cortical cells without a medullary component (1-3). These rests have some clinical significance as they may undergo marked hyperplasia in conditions associated with excessive ACTH production, and occasionally may give rise to neoplasms. The overall incidence of EACT in different studies varies from 1% to 9.3% in pediatric patients. These big series in the literature stick out the importance of recognizing and removing these EACT, whenever encountered, owing to the clinical relevance of these ectopies (2-5).

REFERENCES

1. Lack EE. Heterotopic and Accessory Adrenal Tissues In: Lack EE, (ed.), Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia. Fascicle 19, third series. Washington, DC: Armed Forces Institute of Pathology. 1997; pp. 34-5.
2. Mares AJ, Shkolnik A, Sacks M, Feuchtwanger MM: Aberrant (ectopic) adrenocortical tissue along the spermatic cord. J Pediatr Surg. 1980; 15: 289-92.
3. Savas C, Candir O, Bezir M, Cakmak M: Ectopic adrenocortical nodules along the spermatic cord of children. Int Urol Nephrol. 2001; 32: 681-5.
4. Sullivan JG, Gohel M, Kinder RB: Ectopic adrenocortical tissue found at groin exploration in children: incidence in relation to diagnosis, age and sex. BJU Int. 2005; 95: 407-10.
5. Ferro F, Bosman C, Casterino S et al. Ectopia corticosurrenale nel cordone spermatico: Solo una curiositá anatomica? Acta Urol Ital 5: 415-417, 1988.

Dr. Patrícia S. de Matos
Department of Pathology,
School of Medicine, State University of Campinas
São Paulo, Brazil

Pediatric Urology - Case Report
International Braz J Urol Vol. 32 (2): 208-210, March - April, 2006

Unilateral Renal Agenesia Associated with Partial Epididymis and Vas Deferens Agenesia in a Patient with Abdominal Testicle

Joao L. Pippi Salle, Jacob Langer, Luciano A. Favorito

Department of Urology, Hospital for Sick Children, University of Toronto, Toronto, Canada

ABSTRACT

This study considers a unilateral renal agenesia associated with agenesia of the epididymis body and tail and the vas deferens and non-palpable left testicle in a 20-month-year-old patient. During laparoscopic procedure, the testicle was positioned at approximately 5 cm above the inguinal ring. The size was appropriate for the age and the head of the epididymis was situated in its normal position. The decision was made to perform the first step of the Fowler-Stephens' surgery and the patient presented a good evolution. The association of male duct system agenesia with unilateral renal agenesia in a patient with cryptorchidism diagnosed by laparoscopy is an extremely rare event, however generally in these cases the testicle is of normal size, presents unaltered hormonal function, and must be preserved.

Key words*: testis; cryptorchidism; kidney; urogenital anomalies*
Int Braz J Urol. 2006; 32: 208-10

INTRODUCTION

Urinary and genital systems originate in the intermediary mesoderm located along the posterior wall of the abdominal cavity between the fourth and the tenth week post-conception (1). Alterations in this development before the fourth week can lead to unilateral agenesia of the genitourinary structures (1).

The occurrence of duct anomalies (epididymis, vas deferens, ejaculatory ducts and seminal vesicles) is very frequent in infertile patients and in cryptorchidism (1,2). However, reports of partial agenesia of the epididymis associated with vas deferens and renal agenesia in patients with abdominal testicle is extremely rare. The objective of the present article is to discuss the occurrence of unilateral renal and genital duct agenesia in a patient with an abdominal testicle located during a laparoscopic diagnosis procedure.

CASE REPORT

We discuss the case of a twenty-month-old patient with a non-palpable left testicle and topic right testicle of normal size for his age who presented no other significant alterations during the physical exam. An abdominal ultrasound showed the left testicle in an intra-abdominal position. The patient was submitted to laparoscopic orchidopexy, which revealed the left testicle situated around 5 cm above the internal inguinal ring.

During the procedure, we noticed the absence of the left vas deferens (Figure-1) and agenesia of the epididymis body and tail (Figures-2 and 3) and also of the left kidney. The epididymis head was in its normal situation (Figure-2). As the testicle was of a normal size, we decided to perform the Fowler-Stephens surgery in 2 steps – clamping of the spermatic vessels first with the second step (orchidopexy)

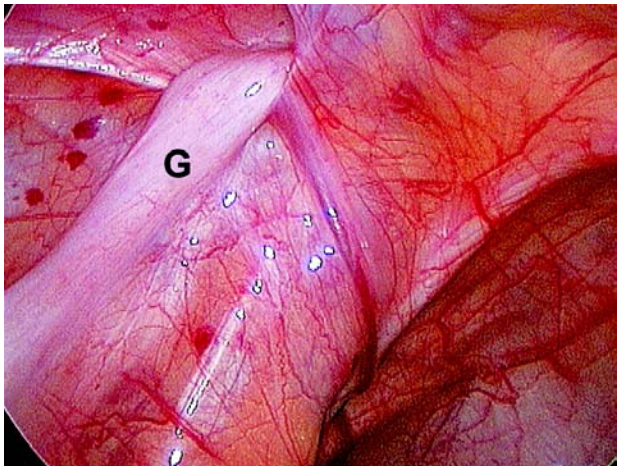


Figure 1 – *Laparoscopic view of the internal inguinal ring. We observe the testicular gubernaculum and vessels crossing the inguinal ring; the deferent duct is not identified. G = gubernaculum.*

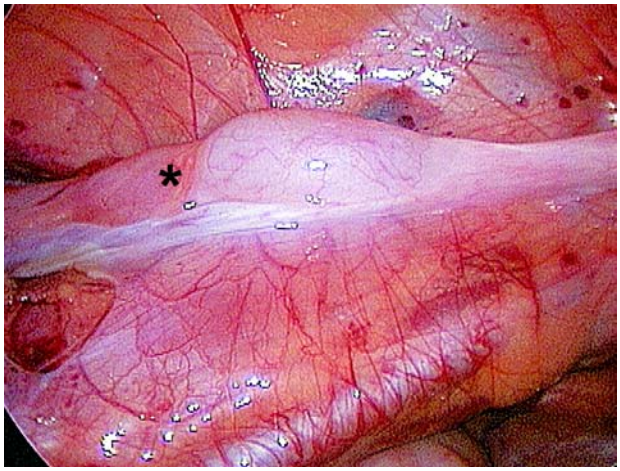


Figure 2 – *Laparoscopic view of the left testicle where we observe the epididymis head (*).*

after 6 months. The patient evolved well and was discharged the day after the procedure.

COMMENTS

Anomalies of the epididymis and the vas deferens can be divided into 2 groups: (a) anomalies associated with cryptorchidism and (b) anomalies observed during infertility investigations. Anomalies of

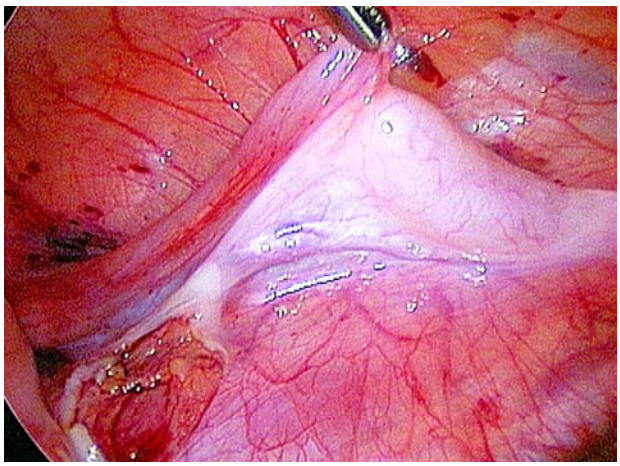


Figure 3 – *Laparoscopic view of the left testicle. When we were mobilizing the testicle, we noticed the absence of the epididymis body and tail.*

the epididymis are associated with cryptorchidism in 36 to 72% of cases (2); however, the existence of epididymis agenesia is one of the rarest epididymis anomalies (2).

Partial agenesia of the epididymis with its head in the habitual position can be explained by alterations in vascularization during the period of mesonefric tubules development before its fusion with the testicular tubules (3).

Renal anomalies in cryptorchidism present an incidence rate similar to the general population, with renal agenesia being one of the most common (1). Of patients with unilateral renal agenesia, 10 to 15% present genital anomalies, and of these patients with genital anomalies, the testicle is generally normal with an occurrence of partial agenesia of the epididymis and of the deferent in 50% of cases (1). In rare cases of cryptorchidism where there is a renal and epididymis agenesia, the testicle generally is normally sized and presents unaltered hormone function, therefore, must be preserved, even though the reproductive function is compromised.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Favorito LA, Cardinot TM, Morais AR, Sampaio FJ: Urogenital anomalies in human male fetuses. Early Hum Dev. 2004; 79: 41-7.
2. Barthold JS, Redman JF: Association of epididymal anomalies with patent processus vaginalis in hernia, hydrocele and cryptorchidism. J Urol. 1996; 156: 2054-6.
3. Gill B, Kogan S, Starr S, Reda E, Levitt S: Significance of epididymal and ductal anomalies associated with testicular maldescent. J Urol. 1989; 142: 556-8; discussion 572.

Accepted:
July 25, 2005

Correspondence address:
Dr. Luciano Alves Favorito
Rua Professor Gabizo, 104/201
Rio de Janeiro, RJ, 20271-320, Brazil
Fax: + 55 21 3872-8802
E-mail: favorito@uerj.br

International Braz J Urol Vol. 32 (2): 211-215, March - April, 2006

Bladder Drainage and Glandular Epithelial Morphometry of the Prostate in Benign Prostatic Hyperplasia with Severe Symptoms

Carlos A. Cury, Reinaldo Azoubel, Fernando Batigalia

Department of Urology, Faculty of Medicine of Sao Jose do Rio Preto (FAMERP), Sao Paulo, SP, Brazil

ABSTRACT

Objective: Morphometrically analyze the cells nuclei of the basal layer of the prostatic glandular epithelium in 20 patients aged between 57 and 85 years presenting benign prostatic hyperplasia with severe symptoms, catheterized or not.
Materials and Methods: Patients with score of severe prostatic symptoms (with indication for transurethral resection of the prostate) were distributed according to the presence or absence of bladder drainage previous to the surgery, in the treated group (n = 10, catheter during 3 months) and in the control group (n = 10, without catheter). After obtaining prostate fragments through transurethral resection and the use of morphometric techniques, 100 nuclei of prostatic glands epithelium cells were studied (as to size and form), and compared to 500 nuclei from patients submitted to catheter drainage and 500 nuclei of non-catheterized patients.
Results: Significantly reduced values of the major, medium and minor nuclear diameters, volume, area and perimeter, contour index and nuclear volume-nuclear area ratio were observed in the treated group in relation to the control group. As to the form, eccentricity and coefficient of nuclear form, there were significant differences between treated and control groups.
Conclusion: Long-term catheter bladder drainage in patients presenting benign prostatic hyperplasia with severe symptoms is associated to the reduction of morphometric parameters of the nuclei of prostatic glands' epithelial cells, suggesting a likely decompressive duct effect.

***Key words**: prostate; BPH; morphometry; acini; adenoma*
Int Braz J Urol. 2006; 32: 211-5

INTRODUCTION

Benign prostatic hyperplasia is the most common disease in older man, standing out in men over 50 years of age (1-3). At the age of 40, approximately 10% of the men present histological evidences of benign prostatic hyperplasia with a progressive increase of the condition according to the age, affecting 90% of the individuals at the age of 80 (4).

The increase of the survival rate exposes male population to the risk of being affected by benign prostatic hyperplasia that also increases the chances of urinary retention. This requires an immediate medical intervention, since men over 60 years old with life expectancy of more than 20 years will present chances of up to 23% to develop urinary retention. In these cases the immediate clinical treatment for urinary retention conditions is catheter bladder drainage (5).

The chronic use of catheter bladder drainage has awakened the interest regarding secondary alterations that the prostatic epithelium cells might develop due to hyperplasia (6) and through the constant contact of the epithelium of the prostatic urethra with the catheter. Histopathologic studies accomplished through transurethral biopsies of the prostatic urethral mucosa reveal inflammatory infiltration with proliferation of the prostatic urethra epithelial and connective tissues (7). However, morphometric studies on the prostatic cells in cases of urethral catheter are rare (8,9).

Therefore, this study aimed at morphometrically analyze nuclear alterations in prostatic gland cells on patients presenting benign prostatic hyperplasia with severe symptoms either catheterized or not, submitted to transurethral resection of the prostate .

MATERIALS AND METHODS

After the approval of the Research Ethics Committee, 20 patients with symptomatic benign prostatic hyperplasia were studied, being 18 white and 2 black, aged between 57 and 85 years (mean of 70 years) seen during the year of 1998.

Clinical history was accomplished according to the International Symptom 7 questions Score index (10), counting on 7 questions with an option of answers with punctuations from 1 to 5 and classification of the symptoms as light (from 1 to 7 points), moderate (from 8 to 18 points) and severe (from 19 to 35 points). Only patients with a score of symptoms classified as severe were selected and those were divided into a treated group (10 patients with mean age of 76 ± 0.9 years submitted to bladder drainage with a conventional 18F Foley catheter for 3 months due to urinary retention caused by benign prostatic hyperplasia, and a control group (10 patients with mean age of 74 ± 2.8 years without bladder drainage presenting severe symptoms). Afterwards, both groups were assessed preoperatively and submitted to a single biopsy of prostatic tissue by the technique of transurethral endoscopic resection (11), with the size of the fragment varying from 0.5 to 1 cm length by 2 to 3 mm thickness. Patients of both groups were not submitted to any other type of postoperative treatment.

The collected material was immediately fixed in 10% formalin, included in paraffin and sectioned with a thickness of 5 μm. The slides were stained with hematoxylin-eosin (five slides per patient) and examined in a light microscope with 1.200X magnification for cariometric analysis. The cell nuclei of the basal layer of the prostate glandular epithelium were assessed, summing up to 500 nuclei per patient of the treated group (with catheter) and 500 nuclei per patient of the control group (without catheter), obtaining a mean value for each morphometric parameter in each patient, that allowed to calculate mean values for each parameter in the 2 groups.

Cariometric assess of the nuclei comprehended the study of major, medium and minor diameters, major/minor diameters ratio, nuclear volume, nuclear area, volume/area ratio, perimeter, contour index, eccentricity, and coefficient of form. For statistical analysis, the Student t test was used with the Welch correction for morphometric data comparison with arithmetic means and different standard deviations in 2 independent samples adopting an alpha error of 5%. The final results were expressed in a table containing the mean values and standard deviations for morphometric parameters of the cell nuclei of the basal layer of the prostate glandular epithelium for both the treated and the control groups.

Morphometric calculations (with conversion of the units in mm) were made by the GMC Basic Software Biologic Research®, 8.1. version, of the Faculty of Dentistry, Riberao Preto, University of Sao Paulo, available on the Internet (12). Statistical analysis was accomplished by means of the program MINITAB®, 12.21 version.

RESULTS

Table-1 shows the mean values and standard deviations for the major, medium and minor diameters, nuclear volume, perimeter, eccentricity, contour index, volume/area ratio and coefficient of form

Table 1 – *Mean values and standard deviations for the major, medium and minor diameters, volume, perimeter, eccentricity, contour index, volume/area ratio, and coefficient of form of the cell nuclei of the basal layer of the prostate glandular epithelium in both the treated and the control groups.*

Variable	Treated Group		Control Group		p Value
	Mean (mm)	Standard Deviation	Mean (mm)	Standard Deviation	
Major diameter	11.67	0.95	15.05	1.36	0.0000*
Minor diameter	7.09	0.91	8.38	0.90	0.0026*
Medium diameter	9.02	0.86	11.10	0.86	0.0001*
Major/Minor diameter	1.71	0.13	1.89	0.22	0.0550
Volume	4.21	1.21	7.74	1.76	0.0001*
Area	66.0	13.1	99.4	15.3	0.0001*
Perimeter	30.00	2.78	37.76	2.97	0.0026*
Eccentricity	0.76	0.03	0.78	0.52	0.1700
Contour Index	3.75	0.59	3.84	0.09	0.021*
Volume/Area ratio	6.01	0.61	7.40	0.57	0.00001*
Coefficient of form	0.89	0.02	0.86	0.04	0.0600

** Significant difference for $p < 0.05$.*

of the cell nuclei of the basal layer of the prostate glandular epithelium of both treated and control groups.

The mean of the major diameter of the prostatic gland cells in the treated group was significantly smaller (p = 0.0000) in relation to the mean of the nuclei diameter in the control group, the same happening to the means of medium (p = 0.0001) and minor (p = 0.0026) diameters. The comparative study of the major diameter mean values ratio in relation to the minor diameter of both groups did not reveal a significant difference (p = 0.055).

The mean value of the nuclear volume in the treated group was significantly smaller (p = 0.0001) in relation to the control group, the same happening to the mean measurements of the nuclear area of the prostatic glands (p = 0.0001), for the volume/area ratio (p = 0.00001) and for the mean of the perimeters of prostatic cell nuclei (p = 0.0026). In addition, the mean of the contour index of the nuclei of the treated group revealed to be significantly smaller (p = 0.021) in relation to the control group.

Mean eccentricity of the nuclei in both the treated and control groups did not present any significant difference (p = 0.17); the same occurred to mean values of the coefficient of form (p = 0.06).

COMMENTS

Even though the benefits obtained with bladder drainage are defined, physiopathological aspects related to voiding improvement under the influence of catheterism are still obscure (13-15). The dynamics of the prostatic function seems to be under the effect of 2 stimuli, the nervous (16,17) and the hormonal, being that the acute obstruction is consequent to the occlusion of the bladder neck (18).

The decrease in the volume of prostatic tissue seems to occur by the installation of a nervous reflex that determines the relaxation of smooth muscles and allow the drainage of the prostatic secretion. Facts that stimulate the sympathetic activity can augment the prostate muscles tonus, the bladder neck and the prostatic urethra, determining not only prostatic congestion but also urinary retention (19,20).

Morphologic alterations in prostatic congestion are characterized by a stasis of various degrees of secretion at the acinar lumen, including corpora amylacea (21). Considering morphologic criteria, the reduction in some dimensions of the nuclei of the epithelial cells in the treated group (with vesical catheter) can suggest the reduction of congestive alterations in

the benign prostatic hyperplasia, be it a phenomenon concomitant to the reduction of nuclear dimensions on the prostatic epithelium, possibly explained by the mechanical compression and the blockage of the ducts that drain the glandular acina an the veins (21).

Nuclear augmentation has been established as one of the criteria used for the diagnosis of prostate adenocarcinoma. Nuclear parameters have been used in computerized morphometric studies for differential diagnosis of the prostate, revealing nuclear area values of 32.5 μm and 39.6 μm in both benign and malignant hyperplasia, respectively (22). The computerized analysis of the image with adaptation to the morphometric grid has been used to quantify relative stroma and epithelium quantities in benign prostatic hyperplasia in patients submitted to transurethral prostatic resection, open prostatectomy or cystoprostatectomy (23,24).

Morphometric image analysis has also been used to help determine the expression of the receptors for epithelial growth factors in benign prostatic hyperplasia (25), besides contributing for the study of the metabolism of satellite hyperplasic epithelial cells affected by growth factors produced by cancerous prostatic cells (26). However, it is fundamental in morphometric studies of the nuclei of prostatic epithelial cells, that there is an initial immediate fixation of the material (27), as it occurred in the present study.

Effects of mechanic tissue deformation over the morphology of intracellular organelles involved in cellular biosynthesis and metabolism have been assessed (28,29), supplying a theoretical basis for the performance of prostatic studies. Nuclear reduction consequent to the application of strengths or mechanic devices over tissues (such as in the passage of a catheter) has been verified. The compression of cartilaginous tissue results in reduction of chondrocytes' volume and its nuclei indicating that a balance between osmotic and mechanic intracellular gradients tends to govern the organelles' alterations of form and volume in case of tissular compression (28). In human hearts, the implant of a left ventricular assistance equipment in cases of severe dilated cardiomyopathy occasioned reduction of cardiac work, reduction in the size and content of the DNA of the cardiac myocytes nuclei and consequently, reversion of cellular hypertrophy r (29).

This study compared the influence of bladder drainage on the morphometry of prostatic glandular epithelial cells nuclei aiming at explaining, in an original way, why certain patients presenting benign prostatic hyperplasia develop urinary retention. We can notice that the presence of bladder drainage was concomitant to the reduction of prostatic epithelial cells nuclei that suggests an association of alterations of nuclear morphometric parameters with the presence of vesical catheter.

CONCLUSION

The use of long-term bladder drainage in patients presenting severe symptoms of benign prostatic hyperplasia is associated to the reduction of morphometric parameters of the nuclei of the prostatic glandular epithelial cells, suggesting a possible decompressive duct effect.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Walsh PC: Campbell's Urology. Philadelphia, WB Saunders. 1986; pp.1248.
2. Koskimaki J, Hakama M, Huhtala H, Tammela TL: Prevalence of lower urinary tract symptoms in Finnish men: a population-based study. Br J Urol. 1998; 81: 364-9.
3. Girman CJ: Population-based studies of the epidemiology of benign prostatic hyperplasia. Br J Urol. 1998; 82 (Suppl 1): 34-43.
4. Berry SJ, Coffey DS, Walsh PC, Ewing LL: The development of human benign prostatic hyperplasia with age. J Urol. 1984; 132: 474-9.
5. Boyle P: Some remarks on the epidemiology of acute urinary retention. Arch Ital Urol Androl. 1998; 70: 77-82.
6. Ichiyanagi O, Nakada T: Correlations between parameters in pressure-flow analysis and histological compositions in prostate in patients with benign prostatic hyperplasia. Urol Int. 1997; 59: 154-60.
7. Bailey DM, Foley SJ, McFarlane JP, O'Neil G, Parkinson MC, Shah PJ: Histological changes associ-

ated with long-term urethral stents. Br J Urol. 1998; 81: 745-9.
8. Shapiro E, Hartanto V, Perlman EJ, Tang R, Wang B, Lepor H: Morphometric analysis of pediatric and nonhyperplastic prostate glands: evidence that BPH is not a unique stromal process. Prostate. 1997; 33: 177-82.
9. Zlota A, Sattar AA, Wespes E, Noel JC, Schulman CC: Is one single prostate biopsy helpful for choosing a medical treatment of benign prostatic hyperplasia? A quantitative computerized morphometric study. Urology. 1996; 47: 329-34.
10. Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al.: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992; 148: 1549-57; discussion 1564.
11. Nesbit RM: Transurethral prostatic resection: a discussion of some principles and problems. J Urol. 1951; 66: 362-72.
12. Campos GM. Programa GMC Basic Software Pesquisa Biológica®, versão 8.1 (de 2002). Faculdade de Odontologia de Ribeirão Preto da Universidade de São Paulo. 2004; http://www.forp.usp.br/restauradora/gmc/gmc.html.
13. Anderson JB, Grant JB: Postoperative retention of urine: a prospective urodynamic study. BMJ. 1991; 302: 894-6.
14. Saranga R, Matzkin H, Braf Z: Local microwave hyperthermia in the treatment of benign prostatic hypertrophy. Br J Urol. 1990; 65: 349-53.
15. Hastie KJ, Dickinson AJ, Ahmad R, Moisey CU: Acute retention of urine: is trial without catheter justified? JR Coll Surg Edinb. 1990; 35: 225-7.
16. Lepor H, Shapiro E: This month in investigative urology: alpha adrenergic innervation of the prostate: insights into pharmacotherapy of BPH. J Urol. 1990; 143: 590-1.
17. Hieble JP, Boyce AJ, Caine M: Comparison of the alpha-adrenoceptor characteristics in human and canine prostate. Fed Proc. 1986; 45: 2609-14.
18. Hauri D: Acute urinary obstruction. Ther Umsch. 1992; 49: 17-22.
19. Abrams PH, Shah PJ, Stone R, Choa RG: Bladder outflow obstruction treated with phenoxybenzamine. Br J Urol. 1982; 54: 527-30.
20. Caine M, Raz S, Zeigler M: Adrenergic and cholinergic receptors in the human prostate, prostatic capsule and bladder neck. Br J Urol. 1975; 47: 193-202.
21. Bierhoff E, Vogel J, Benz M, Giefer T, Wernert N, Pfeifer U: Stromal nodules in benign prostatic hyperplasia. Eur Urol. 1996; 29: 345-54.
22. Unger PD, Hoon V, Stone N, Liu Z, Theise N, Stock R, et al.: Computerized interactive morphometry in the differential diagnosis of irradiated prostates. Anal Quant Cytol Histol. 1995; 17: 100-8.
23. Shapiro E, Becich MJ, Hartanto V, Lepor H: The relative proportion of stromal and epithelial hyperplasia is related to the development of symptomatic benign prostate hyperplasia. J Urol. 1992; 147: 1293-7.
24. Weibel ER: Principles and methods for the morphometric study of the lung and other organs. Lab Invest. 1963; 12: 131-55.
25. Frydenberg M, Foo TM, Jones AS, Grace J, Hensley WJ, Rogers J, et al.: Benign prostatic hyperplasia—video image analysis and its relationship to androgen and epidermal growth factor receptor expression. J Urol. 1991; 146: 872-6.
26. Wilson MJ, Ruhland AR, Quast BJ, Reddy PK, Ewing SL, Sinha AA: Dipeptidylpeptidase IV activities are elevated in prostate cancers and adjacent benign hyperplastic glands. J Androl. 2000; 21: 220-6.
27. Kanamaru H, Zhang YH, Takahashi M, Nakamura N, Ishida H, Akino H, et al.: Analysis of the mechanism of discrepant nuclear morphometric results comparing preoperative biopsy and prostatectomy specimens. Urology. 2000; 56: 342-5.
28. Szafranski JD, Grodzinsky AJ, Burger E, Gaschen V, Hung HH, Hunziker EB: Chondrocyte mechanotransduction: effects of compression on deformation of intracellular organelles and relevance to cellular biosynthesis. Osteoarthritis Cartilage. 2004; 12: 937-46.
29. Rivello HG, Meckert PC, Vigliano C, Favaloro R, Laguens RP: Cardiac myocyte nuclear size and ploidy status decrease after mechanical support. Cardiovasc Pathol. 2001; 10: 53-7.

Accepted after revision:
January 3, 2006

Correspondence address:
Dr. Carlos Abib Cury
Department of Urology
FAMERP
Avenida Brigadeiro Faria Lima, 5416
São José do Rio Preto, SP, 15090-000, Brazil
Fax: + 55 17 227-6404
E-mail: batigalia@riopreto.com.br

International Braz J Urol Vol. 32 (2): 216-221, March - April, 2006

Interference of Enalaprilat on Glomerular Permeability to Macromolecules (IgG) in Acute Unilateral Ureteral Obstruction in Rats

Rene M. Oliveira, Antonio A. Oliveira Neto, Luiz C. Miranda

Section of Urology, Clementino Fraga Filho University Hospital, UFRJ, Rio de Janeiro, RJ, Brazil

ABSTRACT

Introduction: Unilateral ureteral obstruction breaks out events that cause the transitory increase of glomerular permeability to macromolecules, both in the obstructed kidney and in the contralateral kidney, suggesting the presence of some factor, with a systemic action, liberated as a response to the obstruction. We know that the rennin-angiotensin system is activated by acute ureteral obstruction. We have developed an experiment to assess the role of angiotensin II on the glomerular permeability to IgG due to acute ureteral obstruction, using enalaprilat, an angiotensin enzyme conversion inhibitor, to block the effects of the activation of the rennin-angiotensin system.
Materials and Methods: We have used 45 adult Wistar female rats, distributed into 3 main groups: a control group with 5 animals and 2 experiment groups each one with 10 animals submitted to unilateral ureteral obstruction and nephrectomy at 60 and 120 minutes. Each experiment group had its simulation correspondent (sham). We have studied both kidneys through the direct immunofluorescence method.
Results: We have found positive permeation in animals without enalaprilat in both kidneys and negative permeation in those in which the drug was used.
Conclusion: We have concluded that enalaprilat interferes in this alteration of permeability, suggesting that angiotensin II is involved in the loss of selectivity of the glomerular membrane.

Key words*: ureteral obstruction; immunoglobulin G; angiotensin II; enalaprilat; immunofluorescence*
Int Braz J Urol. 2006; 32: 216-21

INTRODUCTION

Acute ureteral obstructions a common situation in urological practice. The obstructed kidney suffers both rough morphologic alterations and microscopic ones, which were demonstrated in experimental studies and through the study of surgical specimens (1-4).

In a line of research on the alterations of glomerular permeability to macromolecules in an experimental situation of acute unilateral ureteral obstruction, Henriques (5) demonstrated the permeation of rat endogenous IgG through the glomerular mesangium of the obstructed kidney. Interestingly enough, he also observed a similar phenomenon in contralateral kidney, without blockage to the urinary flow, in more intensity between 60 and 120 minutes after the obstruction.

This alteration of selectivity of the glomerular blockage on the contralateral kidney makes

us suppose the action of some factor that has been liberated by the acute ureteral obstruction and that has a systemic action.

Acute ureteral obstruction is a potent activator of the rennin-angiotensin system that once activated is capable of promoting systemic actions (6-10). Based on this information, we have developed an experiment using acute unilateral obstruction as a factor to activate the rennin-angiotensin system, both to observe the selectivity alteration of the permeability of the glomerular filtration blockage after this activation and to verify the responsibility of angiotensin II in the phenomenon of the alteration of the selective permeability of the glomerular filtration membrane.

To test our hypothesis we have used an angiotensin I enzyme conversion inhibitor for angiotensin II as a blocker to the events broken out by the activation of the rennin-angiotensin system. We have proceeded to the histopathological analysis, through the direct immunofluorescence technique, both of the obstructed kidney and of the kidney without obstruction.

MATERIALS AND METHODS

We used forty-five Wistar albino female rats with weights varying from 240 to 300g (255.55 ± 9.35 g.) and aged 8 months. Animals were kept in the animal room of the Experimental Lab, in individual cages, were fed with industrialized food used by the animal room and water ad libitum. At the day of the surgery, they were on a fast of solid foods. The weight of each animal was checked before surgery. The experimental protocol was approved by the animal research ethics commission.

Animals were divided into 3 groups: Group 1 - control (5 animals), Group 2 – ureteral ligature (10 animals) and Group 3 – enalaprilat previous to the ureteral ligature (10 animals). All animals were submitted to bilateral nephrectomy. On groups 2 and 3, nephrectomy was accomplished in half of the animals at 60 minutes and on the other half at 120 minutes. Groups 2 and 3 have simulation correspondents (sham).

The enalaprilat was the drug used in the experiment, in the form of injectable solution. The dosage used was 1mg/kg, adequate for the obtainment of the angiotensin enzyme conversion inhibitor effect in animals (11). In those animals in which enalaprilat was used its administration was made by injection in the inferior vena cava 15 minutes before the ureteral ligature, time enough for the distribution of the drug and the obtainment of the angiotensin enzyme conversion inhibitor effect (11). For sham groups we have administered distilled water.

We have used sevoflurane as inhaling anesthetic agent, administered by means of a vaporizing device for small animals anesthesia developed by the experimental lab.

The animals were submitted to median laparotomy, we have identified the left ureter using an optic magnification with a 2.5X surgical magnifier, and we performed the complete ureteral occlusion in its upper 1/3 with cotton 3-0 suture.

Once the ureteral occlusion time set forth in this work's protocol was finished, we performed the bilateral nephrectomy and the animals, still under anesthesia were transposed to a glass shade saturated with sulphuric ether for the euthanasia to be performed.

All surgical specimens at the moment of their extraction were longitudinally cleavage, involved in aluminum paper, identified by group, animal number and side (left or right) and stored in a liquid nitrogen container.

For direct immunofluorescence reaction, we use antiserum for rat IgG (sheep anti rat IgG:FITC – AAR10F).

Histopathologic analysis started after the obtainment of all surgical specimens with the application of the direct immunofluorescence technique, in histological sections of preserved tissue. Group after group the material was prepared and observed in a Zeiss microscope. The elapsed time between the preparation and the reading of each group of slides took no longer than 2 hours, and all histopathological analysis was performed in 4 days. The processed material corresponded to the totality of each kidney, since the organs were not larger than 2 cm in the major axis. We proceeded the observation of all glomeruli and the results were collected from this analysis.

In histopathological analysis, we considered positive mesangial staining when we observed a green brilliant coloration highlighting the glomeruli under the microscope ultraviolet light, and negative when this staining was continuous with background coloration or inexistent.

The most representative fields were selected for illustration with image registration by Nikon-Coolpix de 3.44 megapixels adapted to the microscope with automatic saturation, brightness and contrast adjustment and exposure time of 1/2 second.

Statistical analysis was performed by Fisher exact test to compare positivity among studied groups. The criterion of significance is 5%. Statistical analysis was processed by the statistical software SAS® System.

RESULTS

In the control group the mesangial staining was negative.

All 10 animals of group 2 presented positive mesangial staining, and one animal of the sham group also presented positive staining. We have observed that the proportion of positive results in group 2 was significantly larger than in the sham group ($p < 0.0001$).

All animals of group 3 presented negative mesangial staining but one animal of the sham group presented positive mesangial staining. Statistical analysis demonstrated that there was no significant difference between the 2 groups ($p = 0.50$).

Comparison between group 2 and 3 showed a significant difference with $p < 0.0001$.

On Figure-1 we present the photomicrography of a glomerulus with positive mesangial staining.

COMMENTS

It is a consensus among investigators that, in physiologic conditions, macromolecules the size of IgG (molecular radius of approximately 55 Å, molecular weight of 150.000 Daltons) are not found in significant quantities in the glomerular filter but can be detected in the mesangium. There is, however, a physiological transit of macromolecules through the vascular endothelium fenestrations of the glomerular tuft, but are retained by the basal membrane and by the filtration diaphragm and come back to the intravascular space, via the lymphatics, or they are metabolized by mesangial cells without immunological reaction involved in this process (12-16).

Acute ureteral unilateral obstruction causes alterations in glomerular perfusion and in the glomerular filtration rate. Those alterations act as activators of the rennin-angiotensin system, with the increase in the secretion of rennin through the obstructed kidney, be it by a reduction in the concentration of sodium in the distal tubules, be it by baroreceptors distension localized in the afferent arteriole. (1,3,4).

The hypothesis is that the phenomenon of IgG endogenous permeability by glomerular filtration barrier of the animals submitted to acute unilateral ureteral obstruction, observed both in the obstructed kidney and in the contralateral kidney is related to the effects promoted by endogenous angiotensin II. Liberated from the activation of the rennin-angiotensin system broke out by the acute ureteral obstruction.

Alterations of glomerular filtration during unilateral ureteral obstruction were already described from the 5 to 8 minutes occlusion, in the affected kidney (3). In experimental work of unilateral ureteral

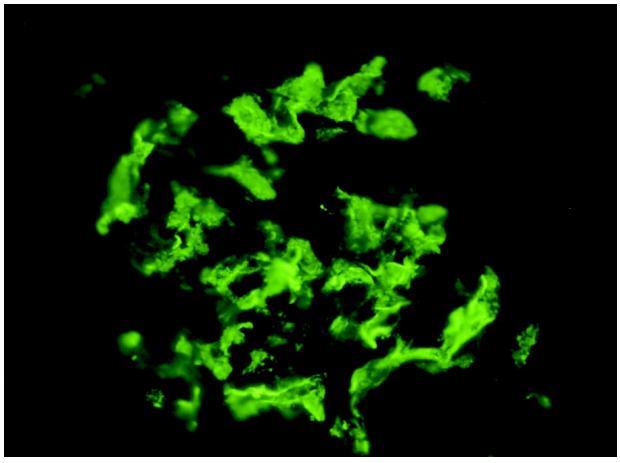


Figure 1 – *Histological study showing positive glomerular staining (direct immunofluorescence, X400).*

obstruction, Henriques (5) demonstrated the passage of macromolecules (IgG) for the mesangium, a precocious and transitory phenomenon that is most intensively manifested between 60 and 120 minutes after the installation of the unilateral ureteral obstruction, and is reduced after 120 minutes of obstruction, but was observed in both kidneys. However, it seemed to be valid to focus our study in this period of time. This is a model that makes more intense the mesangial transit of macromolecules, a phenomenon that can be easily demonstrated by the technique of direct immunofluorescence but does not involve immunologic processes.

We have observed that pertinent literature is poor in relation to this experiment, for, in general, only the obstructed kidney is analyzed. In this work we have considered only the qualitative aspect of the event for we supposed that angiotensin II participates in the alteration of the glomerular filtration barrier selectivity. We did not try to determine the intensity of this action, or if other substances liberated in response to the ureteral obstruction can alter this selectivity. We have made a ureteral obstruction and kidney extraction in subgroups of 60 and 120 minutes after the ureteral obstruction, for we do not have data on the time interval necessary to occur the probable action of the angiotensin II over the glomerular selectivity.

To test our hypothesis that the alteration of the glomerular permeability is related to the action of the angiotensin II, we use the pharmacologic obstruction of the angiotensin conversion enzyme, through the injection of enalaprilat before we performed a ureteral obstruction.

The study of the control group demonstrates that in a normal situation the mesangial transit of endogenous IgG is not detectable through the direct immunofluorescence technique since there was no positive staining in the kidney of those animals.

The study of the animals of group 2 evidences the intense permeability of IgG through the glomerular mesangium, demonstrated by the positive staining of both kidneys.

This mesangial transit can be influenced by the capilar hydrostatic pressure, by the molecular weight and protein electrical charge and by factors related to the mesangial matrix selectivity properties that can be altered as demonstrated in experimental situations, with the infusion of angiotensin II (1,13,14,17).

When we observe the animals of group 2 (sham), we observe that one of the animals sacrificed at 60 minutes presented a positive mesangial staining. This data was not statistically significant, however, we can consider that factors activated by surgical procedure, unchained by the neuroendocrine reaction of the organic trauma, or other humoral mediators involved in the response to the acute unilateral ureteral obstruction, such as aracdonic acid metabolites (eicosanoids), the atrial natriuretic peptide, nitric oxide, endotelin, plaquetary activation factor, clusterin and the growth and transformation factor β can also interfere in the glomerular filtration barrier permselectivity (3). We have made this registration as a possibility to develop other experiments in the same line of research.

The analysis of group 3 demonstrated that the use of an angiotensin enzyme conversion inhibitor interfered in the IgG mesangial transit, for we did not observe positive staining in one of the animals of group 3 (sham), sacrificed at 60 minutes of obstruction, that reinforces considerations over other factors involved in the alteration of the glomerular permeability even though this data does not have any statistical significance to this study.

The alteration of selectivity of the glomerular filtration membrane in the obstructed kidney was previously described (13,17,18), however, the observation of the change in the glomerular filtration permselectivity in the contralateral kidney, observed in this work and previously reported (5,19), makes us suppose the action of some factor that has a systemic action affecting such selectivity at distance, relating the loss of the glomerular filtration barrier selectivity with the increase of the mesangial transit of macromolecules in situation of activation of the rennin-angiotensin system.

When we compare groups 2 and 3, we find a significant difference that points out to the validity of the experiment to demonstrate the increase of the IgG mesangial transit in the ureteral obstruction with positive staining in both kidneys of the ani-

mals of group 2, and the interference caused by the obstruction of the angiotensin conversion enzyme with negative staining in the kidneys of the animals of group 3.

Our interpretation thus, is that there are statistical evidences of the interference of enalaprilat over the permeability of IgG in the acute unilateral ureteral obstruction.

CONCLUSIONS

We concluded that the acute unilateral ureteral obstruction in the rat, causes alteration of the glomerular selective filtration in the kidney free of obstruction, allowing the permeability of endogenous IgG.

There are evidences that the use of enalaprilat presents interference in the endogenous IgG permeability by the glomerular filtration membrane of the kidney free of obstruction in the rat.

Angiotensin II, one of the humoral factors liberated by the acute ureteral obstruction is related to the glomerular filtration membrane permselectivity of the kidney free of obstruction in the rat, observed between 60 and 120 minutes of ureteral obstruction.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. D'Amico G, Bazzi C: Pathophysiology of proteinuria. Kidney Int. 2003; 63: 809-25.
2. Nangaku M: Final common pathways of progression of renal diseases. Clin Exp Nephrol. 2002; 6: 182-9.
3. Gulmi FA, Felse D, Vaugham ED Jr: Pathophysiology of Urinary Tract Obstruction. In: Walsh PC (ed.), Campbell's Urology. Philadelphia, Saunders. 2002; pp. 411-62.
4. Wen JG, Frokiaer J, Jorgensen TM, Djurhuus JC: Obstructive nephropathy: an update of the experimental research. Urol Res. 1999; 27: 29-39.
5. Henriques FP: Immunoglobulin Absorption by the Glomerular Mesangium in Rats with Ureteral Obstruction. Thesis (Doctoral Degree in Surgery). Federal University of Rio de Janeiro, UFRJ, Brazil, 1998. [in Portuguese]
6. Frokiaer J, Pedersen EB, Knudsen L, Djurhuus JC: The impact of total unilateral ureteral obstruction on intrarenal angiotensin II production in the polycalyceal pig kidney. Scand J Urol Nephrol. 1992; 26: 289-95.
7. Frokiaer J, Knudsen L, Nielsen AS, Pedersen EB, Djurhuus JC: Enhanced intrarenal angiotensin II generation in response to obstruction of the pig ureter. Am J Physiol. 1992; 263: F527-33.
8. Klahr S, Ishidoya S, Morrissey J: Role of angiotensin II in the tubulointerstitial fibrosis of obstructive nephropathy. Am J Kidney Dis. 1995; 26: 141-6.
9. Oliw E: Acute unilateral ureteral occlusion increases plasma renin activity and contralateral urinary prostaglandin excretion in rabbits. Eur J Pharmacol. 1978; 53: 95-102.
10. Pimentel JL Jr, Martinez-Maldonado M, Wilcox JN, Wang S, Luo C: Regulation of renin-angiotensin system in unilateral ureteral obstruction. Kidney Int. 1993; 44: 390-400.
11. Tocco DJ, deLuna FA, Duncan AE, Vassil TC, Ulm EH: The physiological disposition and metabolism of enalapril maleate in laboratory animals. Drug Metab Dispos. 1982; 10: 15-9.
12. Deen WM, Lazzara MJ, Myers BD: Structural determinants of glomerular permeability. Am J Physiol Renal Physiol. 2001; 281: F579-96.
13. Keane WF, Raij L: Relationship among altered glomerular barrier permselectivity, angiotensin II, and mesangial uptake of macromolecules. Lab Invest. 1985; 52: 599-604.
14. Michael AF, Keane WF, Raij L, Vernier RL, Mauer SM: The glomerular mesangium. Kidney Int. 1980; 17: 141-54.
15. Olivetti G, Kithier K, Giacomelli F, Wiener J: Glomerular permeability to endogenous proteins in the rat: effects of acute hypertension. Lab Invest. 1981; 44: 127-37.
16. Raij L, Keane WF: Glomerular mesangium: its function and relationship to angiotensin II. Am J Med. 1985; 79: 24-30.
17. Lapinski R, Perico N, Remuzzi A, Sangalli F, Benigni A, Remuzzi G: Angiotensin II modulates glomerular capillary permselectivity in rat isolated perfused kidney. J Am Soc Nephrol. 1996; 7: 653-60.

18. Mayer G, Lafayette RA, Oliver J, Deen WM, Myers BD, Meyer TW: Effects of angiotensin II receptor blockade on remnant glomerular permselectivity. Kidney Int. 1993; 43: 346-53.

19. Miranda LC: Behavior of Immunoglobulin G and M in the Renal Ischemia Reperfusion in Rats. Immunofluorescence Study. Thesis (Doctoral Degree in Surgery). Federal University of Rio de Janeiro, UFRJ, Brazil, 1992; p. 91. [in Portuguese]

Accepted after Revision:
January 5, 2006

Correspondence address:
Dr. René Murilo de Oliveira
Rua Conde de Irajá, 97/404 - Botafogo
Rio de Janeiro, RJ, 22 271-020, Brazil
E-mail: renemurilo@aol.com

Investigative Urology
International Braz J Urol Vol. 32 (2): 222-227, March - April, 2006

Histological and Histochemical Changes of the Intestinal Mucosa at the Urothelial-Enteric Anastomotic Site

Marcos A. Castro, Ubirajara Ferreira, Mario H. Martins, Rafael M. Stoppiglia, N. Rodrigues Netto Jr.

Division of Urology, State University of Campinas, UNICAMP, Campinas, Sao Paulo, Brazil

ABSTRACT

Objective: The incorporation of bowel segments for urinary tract reconstruction may induce intestinal mucosal changes with the development of metabolic, nutritional, gastrointestinal and carcinogenic complications. The early histological and histochemical changes of the intestinal mucosa in contact with the feces-urine mixture, are evaluated in the present study.
Materials and Methods: Twelve rats (operated group) were submitted to a vesico-colonic anastomosis, and 10 rats (control group) underwent a sham operation (the colon was opened and immediately sutured). On the operated group, the left colon was divided into 3 equal portions and the middle segment was used for the bladder-colonic anastomosis. After 20 weeks, the animals were sacrificed and the entire left colon in each group, as well as the bladder and the vesico-colonic anastomosis in the operated group, was removed. The proximal, middle (anastomotic site in the operated group and sutured portion in the control group) and distal colon were used for histological and histochemical studies.
Results: Metaplasia, chronic inflammatory process and fibrosis were significantly greater at the anastomotic site compared to the middle segment of the control group. There were no differences in both groups in terms of dysplasia, atrophy and hypertrophy either on the proximal, middle or anastomotic area and distal portion of the left colon. All animals in the operated group showed a reduced presence of sulfomucin and an increase in the sialomucin content.
Conclusion: The histological changes observed in this study may suggest a precancerous phenomenon.

***Key words**: urinary diversion; colonic urinary reservoirs; mucins; carcinogens; rats*
Int Braz J Urol. 2006; 32: 222-7

INTRODUCTION

The incorporation of bowel segments for urinary tract reconstruction induces intestinal mucosal changes with the development of metabolic, nutritional, gastrointestinal and carcinogenic complications.

The association of urinary-colonic diversions, specially the ureterosigmoidostomy, and the higher incidence of colonic adenocarcinoma are well established and may be multifatorial (1).

There are several theories to explain the carcinogenesis of colon tumors following ureterosigmoisdostomy. Some of these theories include the formation of nitrosamines by bacterially reduced urinary nitrate and endogenous amines in feces and urine mixture (2-4), chronic urothelial irritation by feces, epithelial instability at the anastomotic site (1), the presence of fresh colonic suture (1) and irritative changes of the colonic epithelium caused by the presence of feces-urine mixture (4-6).

A risk factor for neoplasms around the urinary-colonic anastomosis may be alterations of mucous glycoproteins in the surrounding colonic mucosa of the anastomosis. Studying these alterations would be of great value to find a marker of premalignant change in patients at risk of developing these colonic tumors (7).

The aim of this study is to assess the early histological and histochemical changes of the intestinal mucosa in contact with the feces-urine mixture.

MATERIALS AND METHODS

Two groups of adult female Wistar rats (Botucatu, Brazil) weighing 190 to 280g were used. All rats were fed with water ad libitum and standard rat chow.

All rats were anesthetized, after a 12-hour fast, by intraperitoneal injection of pentobarbital sodium (4 mg / 100g of body weight).

Ten rats in the first group (control group) underwent a sham operation (the middle part of the left colon was opened and immediately closed by a running 6-0 polyglycolic suture) (Figure-1).

In the second group (operated group), a vesico-colonic anastomosis was created in 12 rats, according to the ureterosigmoidostomy model already described in the literature (3,8). The left colon was divided into three equal portions of 1.8 cm (Figure-1) above the rectal peritoneal reflection. On the operated group, the middle portion was used for the bladder-colon anastomosis. First, the bladder neck was closed with 4-0 silk suture, the dome of the bladder was opened and a vesico-colonic fistula

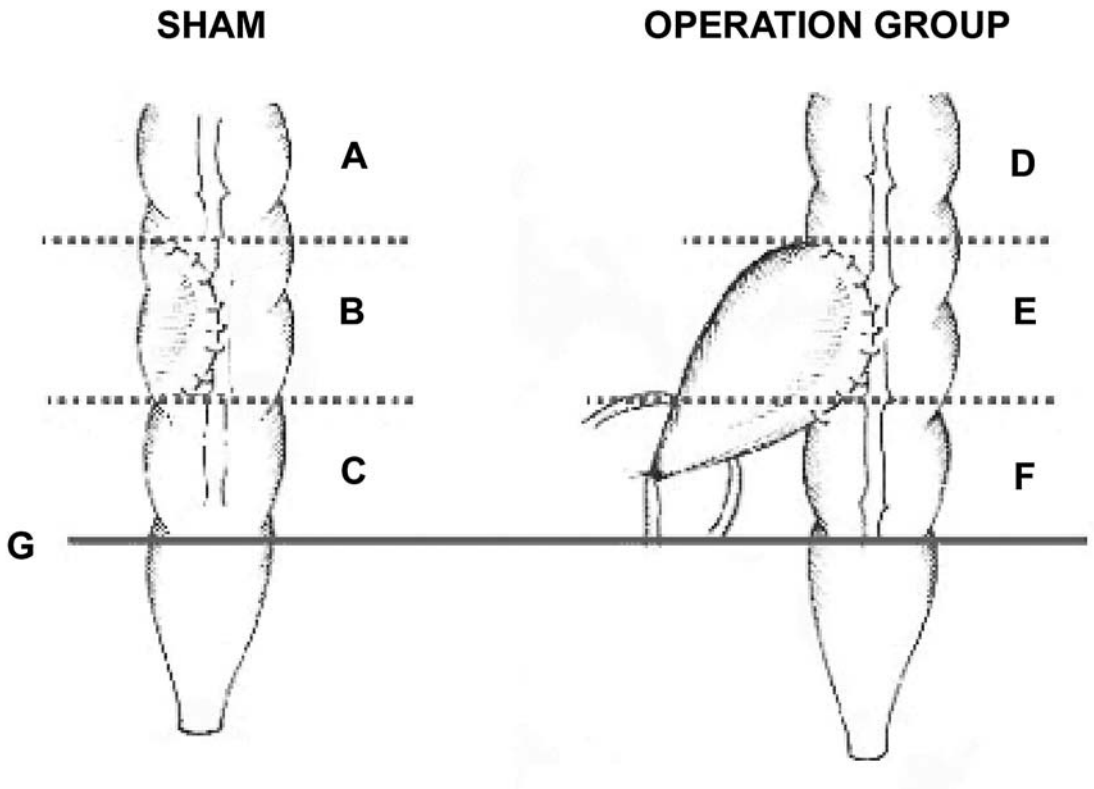


Figure 1 – *Diagram of division of the proximal segments of the left colon above the peritoneal reflection used to collect tissue fragments on the rat's distal colon. Note the vesico-colonic anastomosis and the suture in the left colon. A = proximal colon; B = middle colon; C = distal colon; D = proximal colon; E = anastomotic site; F = distal colon e G = rectal peritoneal reflection.*

was created by a running 6-0 polyglycolic suture (Figure-1).

Antibiotic therapy (cefalexin 1-3 mg / 100 g / day) was added to the drinking water and administered in the experiment.

After 20 weeks all animals were sacrificed and inspected grossly for colonic or bladder lesions. At this time, the body weight of the animals was not different. The entire left colon of the animals in both groups as well as the bladder-colon anastomosis in the operated group were removed in bloc for histological and histochemical studies.

For histological studies, the biopsy specimens were fixed in 10% formalin solution and imbedded in paraffin. Five micrometers thick sections were stained with hematoxylin-eosin for evaluation of the morphology of the epithelial cells and the lamina propria. The epithelial cell sections were examined for the presence of dysplasia and metaplasia. In the lamina propria the amount of fibrosis, and either acute or chronic inflammatory process, were registered. The muscularis propria was examined for atrophy and hypertrophy.

The histochemical studies performed were periodic acid-Schiff (PAS) and alcian blue (AB) stains for the evaluation of neutral mucin and the overall acid mucin content, respectively. The high iron-diamine alcian blue - pH 2.5 - (HIDAB) (7,9) was used to differentiate acid sulfomucins from sialomucins.

The variables were divided into six grades: moderately and mildly reduced or increase (for histochemical studies); and normal, mild, moderate or severe changes (histopathological analysis).

Two pathologists reviewed all slides. Results obtained were evaluated and the statistical differences were analyzed by the non-parametric Mann-Whitney test.

RESULTS

There was no statistical difference on dysplasia in tissue sections between the two groups (Table-1). The metaplasia changes were significantly greater at the anastomosis site compared to the middle segment sutured on the control group ($p < 0.05$) (Table-1).

Although the acute inflammatory process on the lamina propria had been greater in all the three intestinal segments of the animals in the operated group, no statistical differences were noted. The same results were seen with the chronic inflammatory process on the proximal and distal portions of the operated group. However, this process was significantly greater on the anastomotic area as compared to the middle segment of the control group ($p < 0.05$) (Table-1) (Figure-2).

An interesting finding was the presence of mild fibrosis on the proximal and distal segments of the left colon in the operated group. An increased amount of fibrosis was registered at the anastomotic site when compared with the sham group ($p < 0.05$) (Table-1). The muscle layers were normal in the operated group.

A significant reduction in the amount of acid and neutral mucins was noted at the anastomotic site of the operated group ($p < 0.001$). In contrast, only a

Table 1 – *Presence of histological mucosal findings at the anastomotic area.*

	Control Group	Operation Group
Dysplasia	0	+
Metaplasia	0	+++ ♣
Acute inflammatory process	+	++
Chronic inflammatory process	0	+++ ♣
Fibrosis	+	+++ ♣
Atrophy	0	0
Hypertrophy	0	0

0 = not present; + = middle change; +++ = severe change; ♣ = significant difference ($p < 0.05$) (Mann Whitney U-test).

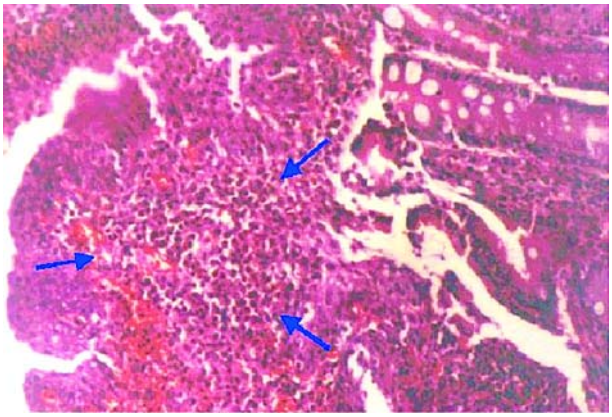


Figure 2 – *Histologic section of the anastomotic site taken from an animal showing marked chronic inflammatory process on the lamina propria, arrows (HE, X100).*

mild amount of acid and neutral mucins was present in the proximal and distal segments of the left colon (Table-2) (Figure-3).

All animals in the operated group presented a decrease in the amount of sulfomucin and an increase in the sialomucin content in the left colon. However, this change in secretion of sulfomucin and sialomucin, was significant only at the anastomotic site ($p < 0.05$) (Table-2) (Figure-3).

COMMENTS

The mucosa of the intestinal segments used in the reconstruction of the urinary tract undergoes structural changes along time. The most important is the appearance of neoplasia, the incidence of colon cancer in the area of the anastomosis is 100 to 500 times higher than in the general population (10-12). In humans, the latency period of the onset of tumors ranges from five to forty-five years, average twenty years (7).

Several theories have been proposed to explain the genesis of the tumors after ureterosigmoidostomy, but the presence of the mixture of urine and feces, the role of bacteria in production of N-nitrosamines, and changes in mucous secretion into the intestines, deserve special attention (7,13,14).

Under experimental conditions, the therapy with ascorbic acid has reduced the production of dimethyl-nitrosamines with no apparent reduction in the incidence of tumors (8).

The surge of cancer at the level of the ureterosigmoidostomy anastomosis is prevented by a

Table 2 – *Presence of histochemical mucosal findings at the anastomotic area.*

Mucines	Control Group	Operation Group
Acid	0	↓↓ *
Neutral	0	↓↓ *
Sulfomucins	0	↓↓ ♣
Sialomucins	0	++ ♣

*0 = not present; ↓↓ = reduced amount; ++ = moderate increase; ♣ = significant difference ($p < 0.05$, Mann Whitney U-test); * = significant difference ($p < 0.001$, Mann Whitney U-test).*

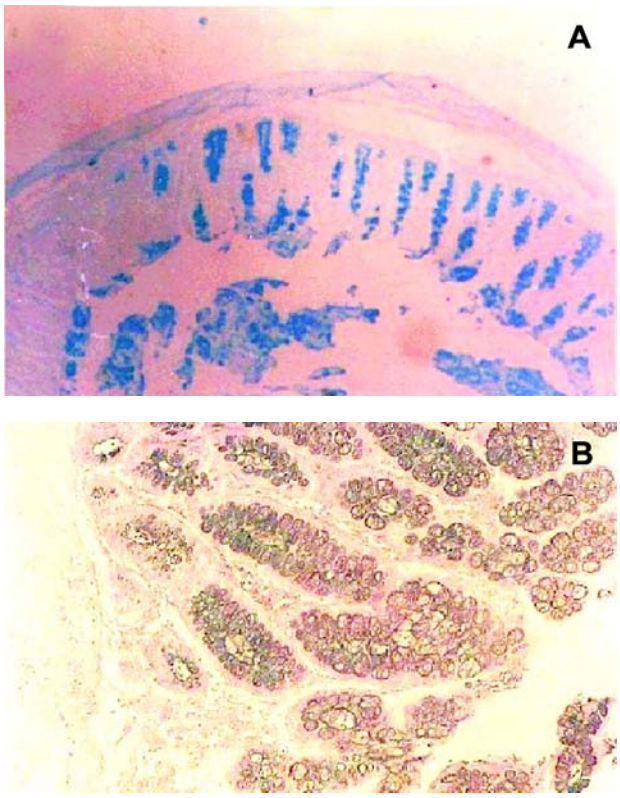


Figure 3 – *Histologic section of biopsy taken from the anastomotic site showing marked reduction of acid mucins in the goblet cells (A), (AB, X40), and an increase of sialomucins and a mild reduction of sulfomucins (B), (HIDAB, X100).*

colostomy proximal to the anastomotic site, which may suggest the existence of fecal carcinogens eventually activated by the urine or by the urothelial epithelium (3).

Previous studies have shown that the intestinal mucosa in contact with the urine undergoes changes beginning three years after surgery (10,12). It is known that the rat lifespan ratio to human is estimated to be 1:30 (15).

The presence of dysplasia is expected after vesico-colonic anastomosis in rats (2,16). In our investigation the presence of dysplasia was not significantly different from the controls, which could possibly be attributed to the timing of the experiment. However, metaplasia was found in the animals of the operated group. Other experimental reports confirm this finding and have suggested the presence of an unstable, artificially produced borderline tissue between transitional cell epithelium and mucosal irritation (17,18). Also chronic inflammation in 15 children submitted to colon-ureterostomies has been reported and established as a precursor of malignancy (5). The same changes were found in the lamina propria, in the present study.

The overall presence of fibrosis was significantly greater at the anastomotic site of the operated group. This finding was also observed in ileo-colonic segments in rats, which perhaps reflects a chronic tissue repair due to aggression (12).

Mucins are high-molecular weight glycoproteins secreted and produced by the goblet cells of the gastrointestinal tract and have a protective effect on the gut. They may be categorized histochemically as neutral or acid and, according to their content of sialic acid or sulphate, the acid mucins are subdivided into sialomucins and sulphomucins.

The decrease in the content of acid and neutral mucins at the anastomotic area with AB and PAS staining was also observed elsewhere (19-21).

The histochemical changes of the content of the goblet cell mucin with the HIDAB staining demonstrated a shift on the standard distribution, that is, an increase on sialomucins and a great decrease of the sulfomucins at the anastomotic area forming the so-called “transitional mucosa”. Some investigators suggested that the presence of sialomucins may be primary or a precancerous phenomenon and not secondary to the tumor (7,22-25).

Although other reports claim that this shift on the sialic mucin content could represent only an unstable colon epithelium exposed to additional aggression, there is enough evidence that greater increases in sialomucin are related to higher risk of developing colon cancer (7,26-29).

Intensive research is required for a better understanding of this subject.

CONCLUSION

The histological and histochemical changes observed in this study may suggest a precancerous phenomenon.

All urinary diversions that include bowel need regular evaluation, and, whenever possible, biopsies must be taken from the surrounding mucosa of the anastomosis for histological and histochemical analysis, looking for premalignant changes.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Gittes RF: Carcinogenesis in ureterosigmoidostomy. Urol Clin North Am. 1986; 13: 201-5.
2. Cohen MS, Hilz ME, Davis CP, Anderson MD: Urinary carcinogen [nitrosamine] production in a rat animal model for ureterosigmoidostomy. J Urol. 1987; 138: 449-52.
3. Crissey MM, Steele GD, Gittes RF: Rat model for carcinogenesis in ureterosigmoidostomy. Science. 1980; 207: 1079-80.
4. Kalble T, Tricker AR, Mohring K, Berger MR, Geiss H, Staehler G: The role of nitrate, nitrite and N-nitrosamines in carcinogenesis of colon tumours following ureterosigmoidostomy. Urol Res. 1990; 18: 123-9.
5. Moorcraft J, DuBoulay CE, Isaacson P, Atwell JD: Changes in the mucosa of colon conduits with particular reference to the risk of malignant change. Br J Urol. 1983; 55: 185-8.

6. Starling JR, Uehling DT, Gilchrist KW: Value of colonoscopy after ureterosigmoidostomy. Surgery. 1984; 96: 784-90.
7. Shimamoto C, Hirata I, Takao Y, Takiuchi H, Morikawa H, Nakagawa Y, et al.: Alteration of colonic mucin after ureterosigmoidostomy. Dis Colon Rectum. 2000; 43: 526-31.
8. Shands C 3rd, McDougal WS, Wright EP: Prevention of cancer at the urothelial enteric anastomotic site. J Urol. 1989; 141: 178-81.
9. Spicer SS: Diamine methods for differentialing mucosubstances histochemically. J Histochem Cytochem. 1965; 13: 211-34.
10. Philipson BM, Kock NG, Hockenstrom T, Norlen LJ, Ahren C, Hansson HA: Ultrastructural and histochemical changes in ileal reservoir mucosa after long-term exposure to urine. A study in patients with continent urostomy (Kock pouch). Scand J Gastroenterol. 1986; 21: 1235-44.
11. Carlen B, Willen R, Mansson W: Mucosal ultrastructure of continent cecal reservoir for urine and its ileal nipple valve 2-9 years after construction. J Urol. 1990; 143: 372-6.
12. Davidsson T, Carlen B, Bak-Jensen E, Willen R, Mansson W: Morphologic changes in intestinal mucosa with urinary contact—effects of urine or disuse? J Urol. 1996; 156: 226-32.
13. Habs M, Schmahl D: Diet and cancer. J Cancer Res Clin Oncol. 1980; 96: 1-10.
14. Stewart M, Hill MJ, Pugh RC, Williams JP: The role of N-nitrosamine in carcinogenesis at the ureterocolic anastomosis. Br J Urol. 1981; 53: 115-8.
15. Peckham JC: Experimental oncology. In: Baker HJ, Lindsey JR, Weisbroth SH, The laboratory rat. Orlando, Academic Press. 1980; pp. 119-46.
16. Daher N, Gautier R, Abourachid H, Decaens C, Bara J: Rat colonic carcinogenesis after ureterosigmoidostomy: pathogenesis and immunohistological study. J Urol. 1988; 139: 1331-6.
17. Weber TR, Westfall SH, Steinhardt GF, Webb L, Sotelo-Avila C, Connors RH: Malignancy associated with ureterosigmoidostomy: detection by mucosa ornithine decarboxylase. J Pediatr Surg. 1988; 23: 1091-4.
18. Miersch WD, Vogel J: Induction of carcinoma at ureterosigmoid anastomosis—with and without faecal stream. Br J Urol. 1992; 69: 499-506.
19. Rubio CA, Rivera F: Quantification of acid mucins in the descending colon of rats having simultaneously growing colonic tumors. APMIS. 1991; 99: 993-6.
20. Shamsuddin AK, Trump BF: Colon epithelium. I. Light microscopic, histochemical, and ultrastructural features of normal colon epithelium of male Fischer 344 rats. J Natl Cancer Inst. 1981; 66: 375-88.
21. Schauffert MD, Simoes MJ, Juliano Y, Novo NF, Ortiz V: Long term histomorphometric evaluation of the villous and ileal goblet cells after ileocystoplasty in female rats. Int Braz J Urol. 2000; 26: 91-6.
22. Filipe MI, Branfoot AC: Abnormal patterns of mucus secretion in apparently normal mucosa of large intestine with carcinoma. Cancer. 1974; 34: 282-90.
23. Filipe MI: Mucous secretion in rat colonic mucosa during carcinogenesis induced by dimethylhydrazine. A morphological and histochemical study. Br J Cancer. 1975; 32: 60-77.
24. Dawson PM, Habib NA, Rees HC, Williamson RC, Wood CB: Influence of sialomucin at the resection margin on local tumour recurrence and survival of patients with colorectal cancer: a multivariate analysis. Br J Surg. 1987; 74: 366-9.
25. Wood CB, Dawson PM, Habib NA: The sialomucin content of colonic resection margins. Dis Colon Rectum. 1985; 28: 260-1.
26. Mori M, Shimono R, Adachi Y, Matsuda H, Kuwano H, Sugimachi K, et al.: Transitional mucosa in human colorectal lesions. Dis Colon Rectum. 1990; 33: 498-501.
27. Isaacson P, Attwood PR: Failure to demonstrate specificity of the morphological and histochemical changes in mucosa adjacent to colonic carcinoma (transitional mucosa). J Clin Pathol. 1979; 32: 214-8.
28. Strachan JR, Rees HC, Williams G: Histochemical changes after ureterosigmoidostomies and colonic diversion. Br J Urol. 1985; 57: 700-2.
29. Strachan JR, Matthews J, Rees HC, Cooke T: Kinetic changes in experimental colonic urinary diversion. Br J Surg. 1987; 74: 1046-8.

Accepted after revision:
January 4, 2006

Correspondence address:
Dr. Ubirajara Ferreira
Rua Vital Brasil, 250, 2o. Andar
Departamento de Cirurgia / Urologia
Cidade Universitária Zeferino Vaz - Barão Geraldo
Campinas, SP, 13083-888, Brazil
Fax: + 55 19 3788-7481
E-mail: ubirafer@uol.com.br

International Braz J Urol Vol. 32 (2): 228-253, March - April, 2006

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

Barry A. Kogan
Albany Medical College
Albany, New York, 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

Arnulf Stenzl
University of Tuenbingen
Tuebingen, Germany

STONE DISEASE

Self-Retaining Ureteral Stents: Analysis of Factors Responsible For Patients' Discomfort

El-Nahas AR, El-Assmy AM, Shoma AM, Eraky I, El-Kenawy MR, El-Kappany HA
Mansoura Urology & Nephrology Center, Mansoura, Egypt
J Endourol. 2006; 20: 33-7

Purpose: To determine factors affecting patients' discomfort during the period self-retaining ureteral stents are in place.
Patients and Methods: Between April 2001 and May 2003, 58 male and 42 female patients underwent temporary double-pigtail stenting. The indications were endopyelotomy in 39 patients, ureteroscopy in 32, laparoscopic pyeloplasty in 18, and endoureterotomy in 11. The stents were silicone in 56 patients and Percuflex in 44. The median stenting period was 8 weeks (range 4-16 weeks). Patient discomfort was evaluated by a questionnaire conducted by the physician before stent removal. Tested variables were patients' sex, side of the stent, urine culture, stent material, stent length and diameter, and stenting duration. The site of the upper coil (renal pelvis or calix), the site of the lower coil (in the same side or crossing the midline), and the shape of the lower coil (complete circle or not) were also tested. Univariate and multivariate analysis were carried out to determine significant independent variables, with $P < 0.05$ being significant.
Results: Of the total, 59 patients experienced discomfort consisting of dysuria, urgency, urge incontinence, loin pain, suprapubic pain, frequency, nocturia, or gross hematuria or some combination. Significant factors associated with discomfort were a positive urine culture, crossing of the lower end of the stent to the opposite side, caliceal position of the upper coil, and longer stenting duration.
Conclusion: Proper positioning of the coils of the stent, eradication of infection, and shorter stenting duration are advised to decrease patient discomfort during the period of ureteral stenting.

Editorial Comment

The authors confirm the significant impact ureteral stents have on patient comfort and quality of life, and they identify the following 3 variables that affect stent morbidity: Location! Duration! Infection! Though previous studies evaluating patient comfort have attempted to focus on stenting of a symptomatic ureteral stone or stenting after uncomplicated ureteroscopy, this study included patients undergoing a wide variety of endourological and laparoscopic procedures. Pain measurements may therefore have been confounded by urinary extravasation after endopyelotomy, port site pain, diaphragmatic irritation by carbon dioxide or other variables. In addition, the length and size of stent used was not standardized. The stent duration in this study was long - typically, we leave a ureteral stent for 4-7 days after an uncomplicated ureteroscopy and 2-3 weeks after an endopyelotomy or endoureterotomy. Noting these limitations, it is important to consider some of the simple method proposed by this study to decrease stent discomfort. Intraoperatively, one should ensure proper positioning of the stent coils such that the bladder coil does not cross midline and the renal coil is in the pelvis. Postoperatively if the patient reports discomfort it may be important to perform a urine culture and eradicate any infection. Lastly, shortening the duration of stenting should be emphasized.

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

Percutaneous Nephrolithotomy in Patients Who Previously Underwent Open Nephrolithotomy

Margel D, Lifshitz DA, Kugel V, Dorfmann D, Lask D, Livne PM
Minimally Invasive Urology, Rabin Medical Center-Golda Campus, Petach Tikva, Israel
J Endourol. 2005; 19: 1161-4

Background and Purpose: Open stone surgery nowadays is rare. However, some patients who are treated today have in the past undergone open nephrolithotomy. The aim of this study was to determine the possible impact of open nephrolithotomy on the efficacy and morbidity of subsequent percutaneous nephrolithotomy (PCNL).
Patients and Methods: We reviewed the files of all 167 patients undergoing PCNL at our institution between December 2000 and December 2003. The same surgeon performed all of the procedures. We compared 21 patients undergoing PCNL after open nephrolithotomy to the same kidney with all other patients undergoing PCNL. The groups did not differ in terms of age or stone burden (mean size, number of stones, percentage with staghorn calculi). The outcomes measured were operating time, necessity for secondary procedures, stone free rate, and intraoperative and postoperative complications.
Results: The operating time (203+/-92 v 177+/-52 minutes) and percentage of secondary procedures (29% v 12%) were significantly higher in patients who had previously undergone open stone surgery. However, the stone-free rate (95% v 93%), intraoperative complication rate (10% v 9%), and postoperative complication rate (10% v 11%) did not differ significantly.
Conclusions: A PCNL in a patient with a history of open nephrolithotomy may take longer and lead to a higher percentage of auxiliary procedures, probably because of scar tissue and anatomic changes in the kidney. However, the morbidity and efficacy of PCNL appear to remain the same in these patients.

Editorial Comment

Preoperative planning for PCNL pays off particularly in the complicated patient who has a prior open renal surgery. Though the authors conclude that efficacy is not affected, the secondary procedure rate was significantly higher if the patient has had a prior open surgery. The authors present some important technical tips to consider during complicated PCNL. Firstly, they utilize contrast-imaging to evaluate for intrarenal scarring that would necessitate a direct puncture onto the stone. Secondly, they utilize an upper pole puncture if an incisional hernia is present at the old subcostal incisional site. Thirdly, they emphasize the need for precise initial alignment of the entry needle as the ability to maneuver the needle once inserted is limited by scarring. Lastly, they employ a step-wise algorithm for dilation of the percutaneous tract - starting with a balloon dilator, using a fascia cutting needle and re-inflating if residual waist is present, proceeding to rigid Amplatz dilators if still not successful, and lastly using telescopic metal dilators if all else fails. It is important to emphasize that experience in each of these techniques is important to ensure access to the stone in these complicated patients. Unfortunately, they did not report how often they resorted to each of these techniques. One can conclude from this study that patients undergoing PCNL who have had prior open renal surgery should undergo contrast-imaging studies to delineate the collecting system anatomy. Having the availability and experience of a range of dilation systems is important for successful percutaneous access.

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

ENDOUROLOGY & LAPAROSCOPY

Meta-Analysis of the Complications of Laparoscopic Renal Surgery: Comparison of Procedures and Techniques

Pareek G, Hedican SP, Gee JR, Bruskewitz RC, Nakada SY
Division of Urology, Department of Surgery, University of Wisconsin Medical School, Madison, Wisconsin, USA
J Urol. 2006; 175: 1208-13

Purpose: We performed a meta-analysis of the literature to define the current expectations of complications during laparoscopic renal surgery.
Materials and Methods: References were searched in the MEDLINE database from 1995 to 2004 using the terms complications and laparoscopic nephrectomy. Inclusion criteria were any series with greater than 20 cases, patient age older than 16 years and any complications listed for certain procedures, including laparoscopic radical nephrectomy, HA laparoscopic radical nephrectomy, LPN, HALPN, laparoscopic donor nephrectomy, HA laparoscopic donor nephrectomy, laparoscopic simple nephrectomy, laparoscopic nephroureterectomy and retroperitoneal laparoscopic nephrectomy. A data extraction form was created to categorize major or minor complications. A 5 member panel adhered to the strict criteria and extracted data from articles that met inclusion criteria. Data were entered into a spreadsheet and a meta-analysis was performed.
Results: Initial review identified 73 of 405 references that were acceptable for retrieval and data extraction, of which 56 met inclusion criteria. The overall major and minor complication rates of laparoscopic renal surgery were 9.5% and 1.9%, respectively. There was a significant difference between the major complication rates of LPN and HALPN (21.0% vs 3.3%, $p < 0.05$).
Conclusions: Our results show that patients who undergo laparoscopic renal surgery may have an overall major complication rate of 9.5%. The highest major complication rate is associated with technically challenging LPN (21%). There appears to be a significantly higher wound complication rate associated with HA surgery in comparison to that of standard laparoscopy (1.9% vs 0.2%, $p < 0.05$).

Editorial Comment

Since the first laparoscopic nephrectomy was performed and documented by Clayman and colleagues, the array of procedures using the laparoscopic approach has evolved. The development of new laparoscopic instruments and technology allowed laparoscopic surgeons to apply the same surgical principles as in open surgery. The authors demonstrated that laparoscopic renal surgery is safe and reproducible. Moreover, laparoscopic partial nephrectomy remains a complex procedure including ablative and reconstructive steps but the aid of hand assist devices may decrease the rate of complications for this particular procedure. Conversely, the hand assisted surgeries compared to pure laparoscopic procedures had higher incidence of wound related complications. In conclusion, the laparoscopic approach for kidney surgery should be considered a “winner” in terms of surgical technique allowing patients to benefit from it for over a decade and half.

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

Intermediate Results of Laparoscopic Cryoablation in 59 Patients at the Medical College of Wisconsin

Lawatsch EJ, Langenstroer P, Byrd GF, See WA, Quiroz FA, Begun FP
Departments of Urology and Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA
J Urol. 2006; 175: 1225-9; discussion 1229

Purpose: We report our experience with LC for small renal tumors.
Materials and Methods: Patients who underwent LC at our institution between February 2000 and September 2004 were included in the study. A retrospective chart review was done for perioperative and postoperative parameters as well as clinical outcomes.
Results: A total of 65 LCs were performed in 59 patients during the period reviewed. Overall 81 renal tumors were cryoablated. Median patient age was 62 years. Median tumor size was 2.5 cm. Median operative time was 190 minutes. Median estimated blood loss was 50 ml. Median hospital stay was 2 days. Conversion to open surgery occurred in 2 patients. Nephrectomy for bleeding occurred in 1 patient. Median followup was 26.8 months. Two recurrences were identified after LC.
Conclusions: LC is an alterative modality to laparoscopic partial nephrectomy or open partial nephrectomy for small renal tumors. Tumor recurrence rates in the studies published to date are comparable to those of partial nephrectomy, although longer followup is needed.

Editorial Comment
Laparoscopic cryoablation of small renal tumors is still in development. The new cryo probes have increased the efficiency of cytotoxic effects to treat the renal lesions and decreased the rate of complications. So far, the technology has demonstrated to be efficient to treat renal tumors. The authors concluded that laparoscopic cryoablation is a potential alternative modality to laparoscopic partial nephrectomy or open partial nephrectomy for small renal tumors but the cryoablation technique requires a basic skill set in laparoscopic surgery, which makes this technique appealing for less experienced laparoscopic surgeons. Moreover, laparoscopic cryoablation may be associated with decreased risks of bleeding and urine leakage in comparison to laparoscopic partial nephrectomy. Future comparative studies are needed to fully validate this technique but initial reports of oncological control are encouraging.

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

IMAGING

Radiation Dose Associated with Unenhanced CT for Suspected Renal Colic: Impact of Repetitive Studies

Katz SI, Saluja S, Brink JA, Forman HP
Department of Radiology, Yale-New Haven Hospital, Yale University School of Medicine, New Haven, CT, USA
AJR Am J Roentgenol. 2006; 186: 1120-4

Objective: The purpose of our study was to assess the dose of ionizing radiation delivered through the use of unenhanced CT for suspected renal colic by determining the incidence of repeated unenhanced CT examinations and the cumulative radiation dose delivered.
Materials and Methods: All unenhanced CT examinations for suspected renal colic performed at our institution over a 6-year period were included, and patient age, sex, and multiplicity of examinations were determined. For the adult patient, this protocol prescribes a fixed tube current of 200 mA, 140 kVp, and a nominal slice width of 5 mm. The dose-length product (DLP) was estimated for 15 randomly chosen single-detector CT (SDCT) and MDCT adult flank pain examinations using manufacturer's software. The mean DLPs for SDCT and MDCT were computed and converted to effective doses. Total effective doses were calculated for patients who underwent more than three examinations, and values were compared with established standards.
Results: A total of 5,564 examinations were performed on 4,562 patients. Of these patients, 2,795 (61%) were women (mean age, 45.5 +/- 16.2 [SD] years) and 1,731 (38%) were men (mean age, 44.7 +/- 16.4 years), with 144 patients (3%) of pediatric age. The mean effective doses for a single study were 6.5 mSv for SDCT and 8.5 mSv for MDCT. A subset of 176 patients (4%) had three or more examinations, with estimated effective doses ranging from 19.5 to 153.7 mSv. All patients with multiple examinations had a known history of nephrolithiasis.
Conclusion: Patients with a history of nephrolithiasis and flank pain are at increased risk for serial CT with potentially high cumulative effective doses.

Editorial Comment

Recent studies have been shown that computed tomography (CT) contribute to 35-45% of total radiation dose to the patient population. Nowadays, radiologists' aim must be to decrease radiation dose to the patient and also check very carefully all indications and recommend alternative imaging methods. Recently several CT protocol imaging have been developed in order to decrease the total amount of radiation dose that a patient receives during abdominal CT. This is a very important study, which discusses all the issues and possibilities regarding those patients that are submitted to repetitive abdominal CT for the evaluation of acute flank pain. The authors showed that a small but significant subset of the patient population (4%) was estimated to receive from 20 to as high as 154 mSv, which is totally undesirable. In order to decrease the amount of radiation dose they suggested that sonography associated with abdominal radiography (KUB), should be used as a first imaging examination in patients known to have chronic stone formation who have a high pretest probability of nephrolithiasis and thus are less likely to have a missed alternative diagnosis. Another useful approach for these patients is to use the reduced radiation-dose technique. When using these optimized CT protocol, the tube current can be reduced to 70 mA in comparison with the higher tube current of multidetector conventional CT protocol (200 mA). By using this optimized low dose protocol, the estimated effective dose is reduced from 8.6 mSv to 1.5 mSv. This reduced radiation-dose protocol result in scans with high accuracy for detecting urinary calculi in patients evaluated for acute flank pain.

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

Conventional MRI Capabilities in the Diagnosis of Prostate Cancer in the Transition Zone

Li H, Sugimura K, Kaji Y, Kitamura Y, Fujii M, Hara I, Tachibana M
Department of Radiology, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan
AJR Am J Roentgenol. 2006; 186: 729-42

Objectives: Our objectives were to evaluate the diagnostic capabilities of conventional MRI for the accurate detection of prostate cancer within the transition zone and to compare the results with histopathologic examination results.
Materials and Methods: One hundred sixteen prostate specimens with prostate cancer were consecutively obtained. Axial, sagittal, and coronal T2- and T1-weighted MR images with gadopentetate dimeglumine were independently reviewed by two radiologists. The diagnostic base criteria of the MR images were determined for detecting transition zone cancer as follows: lesions with A, uniform low intensity on T2-weighted images; B, homogeneous gadolinium enhancement; and C, irregular margins both on gadolinium-enhanced and T2-weighted images. Wilcoxon's rank sum and chi-square tests and receiver operating characteristic curves were used. Differences of less than 0.05 were considered significant.
Results: Eighty-six lesions in the transition zone were analyzed. Histopathologic analysis showed 53 cancers and 33 benign lesions. The diagnostic sensitivity, specificity, and accuracy for cancer were 50%, 51%, and 51%, respectively with criteria A; 68%, 75%, and 71% with criteria B; and 60%, 72%, and 65% with criteria C. When base criteria were combined into criteria A-B, A-C, and B-C and then further divided into three subgroups, accuracy was found to be highest when the lesion satisfied any two criteria from A, B, and C than those of base criteria, combination criteria, and the other two subgroups.
Conclusion: The addition of gadolinium-enhanced MRI to T2-weighted imaging provides better accuracy for detecting cancerous transition zone lesions than the use of T2-weighted imaging alone.

Editorial Comment

Radical prostatectomy studies have demonstrated that 75-85% of cancers arise in the peripheral zone, but up to 25% prostate cancer occurs within the transition zone. Endorectal MR imaging is a useful modality in the detection of the peripheral zone cancers. This technique is able to detect 67-76% of peripheral cancer demonstrated by step-section histopathologic studies but has limitations in the demonstration of cancer in the transition zone. This limitation occurs because the transition zone appears usually as a very heterogeneous region on T2-weighted images due to the presence of nodular hyperplastic changes. Previous studies have suggested some MR imaging features found in transition zone cancer: homogeneous hypointense lesion on T2-weighted images with ill-defined margins and lack of capsule .The authors of this study demonstrates that conventional MR imaging, without the use of an endorectal coil, can be useful for the detection of transition prostate cancer. They added new imaging criteria: homogeneous enhancement and presence of irregular margins .If these additional findings are used, the specificity rates for the detection of transition zone cancer could be increased from 51% to 82%. In the last 2 years, we have been using routinely, in our institution, endorectal MR imaging and spectroscopy for the detection of prostate cancer arising in the transition zone. We have found that diffusion weighted images and the evaluation of the kinetics of gadolinium enhancement by the lesion can be of further value. Thus the, presence of a nodule with ill-defined margins, homogeneous hypointensity on T2 weighted images, with hypointensity on diffusion weighted images and fast contrast enhancement ("wash-in") and fast contrast de-enhancement("wash-out"), is very suggestive of transition zone cancer. Spectroscopy shows only high levels of choline particularly in larger tumors and thus can also be of some value.

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

UROGENITAL TRAUMA

Cystogram Follow-Up in the Management of Traumatic Bladder Disruption

Inaba K, McKenney M, Munera F, de Moya M, Lopez PP, Schulman CI, Habib FA
Division of Trauma and Surgical Critical Care, LAC + USC Medical Center, University of Southern California, Los Angeles, CA, USA
J Trauma. 2006; 60: 23-8

Background: The utility of obtaining a routine cystogram after the repair of intraperitoneal bladder disruption before urethral catheter removal is unknown. This study was designed to examine whether follow-up cystogram evaluation after traumatic bladder disruption affected the clinical management of these injuries. We hypothesized that routine cystograms, after operative repair of intraperitoneal bladder disruptions, provide no clinically useful information and may be eliminated in the management of these injuries.
Methods: Our prospectively collected trauma database was retrospectively reviewed for all ICD-9 867.0 and 867.1 coded bladder injuries over a 6-year period ending in June 2004. Demographics, clinical injury data, detailed operative records, and imaging studies were reviewed for each patient. Bladder injuries were categorized as intraperitoneal (IP) or extraperitoneal (EP) bladder disruptions based on imaging results and operative exploration. Patients with IP injuries were further subdivided into those with "simple" dome disruptions or through-and-through penetrating injuries and "complex" injuries involving the trigone or ureter reimplantation. All patients sustaining isolated ureteric or urethral injury were excluded from further analysis.
Results: In all, 20,647 trauma patients were screened for bladder injury. Out of this group, there were 50 IP (47 simple, 3 complex) and 37 EP injuries available for analysis. All IP injuries underwent operative repair. Eight of the IP injuries (all simple) had no postoperative cystogram and all were doing well at 1- to 4-week follow-up. The remaining 42 patients underwent a postoperative cystogram at 15.3 +/- 7.3 days (range 7 to 36 days). All simple IP injuries had a negative postoperative cystogram. The only positive study was in one of the three complex IP injuries. In the EP group, 21.6% had positive cystograms requiring further follow-up and intervention.
Conclusions: Patients sustaining extraperitoneal and complex intraperitoneal bladder disruptions require routine cystogram follow-up. In those patients undergoing repair of a simple intraperitoneal bladder disruption, however, routine follow-up cystograms did not affect clinical management. Further prospective evaluation to determine the optimal timing of catheter removal in this patient population is warranted.

Editorial Comment

When it comes to diagnosing bladder injuries, in the vast majority, the presenting sign is gross hematuria and pelvic fracture (1). For penetrating bladder injuries, up to 50% will only have microscopic hematuria. Accurate methods for diagnosing and staging the bladder injury are a formal cystogram with retrograde filling until at least 300 mL or bladder spasm, as well as a post-drainage film to look for another potential 10-15% of injuries, hidden behind the contrast on filling. Computed tomography (CT) cystogram is also very accurate for bladder injury, and has the advantage that it can be performed at the same time as the abdominal and pelvic imaging CT. The key is that clamping the Foley often produces inadequate bladder distention for injury diagnosis. Retrograde filling is required in order to avoid missed injuries.

This article nicely illustrates the management and evaluation methods for intraperitoneal (IP) and extraperitoneal (EP) bladder injuries. Inaba et al. divide IP bladder injuries into simple (bladder dome and wall) and complex (involve the trigone and ureteral orifice). Of 39 simple IP bladder injuries closed at the time of celiotomy, 100% were healed by 15 days. They thus effectively argue that after 2 weeks of Foley catheter rest, a cystogram is not required before Foley removal. In contrast, complex bladder injuries (which involve the trigone or ureter) typically also have significant blast injury and require prolonged Foley drainage and thus

cystography to confirm healing. For EP bladder injuries, only 10-15% of pelvic fractures have an associated bladder injury, while over 90% of bladder injuries have a pelvic fracture. Inaba et al. show that 88% of EP bladder injuries heal with Foley catheter alone, by 16 days and the remaining 12% by 47 days. This is consistent with prior reports that most EP injuries heal within 2 weeks and the remaining by 4 to 6 weeks. The only EP bladder injury cases that I have seen that not heal with bladder rest were due to bony pelvic spicules penetrating the bladder, and thus required open surgical repair. Such cases are very rare.

Reference

1. Morey AF, Iverson AJ, Swan A, Harmon WJ, Spore SS, Brandes SB: Bladder rupture after blunt trauma: guidelines for diagnostic imaging. J Trauma. 2001; 51: 683-6.

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

Does Nephrectomy for Trauma Increase the Risk of Renal Failure?

Velmahos GC, Constantinou C, Gkiokas G
Department of Surgery, Division of Trauma and Critical Care, Los Angeles County and University of Southern California Medical Center, Los Angeles, California, USA
World J Surg. 2005; 29: 1472-5

Renal failure is a feared complication following operations for severe trauma. Injuries to the kidney may be managed by nephrectomy or nephrorrhaphy. Nephrectomy may increase the risk of renal failure in already at-risk trauma patients. Nephrectomy for trauma should be avoided to the extent possible because it is associated with renal failure. From a prospectively collected trauma database, 59 patients with nephrectomy were matched at 1:1 ratio with 59 patients with nephrorrhaphy. Matching criteria were age (+/- 5 years), Injury Severity Score (+/- 3), abdominal Abbreviated Injury Score (+/- 1), and mechanism of injury (blunt or penetrating). The rates of renal function compromise (defined as a serum creatinine level >2 mg/dl for more than 2 days) and renal replacement therapy (continuous or intermittent) were compared in the two groups. The two groups were well-matched and similar with regard to injury severity and organs injured. Between nephrectomy and nephrorrhaphy patients, there were no differences in renal function compromise (10% vs. 14%, $p = 0.57$), renal replacement therapy (5% vs. 0%, $p = 0.12$), length of hospital stay (19 +/- 26 vs. 20 +/- 21, $p = 0.8$), and mortality (15% vs. 12%, $p = 0.59$). Salvaging the injured kidney does not seem to offer an obvious clinical benefit regarding postoperative renal function. Given the increased operative complexity of nephrorrhaphy in comparison to nephrectomy and the frequent need to abbreviate the operation in patients with severe trauma, nephrectomy should not be avoided when appropriate.

Editorial Comment

Contemporary trauma management employs a damage control principle. Patients who become cold, coagulopathic, and acidotic have a very high mortality rate. In order to avoid this fatal triad, it was observed that if the trauma patient underwent an abbreviated operation to control bleeding and fecal soiling, followed by ICU resuscitation, then followed by a staged definitive repair, the patient survival rates were dramatically improved. Currently, abbreviated surgeries and staged definitive repair are standard of trauma care and have

been applied to all organ system, including genitourinary. Although as urologists, we are in the kidney preservation business, the overall survival of the patient should not be compromised in order to save the kidney. In other words, do not kill the patient trying to save the kidney. In trauma circles, the way to damage control injures organs is to quickly control bleeding and fecal and urinary soiling. To control bleeding the organ can be packed, quickly repaired or removed. To control urinary spillage, the ureter can be exteriorized, ligated or quickly repaired. The use of damage control to urology was popularized (1). To the trauma surgeons, since most trauma patients are young healthy adults with 2 normal kidneys and a normal creatinine, the kidney can be removed without too much overall kidney function compromise. Velmahos et al., puts up a good argument in the above article, but I would argue a different conclusion. The authors are trying to support the high 50-60% nephrectomy rates of yester-year. I would argue that the nephrectomy rate does not have to be higher the 20% and we can still follow a damage control method. Furthermore, palpating for a normal feeling contralateral kidney can be unreliable. I have personally seen 2 cases of trauma patients with a nonfunctioning contralateral multi-cystic dysplastic kidney and one hypertrophied psoas muscle that was thought to be palpably normal kidney by the trauma service. In the stable blunt trauma patient, all grade 1-4 renal injuries should managed conservatively if possible. In the blunt trauma patient who is explored, a stable, nonpulsatile, nonexpanding, contained perinephric hematoma should be left alone. In the penetrating trauma patient who is explored and the kidney does not have much blast injury and not really bleeding, I would just cover the gunshot holes with a surgi-cell and place a drain. The kidney can also be packed. Once resuscitated on a staged celiotomy, the kidney can be reexamined and a more definitive repair can be performed.

Reference

1. Brandes SB: Damage control for urologic trauma: an approach for improved survival. J Urol. 2003; 169: 69A.

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

PATHOLOGY

Update on the Gleason Grading System for Prostate Cancer: Results of an International Consensus Conference of Urologic Pathologists

Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL
Department of Pathology, Urology and Oncology, The Johns Hopkins Hospital, Baltimore, MD, USA
Adv Anat Pathol. 2006; 13: 57-9

The Gleason system for prostate cancer was based on a study of 270 patients from the Minneapolis Veterans Administration Hospital in 1966-1967. In 1974, Gleason and the Veterans Administrative Cooperative Urological Research Group expanded this study to 1032 men. These studies formed the basis of the Gleason grading system, which is now endorsed as the primary grading system for prostate cancer by the World Health Organization, the Armed Forces Institute of Pathology Fascicle on prostate cancer, the Association of Directors of Anatomic and Surgical Pathology, and the College of American Pathologists. In the nearly 40 years since its

inception, several aspects about prostate cancer and its management have changed, most notably serum prostate-specific antigen, transrectal ultrasonography, 18-gauge needle biopsy sampling, immunohistochemistry for the diagnosis of cancer, and radical prostatectomy and radiation therapy as primary treatment modalities. Several aspects of the disease, and consequently the reporting needs, have changed such as reporting cancer on multiple cases in needle biopsies, multiple nodules in prostatectomy, tertiary patterns, variants and variations in prostate cancer. The application of the Gleason system, therefore, has varied considerably in contemporary surgical pathology practice. An International Consensus Conference attended by 80 urologic pathologists from 20 countries was convened to discuss clarifications and modifications to the Gleason system. This article serves as a brief overview and summary of the proceedings that have been published in detail in recent literature.

Editorial Comment

In 2005 during the USCAP (United States and Canadian Academy of Pathology) meeting in San Antonio, Texas, there was a Consensus Conference on Gleason grading system sponsored by the International Society of Urological Pathology (ISUP). The results were published in the November issue of the American Journal of Surgical Pathology (1). There are several arguments favoring a need for a consensus on Gleason grading: 1) In the 1960s, there was no screening for prostate cancer other than by digital rectal examination; 2) The use of 18-gauge thin biopsy needles and the concept of sextant needle biopsies to more extensively sample the prostate were not developed until the 1980s; 3) Tertiary patterns were not addressed within the original Gleason system; 4) The Gleason system predated the use of immunohistochemistry (it is likely that many of Gleason's original 1 + 1 = 2 adenocarcinomas would today be regarded as adenosis; 5) The original Gleason grading system was not applied to newly described variants of adenocarcinoma of the prostate; and, 6) The Gleason system varies considerably in contemporary surgical pathology practice and has led to several recent attempts to achieve consensus on Gleason grading.

Some of the recommendations of the consensus conference are the following: 1) Cribriform pattern 3 should only be diagnosed for well circumscribed glands of the same size of normal glands; 2) Ill-defined glands with poorly formed glandular lumina also warrant the diagnosis of Gleason pattern 4; 3) In high-grade cancer, lower grade patterns should be ignored if they occupy less than 5% of the area of the tumor; and 4) For tertiary Gleason patterns, both the primary and the highest grade are recorded.

A recent study described the impact of the consensus recommendations on a series of 172 consecutive needle prostatic biopsies of patients subsequently submitted to radical prostatectomy previously graded according to the standard Gleason system (2). There was a grading concordance in 83.14%, 63.37%, and 68.02% biopsies for Gleason primary pattern, Gleason secondary pattern, and Gleason score, respectively. There was a change of prognostic Gleason grading groups in 2.33% and 26.74% biopsies toward a lower group and toward a higher group, respectively. There was a change in 15.7%, 9.88%, 0.58% and 0.58% biopsies from group 5-6 toward group 7, 7 toward 8-10, 5-6 toward 8-10, and 2-4 toward 5-6, respectively. The conclusion was that the highest impact of the consensus recommendations was seen on the secondary pattern that had the lowest percentage of concordance. It reflected in a change toward a higher Gleason grading group in 46/172 (26.74%) of the cases. A further study is warranted to show how different are these 46 cases according to several clinicopathologic variables: preoperative PSA, positive surgical margins, tumor extent, pathologic staging and biochemical progression following radical prostatectomy.

References

1. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL; ISUP Grading Committee: The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol. 2005; 29: 1228-42.

2. Guimaraes MS, Billis A, Quintal MM, Magna LA, Ferreira U. The impact of the 2005 International Society of Urological Pathology (ISUP) Consensus Conference on standard Gleason grading of prostatic carcinoma. Mod Pathol Suppl. 2006; 1: 139A.

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

Prostate Needle Biopsies Containing Prostatic Intraepithelial Neoplasia or Atypical Foci Suspicious For Carcinoma: Implications for Patient Care

Epstein JI, Herawi M
Department of Pathology, The Johns Hopkins University School of Medicine, The James Brady Urological Institute, The Johns Hospital, Baltimore, Maryland, USA
J Urol. 2006; 175 (3 Pt 1): 820-34

Purpose: We identified information critical for patient treatment on prostate needle biopsies diagnosed with prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma.
Materials and Methods: A search was performed using the MEDLINE database and referenced lists of relevant studies to obtain articles addressing the significance of finding PIN or atypical foci suspicious for carcinoma on needle biopsy.
Results: There were certain results concerning PIN. 1) Low grade PIN should not be documented in pathology reports due to poor interobserver reproducibility and a relatively low risk of cancer following re-biopsy. 2) The expected incidence of HGPIN on needle biopsy is between 5% and 8%. 3) Although the diagnosis of HGPIN is subjective, interobserver reproducibility for its diagnosis is fairly high among urological pathologists, and yet only moderate among pathologists without special expertise in prostate pathology. 4) The median risk recorded in the literature for cancer following the diagnosis of HGPIN on needle biopsy is 24.1%, which is not much higher than the risk reported in the literature for repeat biopsy following a benign diagnosis. 5) The majority of publications that compared the risk of cancer in the same study following a needle biopsy diagnosis of HGPIN to the risk of cancer following a benign diagnosis on needle biopsy show no differences between the 2 groups. 6) Clinical and pathological parameters do not help stratify which men with HGPIN are at increased risk for a cancer diagnosis. 7) A major factor contributing to the decreased incidence of cancer following a diagnosis of HGPIN on needle biopsy in the contemporary era is related to increased needle biopsy core sampling, which detects many associated cancers on initial biopsy, such that re-biopsy, even with good sampling, does not detect many additional cancers. 8) It is recommended that men do not need routine repeat needle biopsy within the first year following the diagnosis of HGPIN, while further studies are needed to confirm whether routine repeat biopsies should be performed several years following a HGPIN diagnosis on needle biopsy. There were certain results concerning atypical glands suspicious for carcinoma. 1) An average of 5% of needle biopsy pathology reports are diagnosed as atypical glands suspicious for carcinoma. 2) Cases diagnosed as atypical have the highest likelihood of being changed upon expert review and urologists should consider sending such cases for consultation in an attempt to resolve the diagnosis as definitively benign or malignant before subjecting the patient to repeat biopsy. 3) Ancillary techniques using basal cell markers and AMACR (alpha-methyl-acyl-coenzyme A racemase) can decrease the number of atypical diagnoses, and yet one must use these techniques with caution since there are numerous false-positive and false-negative results. 4) The average risk of cancer following an atypical diagnosis is approximately 40%. 5) Clinical and pathological parameters do not help

predict which men with an atypical diagnosis have cancer on repeat biopsy. 6) Repeat biopsy should include increased sampling of the initial atypical site, and adjacent ipsilateral and contralateral sites with routine sampling of all sextant sites. Therefore, it is critical for urologists to submit needle biopsy specimens in a manner in which the sextant location of each core can be determined. 7) All men with an atypical diagnosis need re-biopsy within 3 to 6 months.
Conclusions: It is critical for urologists to distinguish between a diagnosis of HGPIN and that of atypical foci suspicious for cancer on needle biopsy. These 2 entities indicate different risks of carcinoma on re-biopsy and different recommendations for followup.

Editorial Comment

This is an excellent review of two important diagnoses on needle prostatic biopsies. Urologists should clearly distinguish these two pathologic conditions. High-grade prostatic intraepithelial neoplasia (high-grade PIN) is diagnosed whenever acinar cells show nucleomegaly and conspicuous nucleoli. This finding is indistinguishable from prostate cancer, however, in high-grade PIN, there is no acinar architectural disarrangement and, very important, basal cells are present. High-grade PIN corresponds to grade 2 or 3 prostatic intraepithelial neoplasia. Low-grade PIN corresponds to grade 1 and should not be reported by the pathologist due to poor interobserver reproducibility and a relatively low risk of cancer following re-biopsy. On the other hand, high-grade PIN is associated with a moderate risk of cancer following re-biopsy, however, due to an increased needle biopsy core sampling, which detects many associated cancers on initial biopsy, there is a decreased incidence of cancer following a diagnosis of high-grade PIN. Due to these facts, it is recommended that men do not need routine repeat needle biopsy within the first year following the diagnosis of high-grade PIN.

Atypical foci suspicious for carcinoma are a completely different condition that urologists should not interpret as high-grade PIN, adenosis, or any other pathologic entity. It refers to a condition in which the pathologist is not able to make a diagnosis of adenocarcinoma with confidence. This happens in 3 main conditions: 1. the suspicious focus is very small; 2. the focus disappears in further sectioning of the paraffin block; and, 3. absence of cytologic criteria for the diagnosis of adenocarcinoma (1). Atypical focus suspicious for carcinoma was formerly known as ASAP (atypical small acinar proliferation). This term should not be used because may be erroneously interpreted by the urologist as a pathologic entity such as high-grade PIN, adenosis or any other one (2). Furthermore, not all suspicious foci for carcinoma show small acini; large acini may also be suspicious.

Differently from high-grade PIN, atypical foci suspicious for carcinoma have a high risk of cancer on a repeat biopsy. All men with a pathology report “suspicious but not diagnostic for adenocarcinoma” need re-biopsy within 3 to 6 months. Repeat biopsy should include increasing sampling from the suspicious site. This is very important and emphasizes the need for properly identifying the cores from the different regions biopsied, which must be sent in separate containers to the pathology laboratory.

References

1. Iczkowski KA, MacLennan GT, Bostwick DG: Atypical small acinar proliferation suspicious for malignancy in prostate needle biopsies: clinical significance in 33 cases. Am J Surg Pathol. 1997; 21: 1489-95.
2. Amin M, Boccon-Gibod L, Egevad L, Epstein JI, Humphrey PA, Mikuz G, t al.: Prognostic and predictive factors and reporting of prostate carcinoma in prostate needle biopsy specimens. Scand J Urol Nephrol Suppl. 2005; 216: 20-33.

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

INVESTIGATIVE UROLOGY

Prevalence of Peyronie's Disease among Patients with Erectile Dysfunction

El-Sakka AI
Department of Urology, Suez Canal University, School of Medicine Ismailia, Egypt and Al-Noor Specialist Hospital, Makkah, Saudi Arabia
Eur Urol. 2006; 49: 564-9

Purpose: To assess the prevalence of Peyronie's disease (PD) among patients with erectile dysfunction (ED).
Materials and Methods: A total of 1,440 male patients with ED were enrolled in this study. Patients were interviewed for ED using the International Index of Erectile Function (IIEF). All patients were also screened for socio-demographic data and risk factors for ED that included age, smoking, diabetes, hypertension, dyslipidemia, Ischemic Heart Disease (IHD), and psychological disorders. The diagnosis of PD was based on a palpable penile plaque or acquired penile curvature. Patients underwent routine laboratory investigation in addition to testosterone and prolactin assessment.
Results: Mean ages +/-SD were 54.1 +/- 6.9 (range 42-71) and 52.5 +/- 11.9 (range 20-84) years for patients with and without PD respectively. Of the patients, 11.8% had mild, 38.3% had moderate and 49.9% had severe ED. 7.9% of the patients had PD. Significant associations between PD and both the longer duration and the increased severity of ED were detected. There were also significant associations between PD and the following socio-demographic risk factors of ED: age, obesity, smoking, duration and number of cigarettes smoked per day. Concomitant diseases and medical comorbidities such as diabetes, dyslipidemia, psychological disorders and the presence of at least one risk factor were significantly associated with PD in patients with ED.
Conclusions: Peyronie's disease was not rare among the study population. There were significant associations between ED risk factors and PD. Further studies are needed to investigate how much ED and PD influence each other.

Editorial Comment

This is an interesting paper studying the incidence of Peyronie's disease (PD) and erectile dysfunction (ED). Peyronie's disease affects up to 9% of male adult population (1) and the present findings are not so much different form the general data.

Other recent study (2) investigated the erectile function status of men presenting with Peyronie's disease. Demographics of patients regarding age, duration of PD, nature of deformity and comorbidities were compared between the patients with PD, with and without erectile dysfunction. 35% of the patients had had ED. The mean age of patients with PD and ED was 52 +/- 22 years old. Hypertension (71.5%), hyperlipidemia (60.4%) and smoking (49.2%) were the leading comorbidities, which are also similar to those found by El-Sakka.

An interesting recent study using penile ultrasound color Doppler (USCD) for assessing ED, detected in 8.7% of the patients, with no clinical symptoms or any clinical findings, minimal lesions suggestive of Peyronie's disease (3).

In spite of further studies to investigate how much ED and PD influence each other, the association is clear, and, therefore, treatment algorithms for men with combined Peyronie's disease and erectile dysfunction must be defined based on functional and satisfaction outcomes (4).

References

1. Gonzalez-Cadavid NF, Rajfer J: Mechanisms of disease: new insights into the cellular and molecular pathology of Peyronie's disease. Nat Clin Pract Urol. 2005; 2: 291-7.

2. Deveci S, Palese M, Parker M, Guhring P, Mulhall JP: Erectile function profiles in men with Peyronie's disease. J Urol. 2006; 175: 1807-11; discussion 1811.
3. Mander A, Palleschi G, Gentile V, Gezeroglou H, Dornbusch T, Pastore AL, Carbone A: Early echographical assessment of minimal lesions of cavernosum corpora and tunica albuginea in subjects with erectile dysfunction, suggestive of La Peyronie's disease. Int J Impot Res. 2006 Mar 9; [Epub ahead of print].
4. Mulhall J, Anderson M, Parker M: A surgical algorithm for men with combined Peyronie's disease and erectile dysfunction: functional and satisfaction outcomes. J Sex Med. 2005; 2: 132-8.

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

Long-Term Effect of Experimental Hypercholesterolemia on Cavernosal Tissues

Karaboga R, Kilic O, Yaman O, Percinel S, Anafarta K
Department of Urology, Ankara University Medical Faculty, Ankara, Turkey
Urology. 2006; 67: 431-4

Objectives: To determine the effect of long-term experimental hypercholesterolemia on cavernosal tissues and to evaluate whether these alterations are reversible after improvement of hypercholesterolemia.
Methods: Thirty-seven New Zealand male rabbits with a mean age of 5 to 6 months and a weight of 2 to 2.5 kg were included in this study. The control group (group 1, n = 7) was fed with normal standard rabbit chow for 24 weeks, the hypercholesterolemia group (group 2, n = 17) was fed with a 1% pure cholesterol diet for 24 weeks, and the reversibility group (group 3, n = 13) was fed first with the 1% pure cholesterol diet for 24 weeks and then with normal standard rabbit chow for 12 weeks. The basal and 24-week serum lipid profiles of all groups and the 36-week serum lipid profiles of group 3 were measured. Core tissue samples 4 mm in diameter taken from formalin-fixed, paraffin-embedded tissue blocks of rabbit corpus cavernosum were examined for Masson trichrome histochemically and desmin and smooth muscle actin by the tissue array method using immunohistochemistry.
Results: Hypercholesterolemia was observed in groups 2 and 3 at 24 weeks compared with group 1. In group 3, at 36 weeks, the cholesterol levels were decreased. A statistically significant ($P < 0.05$) irreversible decrease was observed in smooth muscle actin level in group 3 (reversibility group) by immunohistochemical analysis. The decrease in desmin was reversible, and no significant difference was observed in collagen among the three groups.
Conclusions: Long-term chronic effects of experimental hypercholesterolemia on cavernosal smooth muscles might be irreversible and this might alter erectile function.

Editorial Comment

Conditions associated with altered function of nerves and endothelium, such as hypertension, smoking, hypercholesterolemia, diabetes, etc. may cause circulatory and structural changes in the penile erectile tissue and can result in arterial insufficiency and impaired smooth muscle relaxation (1). Hypercholesterolemia is considered one of the main risk factors of cardiovascular diseases and also for vasculogenic erectile dysfunction. It was demonstrated more than 5 years ago that hypercholesterolemia may cause impairment of endothelium-dependent relaxation and that oxidized LDL is the major causative cholesterol of the impaired

relaxation response (2). The vascular endothelial growth factor (VEGF), which is an angiogenic growth factor and an endothelial cell-specific mitogen, and whose actions are coupled to nitric oxide, is probably involved in this kind of injury, because it was found that intracavernosal injections of VEGF appear to protect corporal endothelium from hypercholesterolemia induced injury, preserving endothelial dependent corporal smooth muscle relaxation in hypercholesterolaemic rabbit (3). Recently, it was found a significantly lower in vivo and in vitro erectile response to phosphodiesterase-5 inhibition in hypercholesterolaemic rabbits than in controls (4).

The effect of experimental hypercholesterolemia on the ultrastructure of cavernosal smooth muscle cells, endothelial cells, elastic fibers, and collagen, which are the key structures for erection, were morphologically analyzed in hypercholesterolaemic rabbits, 5 years ago, by the same research group of the present paper (5). The findings shown that hypercholesterolemia in this animal model affect the percentage of staining for smooth muscle actin, endothelial cells, elastin, and collagen III and IV. However, the authors stated that this effect is temporary depending on the blood cholesterol levels, and, therefore, might not alter the erectile function.

The present study, by Karaboga et al., is very much important because demonstrates by the first time, in our knowledge, that the long-term chronic effects of experimental hypercholesterolemia on cavernosal smooth muscles might be irreversible and therefore might alter erectile function.

References

1. Andersson KE: Erectile physiological and pathophysiological pathways involved in erectile dysfunction. J Urol. 2003; 170(2 Pt 2): S6-13; discussion S13-4.
2. Kim SC: Hyperlipidemia and erectile dysfunction. Asian J Androl. 2000; 2: 161-6.
3. Henry GD, Byrne R, Hunyh TT, Abraham V, Annex BH, Hagen PO, Donatucci CF: Intracavernosal injections of vascular endothelial growth factor protects endothelial dependent corpora cavernosal smooth muscle relaxation in the hypercholesterolemic rabbit: a preliminary study. Int J Impot Res. 2000; 12: 334-9.
4. Firoozi F, Longhurst PA, White MD: In vivo and in vitro response of corpus cavernosum to phosphodiesterase-5 inhibition in the hypercholesterolaemic rabbit. BJU Int. 2005; 96: 164-8. Comment in: BJU Int. 2005; 96: 1424.
5. Yesilli C, Yaman O, Anafarta K: Effect of experimental hypercholesterolemia on cavernosal structures. Urology. 2001; 57: 1184-8.

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

RECONSTRUCTIVE UROLOGY

The Anatomy and Embryology of Posterior Urethral Valves

Krishnan A, de Souza A, Konijeti R, Baskin LS
Department of Urology, University of California-San Francisco Children's Medical Center, University of California, San Francisco, California, USA
J Urol. 2006; 175: 1214-20

Purpose: We reviewed the literature to better elucidate the history behind our understanding of the anatomy, classification and embryology of posterior urethral valves.
Materials and Methods: A directed MEDLINE literature review of the anatomy, classification and embryology of posterior urethral valves was performed. An effort was made to focus on the most frequently cited historical articles as well as those including detailed anatomical analyses of fetal specimens. Also included was the analysis of a specimen obtained at our institution in a novel manner that to our knowledge has not been previously described in the literature with respect to the anatomy of posterior urethral valves.
Results: The precise origins regarding the anatomy and embryology of posterior urethral valves remain undefined. However, the literature is abundant in theories regarding the origin of posterior urethral valves, based primarily on small uncontrolled series or case reports. There are a limited number of reports of the anatomy of posterior urethral valves in methodical fashion using reproducible scientific techniques such as histopathology. These reports are invaluable for providing a foundation of how to properly study and define the origins of posterior urethral valves.
Conclusions: Elucidating this most fundamental feature of a congenital condition central to the practice of pediatric urology is essential. More well designed studies specifically with this goal in mind are necessary. Incorporating new reconstructive imaging modalities may assist us in pinpointing the elusive origins of the embryology and anatomy of posterior urethral valves.

Editorial Comment

Although posterior urethral valves have a recognized incidence of 1/5000 to 8000 in male newborns, it is not known how common it might cause fetal demise (1).

Almost 2 centuries after its first description, the posterior urethral valves is newly investigated by Krishnan et al. with modern computer imaging in combination with histopathology in one of the few virgin cases of an untreated malformation known as a posterior urethral valve which helped to clarify its origin.

Until week 9, male and female urethral development is identical; whereas by week 14, the male urethra completes its development (2). Many of the former anatomical descriptions were misleading because of prior manipulations to the histological investigations with the result of several different described types first recognized by Dewan & Goh (3).

Krishnan et al. investigated the rare case of an untreated posterior urethral valve histologically by cross sectioning and reconstructed by three-dimensionally using computer imaging from the histology of the infant's urethra. With this investigation they revealed, as several times prior (4,5), the results of anatomical development in normal and malformed urethras. They demonstrated, with their outstanding work after an all-around literature analysis that the theory of Dewan et al. (6), seems to be the most likely with the single congenital obstructing posterior urethral membrane (COPUM).

Works similar to Krishnan et al. need our recognition/attention because they complete the understanding of the embryological development. This combination of histology and three-dimensional reconstruction helps to recognize and understand the embryonic development and will help to improve early treatment.

References

1. Park JM: Normal and Anomalous Development of the Urogenital System. In: Walsh PC, Retik AB, Vaughan ED, Wein Jr AJ (eds.), Campbell's Urology. Philadelphia, WB Saunders Co., 8th ed., vol 3, chapt. 49, pp.1735-1764, 2002.
2. Marsden RT: Posterior urethral valves in adults. Br J Urol. 1969; 41: 586-91.
3. Dewan PA, Goh DG: Variable expression of the congenital obstructive posterior urethral membrane. Urology. 1995; 45: 507-9.
4. Yucel S, Baskin LS: Neuroanatomy of the male urethra and perineum. BJU Int. 2003; 92: 624-30.

5. Kurzrock EA, Baskin LS, Cunha GR: Ontogeny of the male urethra: theory of endodermale differentation. Differentation. 1999; 64: 115-22.
6. Dewan PA, Keenan RJ, Morris LL, Le Quesne GW: Congenital urethral obstruction: Cobb's collar or prolapsed congenital obstruction posterior urethral membrane (COPUM). Br J Urol. 1994; 73: 91-5.

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

Facilitatory Neuromodulative Effect of Duloxetine on Pudendal Motor Neurons Controlling the Urethral Pressure: A Functional Urodynamic Study in Healthy Women

Boy S, Reitz A, Wirth B, Knapp PA, Braun PM, Haferkamp A, Schurch B
Neuro-Urology, Swiss Paraplegic Center, Balgrist University Hospital, Zurich, Switzerland
Eur Urol. 2006 Jan 18; [Epub ahead of print]

Objective: The aim of this functional urodynamic experiment in healthy women was to study the effect of duloxetine, which is a combined serotonin and norepinephrine (5-HT/NE) reuptake inhibitor, on urethral resting pressure, excitability of pudendal motor neurons, and urethral sphincter contractility.
Methods: In 11 healthy female subjects three baseline urethral pressure profiles (UPPs) were obtained to study resting pressure. Afterward the individual motor threshold (MT) for external urethral sphincter (EUS) contraction in response to transcranial magnetic stimulation (TMS) was determined to study the excitability of pudendal motor neurons. Another three UPPs were recorded while sacral root magnetic stimulation (SMS) was performed to evoke reproducible urethral contractions to study urethral sphincter contractility. Then the women received 40 mg duloxetine and the protocol was repeated 4h after drug administration. The resting pressure values, MT values following TMS, and the EUS pressure amplitudes in response to SMS obtained at baseline were statistically compared to the corresponding values at follow-up after duloxetine.
Results: Oral administration of duloxetine significantly lowered MT for EUS contraction in response to TMS ($p = 0.013$). In addition, duloxetine significantly increased EUS pressure amplitudes in response to SMS ($p = 0.0007$, 5 of 11 subjects evaluated) but did not change urethral resting pressures.
Conclusions: This is the first functional, urodynamic controlled study to show that the combined 5-HT/NE reuptake inhibitor duloxetine has a significant effect on the excitability of pudendal motor neurons and on urethral sphincter contractility in healthy women in vivo but no significant effect on urethral resting tone. Our data confirm a facilitatory neuromodulative effect of duloxetine on sphincter motor neurons in humans.

Editorial Comment

The first investigation regarding the norepinephrine-serotonin (NE/5-HT) reuptake inhibitor duloxetine was performed in the cat model with induced cystitis causing the symptom of overactive bladder and stress urinary incontinence. The authors reported relaxing the bladder and increasing the outlet resistance (1). The paper presented here is the first dealing with the influence of the NE/5-HT reuptake inhibitor to the pelvic floor muscles in females. The authors recorded responses of transcranial and spinal cord magnetic stimulation thereby

demonstrating individual increases in the urethral sphincter pressure with duloxetine. Although it is an elegant way to demonstrate the effect of the NE/5-HT reuptake inhibitor, the magnetic stimulation field is not very selective and stimulates all (efferent as well as afferent) nerve fibers in the field of the coil. Efferent motor neurons stimulated by these methods supply the striated muscles of the pelvis but cannot be subdivided to the urethral sphincter only. Vodusek & Zidar suggested using a needle to record from the sphincter to identify specific urethral muscle functions from a general "mass contraction" (2).

The authors reported a decreased threshold for significant urethral pressure spikes in the mid urethra after sacral root magnetic stimulation through the influence of the NE/5-HT reuptake inhibitor in 45% of the subjects. This is in line with reports of decreased incontinence episode frequency of 50 – 100% in 51.4% of the trial group (n = 344) receiving duloxetine (3). An additional double-blind trial with a more representative sample of subjects should validate the drug effect on urethral pressure after magnetic stimulation.

In addition, the outcome of the single intake of the NE/5-HT reuptake inhibitor causes under normal physiological conditions does not lead to significant stimulation of postsynaptic 5-HT receptors.

After the administration of a NE/5-HT reuptake inhibitor all 5-HT transporters at the pre-synaptic membrane are blocked, leading to higher 5-HT levels in the synaptic cleft. At the same time, these increased 5-HT levels activate 5-HT1A and 5-HT1B auto-receptors, located at the pre-synaptic membrane. These pre-synaptic auto-receptors inhibit as negative feedback regulators the release of 5-HT (4-6). The simulated on-demand use causes only a mild or no increase of 5-HT neurotransmission, which might be an explanation of the experimental outcome.

Still this elegant approach might serve as a single dose-screening test to predict patients with beneficial treatment responses to the duloxetine effect in a potential patient avoiding possible side effects. The blood pressure rises induced by the magnetic coil stimulation might ask for other tests than the magnet coil stimulation to underline the outcome of this approach and demonstrate the effect to motor thresholds resulting in increased urethral pressure amplitude even in a higher proportion of subjects.

References

1. Danuser H, Thor KB: Spinal 5-HT2 receptor-mediated facilitation of pudendal nerve reflex in the anesthetized cat. Br. J. Pharmacol. 1996; 118: 150-4.
2. Vodusek D, Zidar J: Perineal motor evoked responds. Neurourol Urodyn. 1988; 7: 236-7.
3. Dmochowski RR, Miklos JR, Norton PA, Zinner NR, Yalcin I, Bump RC: Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. J Urol. 2003; 170 (4 Pt 1): 1259-63.
4. Fuller RW: Uptake inhibitors increase extracellular serotonin concentration measured by brain microdialysis. Life Sci. 1994; 55: 163-7.
5. Waldinger MD, Schweitzer DH, Olivier B: On-demand SSRI treatment of premature ejaculation: pharmacodynamic limitations for relevant ejaculation delay and consequent solutions. J Sex Med. 2005; 2: 121-31.
6. Blier P, Chaput Y, de Montigny C: Long-term 5-HT reuptake blockade, but not monoamine oxidase inhibition, decreases the function of terminal 5-HT autoreceptors: an electrophysiological study in the rat brain. Naunyn Schmiedebergs Arch Pharmacol. 1988; 337: 246-54.

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

UROLOGICAL ONCOLOGY

Risk of Prostate Cancer-Specific Mortality Following Biochemical Recurrence after Radical Prostatectomy

Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, Partin AW
The James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, Maryland, USA
JAMA. 2005; 294: 433-9; Comment in: JAMA. 2005; 294: 2969; author reply 2969-70, and Comment in: JAMA. 2005; 294: 493-4

Context: The natural history of biochemical recurrence after radical prostatectomy can be long but variable. Better risk assessment models are needed to identify men who are at high risk for prostate cancer death early and who may benefit from aggressive salvage treatment and to identify men who are at low risk for prostate cancer death and can be safely observed.
Objectives: To define risk factors for prostate cancer death following radical prostatectomy and to develop tables to risk stratify for prostate cancer-specific survival.
Design, Setting, and Patients: Retrospective cohort study of 379 men who had undergone radical prostatectomy at an urban tertiary care hospital between 1982 and 2000 and who had a biochemical recurrence and after biochemical failure had at least 2 prostate-specific antigen (PSA) values at least 3 months apart in order to calculate PSA doubling time (PSADT). The mean (SD) follow-up after surgery was 10.3 (4.7) years and median follow-up was 10 years (range, 1-20 years).
Main Outcome Measure: Prostate cancer-specific mortality.
Results: Median survival had not been reached after 16 years of follow-up after biochemical recurrence. Prostate-specific doubling time (< 3.0 vs 3.0-8.9 vs 9.0-14.9 vs > or =15.0 months), pathological Gleason score (< or =7 vs 8-10), and time from surgery to biochemical recurrence (< or =3 vs > 3 years) were all significant risk factors for time to prostate-specific mortality. Using these 3 variables, tables were constructed to estimate the risk of prostate cancer-specific survival at year 15 after biochemical recurrence.
Conclusion: Clinical parameters (PSADT, pathological Gleason score, and time from surgery to biochemical recurrence) can help risk stratify patients for prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. These preliminary findings may serve as useful guides to patients and their physicians to identify patients at high risk for prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy to enroll them in early aggressive treatment trials. In addition, these preliminary findings highlight that survival in low-risk patients can be quite prolonged.

Editorial Comment

How long does a patient live with a PSA recurrence after radical prostatectomy? The authors address this important issue in a rather small retrospective analysis of 379 men. Median time to biochemical progression after radical prostatectomy was 2 years. 17% of patients died within the median follow-up of 10 years.

The 10 and 15 years cause-specific survival from the time of PSA recurrence was 73% and 55%, respectively. Gleason score and PSA doubling time were predictors of death from prostate cancer.

The problem of a correct indication for surgical intervention and correct counseling of patient is again underlined by these data.

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

Postoperative Radiotherapy After Radical Prostatectomy: A Randomised Controlled Trial

(EORTC trial 22911)

Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, de Reijke TM, Verbaeys A, Bosset JF, van Velthoven R, Marechal JM, Scalliet P, Haustermans K, Pierart M; European Organization for Research and Treatment of Cancer

Department of Radiation Oncology, Centre Hospitalier Universitaire A Michallon, Grenoble, France

Lancet. 2005; 366 (9485): 572-8; Comment in: Lancet. 2005; 366 (9485): 524-5.

Background: Local failure after prostatectomy can arise in patients with cancer extending beyond the capsule. We did a randomised controlled trial to compare radical prostatectomy followed by immediate external irradiation with prostatectomy alone for patients with positive surgical margin or pT3 prostate cancer.

Methods: After undergoing radical retropubic prostatectomy, 503 patients were randomly assigned to a wait-and-see policy, and 502 to immediate postoperative radiotherapy (60 Gy conventional irradiation delivered over 6 weeks). Eligible patients had pN0M0 tumours and one or more pathological risk factors: capsule perforation, positive surgical margins, invasion of seminal vesicles. Our revised primary endpoint was biochemical progression-free survival. Analysis was by intention to treat.

Findings: The median age was 65 years (IQR 61-69). After a median follow-up of 5 years, biochemical progression-free survival was significantly improved in the irradiated group (74.0%, 98% CI 68.7-79.3 vs 52.6%, 46.6-58.5; $p < 0.0001$). Clinical progression-free survival was also significantly improved ($p = 0.0009$). The cumulative rate of locoregional failure was significantly lower in the irradiated group ($p < 0.0001$). Grade 2 or 3 late effects were significantly more frequent in the postoperative irradiation group ($p = 0.0005$), but severe toxic toxicity (grade 3 or higher) were rare, with a 5-year rate of 2.6% in the wait-and-see group and 4.2% in the postoperative irradiation group ($p = 0.0726$).

Interpretation: Immediate external irradiation after radical prostatectomy improves biochemical progression-free survival and local control in patients with positive surgical margins or pT3 prostate cancer who are at high risk of progression. Further follow-up is needed to assess the effect on overall survival.

Editorial Comment

The problem of positive surgical margins after radical prostatectomy is common. The question is the best adjuvant treatment in this scenario, immediate or deferred radiotherapy? This important paper gives a definite answer.

Time to failure was significantly longer in the immediate radiotherapy group, with 21.4% of patients failing after 5 years in this group vs 44.2% in the deferred treatment group. Data on survival differences are not mature yet.

Immediate adjuvant radiation should be considered in margin-positive patients after radical therapy.

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

NEUROUROLOGY & FEMALE UROLOGY

What Are the Supportive Structures of the Female Urethra?

Fritsch H, Pinggera GM, Lienemann A, Mitterberger M, Bartsch G, Strasser H
Institute of Anatomy and Histology, University of Innsbruck, Innsbruck, Austria
Neurourol Urodyn. 2006; 25: 128-34

Aims: Female stress urinary incontinence is thought to result from impairment of the connective tissue "ligaments" of the urethra. Surgical repair of female incontinence mainly involves fixation of the urethra to the pubic bone or other surrounding structures. In the present anatomical-radiological study, the anatomy of the connective tissue structures around the female urethra was investigated to determine the anatomical structures that support the urethra and the rhabdosphincter.
Materials and Methods: The topography of the anterior compartment of the female pelvis was studied in serial sections and one anatomical preparation of 30 female fetuses and of six adult females. The pelves of 29 female fetuses were processed according to plastination histology technique. The pelves of the six adult specimens were processed according to sheet plastination technique. In addition, the anatomical findings were compared with MR images of 41 adult female volunteers.
Results: The ventro-lateral aspect of the urethra remains free of fixating ligaments throughout its pelvic course. Ventro-laterally the urethra is enclosed by the ventral parts of the levator ani, its fasciae and a ventral urethral connective tissue bridge connecting both sides. Dorsally, the urethra is intimately connected to the wall of the vagina.
Conclusions: The female urethra has no direct ligamentous fixation to the pubic bone. Urethral continence after pregnancy and childbirth may be explained by a widening of the hiatus of the levator ani or the anterior vaginal wall, resulting in overstretching of the ventral urethral connective tissue bridge or the disruption of the fixation between urethra and vagina.

Editorial Comment

The authors analyze the anatomy of the female urethra with regards to the support of the urethra and rhabdosphincter. This was accomplished through analysis of the pelves of 30 female fetuses and 6 female adults. The authors find that there is no pubourethral ligament attaching the urethra to the pubic bone; instead the tissues attaching the pubic bone to the bladder neck are mostly tissue containing smooth muscle cells. In addition, the dorsal end of the rhabdosphincter is connected at its dorsal end through a strong connective tissue fixation to the ventral wall of the vagina. The neurovascular bundles are identified in the dorsal lateral pelvic wall in the ventral lateral aspects of the urethra.

This excellent article is extremely well written with beautiful anatomical pictures. That the investigators were not able to find the existence of any true pubourethral ligaments helps explain the ability of a patient to continue with urinary continence after a transvaginal urethrolysis, especially one utilizing the suprameatal transvaginal technique (1). That the authors found that the neurovascular bundles ran in the dorsal lateral pelvic wall on the lateral and ventral aspects of the urethra may explain a potentiality for sexual dysfunction after formal urethrolysis. There is an excellent discussion with regards to 3 supportive structures of the urethra and rhabdosphincter, which were identified, and the pathologic effects on same, which may lead to voiding dysfunction.

Reference
1. Petrou SP, Brown JA, Blaivas JG: Suprameatal transvaginal urethrolysis J Urol. 1999; 161: 1268-71.

Dr. Steven P. Petrou
Associate Professor of Urology
Associate Dean, Mayo Clinic College of Medicine
Jacksonville, Florida, USA

How do the Prevalences of Urogenital Symptoms Change During Pregnancy?

van Brummen HJ, Bruinse HW, van der Bom JG, Heintz AP, van der Vaart CH
Department of Perinatology and Gynecology, University Medical Center Utrecht, Utrecht, The Netherlands
Neurourol Urodyn. 2006; 25: 135-9

Aim: The aim of this study was to report the changes in prevalences of urogenital symptoms during pregnancy and to evaluate the amount of bother nulliparous pregnant women experience from these symptoms.
Methods: We have used a prospective longitudinal cohort study design. Five hundred fifteen nulliparous women with a singleton pregnancy were recruited from 10 midwifery practices between January 2002 and July 2003. The women received postal questionnaires. Urogenital symptoms were assessed with the Dutch version of the standardized and validated Urogenital Distress Inventory (UDI). We analyzed our data on item level and on the clustering of items.
Results: The prevalences of the frequency and urgency symptoms are high at 12 weeks (74% and 63%) and remain stable during pregnancy. The prevalences of urinary incontinence and voiding difficulties increase with gestational age. Frequency disappears in 12% in late pregnancy, urgency in 22%, and stress incontinence in 23%. The prevalence of bothersome frequency symptoms is much higher than of urinary incontinence (21% compared to 6%). All UDI subscales increase significantly during pregnancy.
Conclusions: Urogenital symptoms occur in almost all women during pregnancy. Whereas the prevalence of overactive bladder symptoms is high and remains stable from early pregnancy on, the prevalences of urinary incontinence symptoms increase with gestational age. Despite the high prevalences of symptoms, the majority of women report not to be bothered by it.

Editorial Comment

The authors study a large number of women during their first pregnancy and quantify both the prevalence and level of bother of the voiding symptoms that developed during this period. The investigation found that by twelve weeks of pregnancy, urgency and frequency had been identified and this symptom remained stable during pregnancy. In contrast, the incidence of urinary incontinence increased as the pregnancy matured. The authors concluded that though almost all women in pregnancy have some voiding dysfunction and the prevalence of overactive bladder symptoms is quite high from early on, the majority of women are not bothered by these symptoms.

That nulliparous women have a known rate of voiding dysfunction is well known and quoted by the authors of this manuscript. Perhaps the pregnant women of this study felt almost no bother from their urinary symptoms secondary due to the understanding that this was a self limited phenomena that would cease because of: it was the miracle of childbirth; or, the life changes and challenges associated with a maturing pregnancy reduced voiding dysfunction to a lower priority on the list of physical, mental and situational events that may affect and bother the pregnant female. A clear message from this article is that almost all women who are pregnant will have some kind of voiding dysfunction with urge and frequency starting early and urinary

incontinence continuing to worsen as the pregnancy continues; nevertheless, the physician probably will not be challenged to find a solution to this problem for the pregnant woman does not view it as a significant bother.

Dr. Steven P. Petrou
Associate Professor of Urology
Associate Dean, Mayo Clinic College of Medicine
Jacksonville, Florida, USA

PEDIATRIC UROLOGY

Antegrade Scrotal Sclerotherapy for Treating Primary Varicocele in Children

Zaupa P, Mayr J, Hollwarth ME
Department of Paediatric Surgery, Medical University of Graz, Graz, Austria
BJU Int. 2006; 97: 809-12

Objective: To evaluate the effectiveness and limitations of antegrade sclerotherapy (AS) for the treatment of primary varicocele in childhood.
Patients and Methods: From December 1996 to December 2004, 88 patients (mean age 13.3 years, range 9-18) with primary varicocele underwent AS (91 varicocele ablations in all). The indications for surgery were testicular pain (16 boys, 18%), a large varicocele with cosmetic implications, testicular hypotrophy (one) and in 71 (81%) the varicocele was detected incidentally during a routine physical examination; all were left-sided. According to the classification used by Tauber, 46 (52%) varicoceles were grade II and 42 (48%) grade III. The clinical and ultrasonography (US) results were evaluated over a median (range) follow-up of 11 (3-60) months, and the operative duration, X-ray exposure time, persistence rate of varicoceles and complications were compared with those using other techniques. RESULTS: In 11 patients there was a palpable difference in size between the testicles, but in only five (6%) was testicular hypotrophy (testicular volume (< 75% testicular volume vs the normal side) confirmed by US. The mean (SEM) operative duration for AS was 33.2 (2.14) min. In 16 (18%) patients it was necessary to expose a second or third vein because the first vein chosen was unsuitable for sclerotherapy. The mean operative radiation exposure was 2.18 (0.21) s. One patient (1%) was treated with a high ligature of the testicular vein (Palomo procedure) after initial unsuccessful AS, and was excluded from the analysis. Eighty-four (97%) patients were eligible for follow-up: six (7%) had a persistent varicocele (four grade II, two grade III), four of whom had repeat sclerotherapy successfully (no recurrence at follow-up). Fourteen (15%) patients had enlarged testicular veins only on US (varicocele grade 0). No patient developed a hydrocele after AS, There were complications after surgery in three (3%) patients (two superficial wound infections, one scrotal haematoma together with focal testicular necrosis).
Conclusions: AS is an efficient minimally invasive surgical method for correcting varicoceles in older children, although the operative duration is sometimes longer than in adults, and surgery can be more difficult because of the smaller veins. Partial testicular necrosis, despite correct AS, is a very rare but serious complication.

Editorial Comment
This paper provides more data on a new, innovative and “minimally invasive” treatment for varicocele. The technique, which uses a short time of fluoroscopy to assess venous drainage and a venous injection of a sclerosing agent, should be associated with minimal postoperative morbidity.

The authors used the technique in 88 patients over 6 years. Mean fluoroscopy time was 2 seconds and mean operative time was 33 minutes. In recent years, the procedure has been done as a “day surgery”. The authors report that there was a persistent varicocele in only 6 patients and no postoperative hydroceles. There was a postoperative increase in relative volume of the affected testis in 4 of 5 evaluable cases. One patient had an ischemic necrosis of the upper pole of the testis, presumably due to the sclerosing agent entering the testicular circulation.

The series is a bit unusual in that very few of the patients had testicular hypertrophy/atrophy. In our experience, a small left testis is the primary reason for operative intervention. If there is only a limited benefit to the procedure, then the risk of the procedure may be more than the benefit. Concerning also is a 7% recurrence rate (and this seems to exclude one patient who underwent a Palomo repair for a failure!). This is higher than anticipated, as is the wound infection rate of 2% and the incident of testicular ischemia.

Overall, this is an interesting contribution on a minimally invasive treatment of varicocele in adolescents. It is a technique worth exploring, but is clearly not without complications. In my opinion it should be reserved for patients with stronger indications.

Dr. Barry A. Kogan
Chief and Professor of Urology and Pediatrics
Albany Medical College
Albany, New York, USA

Clinical Significance of Primary Vesicoureteral Reflux and Urinary Antibiotic Prophylaxis after Acute Pyelonephritis: A Multicenter, Randomized, Controlled Study

Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L
Department of Pediatrics, University of South Florida, Tampa, Florida, USA
Pediatrics. 2006; 117: 626-32; Comment in: Pediatrics. 2006; 117: 919-22

Objectives: To evaluate the role of primary vesicoureteral reflux (VUR) in increasing the frequency and severity of urinary tract infections (UTIs) and renal parenchymal damage among patients with acute pyelonephritis and to determine whether urinary antibiotic prophylaxis reduces the frequency and/or severity of UTIs and/or prevents renal parenchymal damage among patients with mild/moderate VUR.
Methods: Patients 3 months to 18 years of age with acute pyelonephritis, with or without VUR, were assigned randomly to receive urinary antibiotic prophylaxis or not. Patients were monitored every 3 months for 1 year. Dimercaptosuccinic acid renal scans were repeated at 6 months or if there was a recurrence of febrile UTI. Urinalysis and urine culture were performed at each clinic visit. Renal ultrasound scans and voiding cystourethrograms were repeated at the end of 1 year of follow-up monitoring.
Results: Of the 236 patients enrolled in the study, 218 completed the 1-year follow-up monitoring. Groups were similar with respect to age, gender, and reflux grade distribution for those with VUR. No statistically significant differences were found among the groups with respect to rate of recurrent UTI, type of recurrence, rate of subsequent pyelonephritis, and development of renal parenchymal scars. Conclusions: After 1 year of follow-up monitoring, mild/moderate VUR does not increase the incidence of UTI, pyelonephritis, or renal scarring after acute pyelonephritis. Moreover, a role for urinary antibiotic prophylaxis in preventing the recurrence of infection and the development of renal scars is not supported by this study.

Editorial Comment

The authors present a very important study of the effects of reflux on the outcome of patient with UTIs and the benefits of prophylactic antimicrobials. Their findings suggest: 1) that reflux is not a cause of UTIs (many studies would support this notion, as an abnormality of host resistance is more likely); 2) that reflux is not associated with a statistically significant increase in pyelonephritis or renal scarring (the former tends to disagree with the previous literature and the latter is in agreement with the literature); 3) and strikingly, that antibiotic prophylaxis was associated with more UTIs and pyelonephritis than those on no therapy (a very controversial finding).

The findings, especially that prophylaxis was of no benefit (and might have been harmful), are important and suggest a change in clinical management. On the other hand, there are some significant weaknesses in this study. First, the study was not blinded. The control group was not on any medications (vs. being treated with placebo). Hence these patients may have been evaluated differently. Indeed, some of them must have been treated with antibiotics for other illnesses during the study (e.g. ear infections). There is no mention of this. Second, the statistical analysis excluded patients who were non-compliant. A more appropriate analysis would have been an “intention to treat” analysis. Furthermore, the authors state that they needed 60 patients in each group for appropriate recruitment, hence the study was underpowered. Third, clinicians have been aware that abnormalities of host resistance are the main cause of UTIs, but the authors make no mention of voiding dysfunction or constipation. Fourth, the study only lasted 1 year and during that time, only 20% of the patients resolved their reflux. To answer the question that the authors attempt to deal with, a much longer follow-up period is needed.

Despite these misgivings, the authors did find a much higher rate of pyelonephritis in those getting prophylaxis than in those on no medications (12.9% vs 1.7%). This finding is very provocative and warrants further scientific study. If substantiated, this could lead to a paradigm shift in the management of children with reflux.

Dr. Barry A. Kogan
Chief and Professor of Urology and Pediatrics
Albany Medical College
Albany, New York, USA