

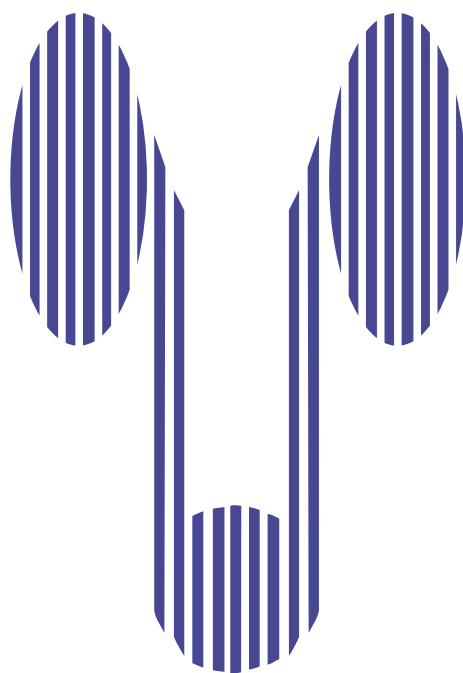


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EDITOR'S COMMENT

Epididymo-Testicular Descent

The May – June 2007 issue of the International Braz J Urol presents interesting contributions from different countries, and as usual, the editor's comment highlights some papers.

Doctors Hadziselimovic and Adham, from the Kindertagesklinik, Liestal, Switzerland, and Institute of Human Genetics, University of Gottingen, Germany, evaluated on page 407 the epididymal development in *Ins13*-deficient mice. Heterozygous and homozygous *Ins13* mutants of a mixed CD1 X 129/Sv genetic background were generated by breeding *Ins13*^{-/-} females with *Ins13*^{+/-} males, and their genotypes were determined by polymerase chain reaction. On the first postnatal day, newborn males were sacrificed, embedded in paraffin, and studied with histochemistry and immunohistochemistry. The authors found an arrest in the development of the epididymis in all homozygous mice. The cauda and corpus of the epididymis were undersized. Compared to the heterozygous epididymis, the homozygous epididymis had fewer peritubular layers and dwarfish musculature. The authors stated that the defective development of the smooth musculature in the epididymis of *Ins13* homozygous mutant mice, combined with its high intraabdominal undescended position, supports previous observations regarding the importance of intact epididymis morphology and function for descent of the epididymo-testicular unit. Doctor Tanyel, from Hacettepe University, Ankara, Turkey, and Dr. Taskinen, from University of Helsinki, Finland, provided interesting editorial comments on this paper.

Doctor Taskinen and colleagues, from the Hospital for Children and Adolescents, Helsinki University, Helsinki, Finland, presented on page 395 the preliminary results in the treatment of urinary incontinence due to sphincter insufficiency with mini-invasive collagen sling procedure. They studied patients with myelomeningocele (n = 8), bladder exstrophy (n = 3), tethered spinal cord (n = 1) and epispadia (n = 1), who underwent sling procedure with porcine dermis acellular collagen matrix. The median age was 15.5 (range 8.9-27.5) years. The median leak point pressure increased from 21.5 (range 5-25) cm H₂O to 85 (range 70-100) cm H₂O. At 1 month, 8 patients, and at 6 months, 3 patients, out of 13 patients were dry. At 12 months, none out of 11 patients was completely dry. The authors concluded that although immediate results were promising in neuropathic incontinence, the results seem to deteriorate to unacceptable low level already during the first year. The authors advised that in exstrophy patients the results are generally poor. Doctor Albouy, from the Rouen University Hospital, France, Dr. Pereira, from the University Hospital La Paz, Madrid, Spain, Dr. Stein, from the Johannes Gutenberg University, Mainz, Germany, and Dr. Snodgrass, from the University of Texas, USA, provided important editorial comments on this paper.

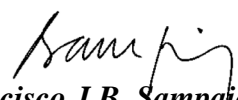
Doctor Nakamura and co-workers from the University of Florida, Jacksonville, USA, assessed on page 347 the utility of enoxaparin in prevention of venous thromboembolism (VTE) in the immediate post-operative period after a radical retropubic prostatectomy (RP). All patients were started on enoxaparin 40 mg

EDITOR'S COMMENT - *continued*

subcutaneously 6-8 hours postoperatively and daily while hospitalized. In addition to RP, 41 men (87%) underwent a pelvic lymph node dissection. Median operative time was 231 minutes. Median estimated blood loss was 700 mL. Two patients developed pulmonary embolism requiring long-term anticoagulation. There were no mortalities. The authors concluded that in men non-compliant with pneumatic compression stockings, initiation of enoxaparin in the immediate postoperative setting was well tolerated and maintained a low (4%) rate of VTE. Thus, enoxaparin may be useful in adjunct with PCS in these patients. Doctor Uemura, from the Kinki University, Osaka, Japan and Doctor Daniela Poli, from the Thrombosis Center, Florence, Italy, provided editorial comments on this manuscript.

Doctor Paez and colleagues, from the Hospital De Fuenlabrada, Madrid, Spain, identified on page 330 the parameters associated with postoperative complications within 30 days in 1,420 consecutive patients operated on an outpatient basis for urological diseases. Postoperative course was complicated in 5% of the patients. Discharge schedule was not completed in 1.1% while unplanned visits resulted in admission in 0.5%. The authors concluded that ambulatory urological surgery could be safe in terms of postoperative complications. It was advised that surgery under general anesthesia, or a higher diagnosis-related group (DRG) relative-weight procedure, increased the risk of complications compared to surgery under regional or local anesthesia or lower DRG relative weight operations.

Doctor Weiland and collaborators, from the University of Minnesota, Minneapolis, USA, conducted on page 313 a prospective randomized single-blind comparison of two nephrostomy catheter designs (8.3F pigtail nephrostomy tube or 8.2F nephroureteral stent), evaluating specifically intraoperative placement and postoperative comfort. The authors concluded that following percutaneous nephrolithotomy, the use of a small pigtail nephrostomy tube results in greater ease of placement and less postoperative pain than a nephroureteral catheter. Doctor Schick, from Gehrden, Germany, Dr. Munver, from Hackensack University Medical Center, Hackensack, New Jersey, USA, and Dr. Turna, from Ege University, Izmir, Turkey, provided important editorial comments on this paper.


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

Preoperative Planning for Renal Cell Carcinoma - Benefits of 64-Slice CT Imaging

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ABSTRACT

Surgery is the primary form of treatment in localized renal cell carcinoma. Adrenal-sparing nephrectomy, laparoscopic nephrectomy and nephron-sparing partial nephrectomy are growing trends for more limited surgical resection. Accurate preoperative imaging is essential for planning the surgical approach. Multislice CT and MR are regarded as the most efficient modalities for imaging renal neoplasms. Development of faster CT systems like 64-slice CT with improved resolution and capability to achieve isotropic reformats have significantly enhanced the role of CT in imaging of renal neoplasms. This review article describes the present state, technique and benefits of 64-slice CT scanning in preoperative planning for RCC.

Key words: renal cell carcinoma; imaging, three-dimensional; surgery
Int Braz J Urol. 2007; 33: 305-12

INTRODUCTION

Renal cell carcinoma (RCC) is the fifth most common cancer in adults and accounts for 85% of all malignant tumors of the kidney (1). It represents 3% of all male and 2% of female cancers. The incidence of RCC is 6.0 - 8.0 per 100,000 of the population (2). Surgery is the primary form of treatment in localized renal cell carcinoma. In addition, adrenal-sparing nephrectomy, laparoscopic nephrectomy and nephron-sparing partial nephrectomy are growing trends for more limited surgical resection (3). The aims of preoperative imaging are to characterize the lesion, identify accessory vessels, define adjacent organ extension, identify lymph nodal or visceral metastases, reliably predict the presence and extent of any

thrombus in the renal vein, vena cava and heart and evaluate the other kidney.

Multislice CT and MR are regarded as the most effective modalities for imaging renal neoplasms. Development of faster CT systems like the 64-slice CT scanner with improved resolution and capability to achieve isotropic reformats have significantly enhanced the role of CT in preoperative imaging of renal neoplasms.

IMAGING TECHNIQUE AND PROTOCOLS WITH 64 SLICE MULTIDETECTOR TECHNOLOGY

Helical CT has dramatically refined the diagnostic evaluation of renal pathologic conditions by al-

lowing image acquisition through the entire kidney during various phases of contrast enhancement after the administration of a single bolus of intravenous contrast material (4-7). Multi-detector 64-slice CT technology takes advantage of significantly reduced image acquisition time for multi-phasic, thin-slice image acquisitions of the kidneys in a single breath-hold with superior contrast bolus utilization.

A precontrast phase provides a baseline from which to measure the enhancement within the lesion after the administration of intravenous contrast material. Calcifications are also seen in 30% of cases of RCC. The enhancement characteristic is important in distinguishing hyperdense cysts from solid tumors (Figures-1A and 1B). Because most renal cell carcinomas have a rich vascular supply, they enhance significantly after administration of intravascular contrast material. Enhancement values of more than 15-20 HU are considered suspicious for malignancy (8); more variation in enhancement is found with small masses due to the dense opacification of adjacent normal parenchyma.

Generally, dual phase imaging with a nephrographic phase and a delayed phase is used for evaluating suspected renal neoplasms and depicting perinephric extension and vascular anatomy. For dual phase imaging, 150 ml of non-ionic lower osmolality contrast media (320 mg ml^{-1}) is injected at 3 cc/sec and images are acquired following delays of approximately 90 seconds and 6 minutes for the nephrographic and pyelographic phases, respectively. In some institutions, an initial scan is also performed in the corticomedullary phase. In the corticomedullary phase, the contrast material is primarily in the cortical capillaries, peritubular spaces, and cortical tubular lamina and has not yet filtered through the more distal renal tubules (9). In the nephrographic phase, the contrast material filters through the glomeruli into the loops of Henle and collecting tubules (9). The renal parenchyma enhances homogeneously during this phase, due to tubular accumulation. Renal tumors enhance less than the surrounding parenchyma in this phase, because they lack normal glomerular-tubular function and hence this phase is most valuable for detecting renal masses and characterizing indeterminate lesions (10). The contrast reaches the collecting system during the delayed or the excretory phase and, as a result, the attenuation of the

nephrogram progressively decreases (Figure-1C). Macari & Bosniak (11) have suggested that measurement of the washout of contrast material from a lesion at 15 minutes allows differentiation between hyperdense cysts and renal neoplasms. In their study, there was no change in the attenuation of high-density cysts between the initial contrast-enhanced CT scan and the 15-minute-delayed images. In comparison, all lesions that proved to be neoplasms at surgery or follow-up studies showed a decrease in attenuation or “de-enhancement” of at least 15 HU at delayed CT, which was attributed to the washout of contrast material from the vascular bed of the tumor (11).

Contiguous thin sections are obtained using protocols dependent on machine manufacturer to enable overlapping reconstruction. At our institution, multiphase CT scans are obtained on GE Lightspeed VCT™ 64 slice scanner at 0.625 mm thickness at a pitch of 1.375:1. These slices are reconstructed at 2.5 mm thickness in the axial plane and coronal reformats are obtained at 5 mm intervals. Sagittal reformats and 3D reconstruction are performed on a case specific basis. Cardiac gated studies are performed for patients with IVC extension (see Figure-4). Multiphase CT of the abdomen is performed from top of the liver to 1 cm below the lowest kidney. A 15 minute scanogram is performed at the end of the exam to assess the ureters. The protocol used at our institution is illustrated in Table-1.

With the rapid acquisition of multiple simultaneous slices and thin-section reformatted coronal and/or sagittal images, the 64-slice CT scanner provides excellent detail in demonstrating local extension to the bowel and retroperitoneum (see Figures-2, 3, 5, 6 and 7). Multiplanar three-dimensional reconstruction techniques including volume rendering, maximum intensity projection and shaded surface display provide comprehensive information about the relationships and possible involvement of vascular structures in renal neoplasms.

TECHNICAL CONSIDERATIONS

Standard oral contrast media for pre-operative assessment of renal neoplasm and vasculature is

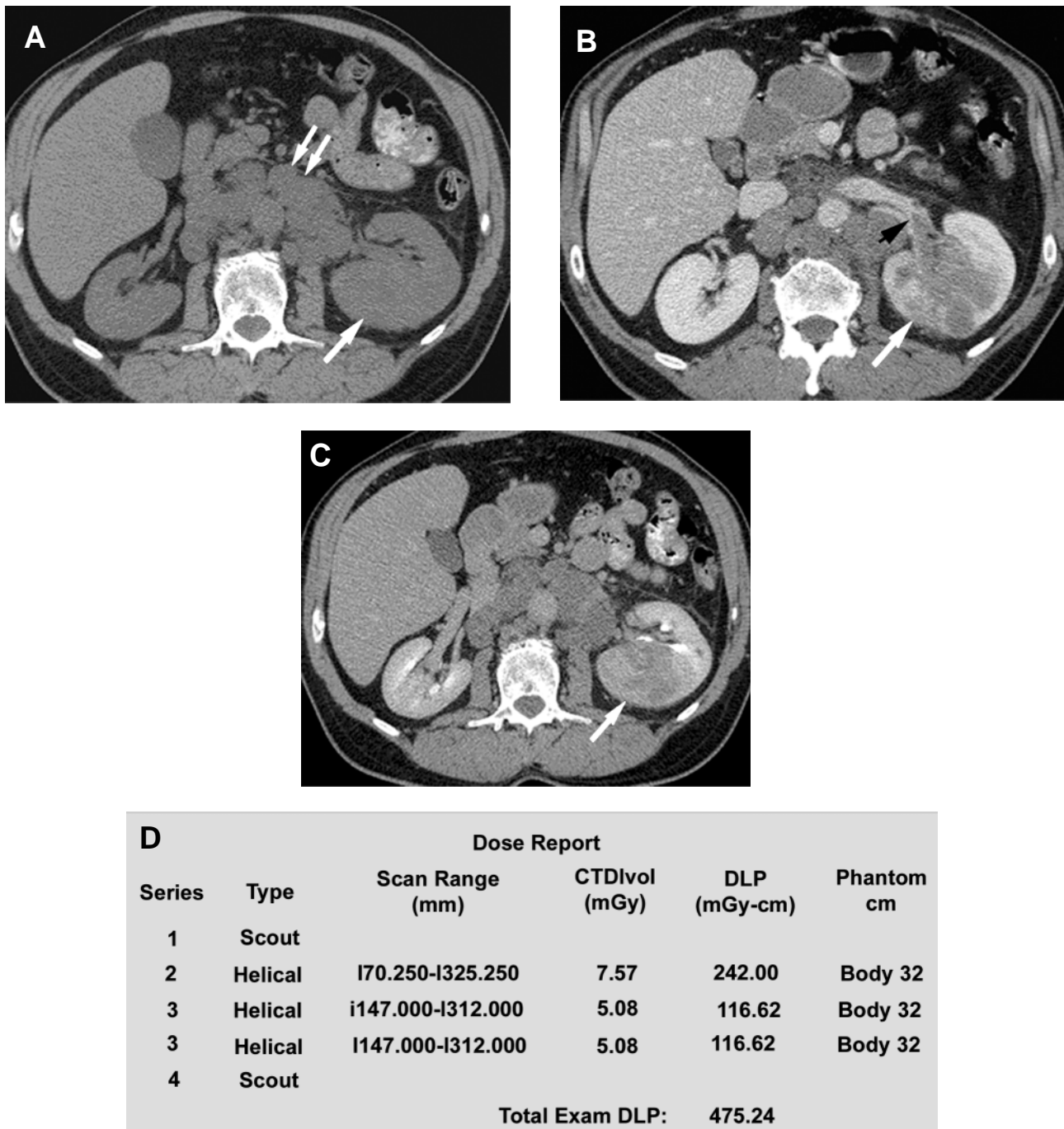


Figure 1 – Axial CT scan of the abdomen showing renal cell carcinoma. A) The tumor is involving the left kidney (arrow) with nodal metastases in the retroperitoneum (double arrow). Note the noncontrast isodense appearance of the mass compared to the rest of the kidney. B) This image illustrates the enhancement in the mass on contrast administration where it increased in enhancement from 20 HU to 110 HU. Note the small thrombus in the proximal left renal vein (black arrowhead). C) Delayed image through the kidney showing the close proximity of the mass to the renal collecting system. D) A typical dose report generated automatically by the scanner for a patient. Dose given is calculated for each scan (noncontrast [series 2], nephrographic [series 3a] and delayed phase [series 3b] with the total dose of 475.24 mGy-cm for this patient).

Table 1 – Protocol used in our institution.

IV contrast	150 cc Optiray™ 320, 3cc/sec
Precontrast	Diaphragm to iliac crest
90 sec delay	1 cm above the top of the kidney to 1 cm below the lowest kidney
6 min delay	1 cm above the top of the kidney to 1 cm below the lowest kidney
15 min delay	AP scout view from diaphragm to base of bladder
Pitch	1.375:1
Slice thickness	0.625 mm
kVp/helical rotation	120-140/0.4-0.8 sec
Recon 1	2.5 mm standard
Recon 2	Coronal 5 mm

unnecessary and may, in fact, obscure intravascular contrast. The radiation dose in our CT scanners is regulated using the Smart mA™ feature, in which the mAs used is regulated according to the amount of tissue (bone/soft tissue) that has to be traversed in x, y and z axes. For example, the mAs used in the mid-abdomen is less than the mAs used in the pelvis due to the bony structures in the pelvis. The radiation dose given also depends on the patient's size with more dose required for larger patients and less for smaller patients. This is regulated according to the body thick-

ness as illustrated in Table-2. Maximum mAs to be used can also be set in this Auto-mA™ feature. Figure-1D illustrates the average dose generated during each scan and the total dose report.

IMAGING AND SURGICAL PLANNING

Surgical planning is usually enhanced by the information obtained from imaging studies: extent of the tumor and its location in the kidney; proximity to

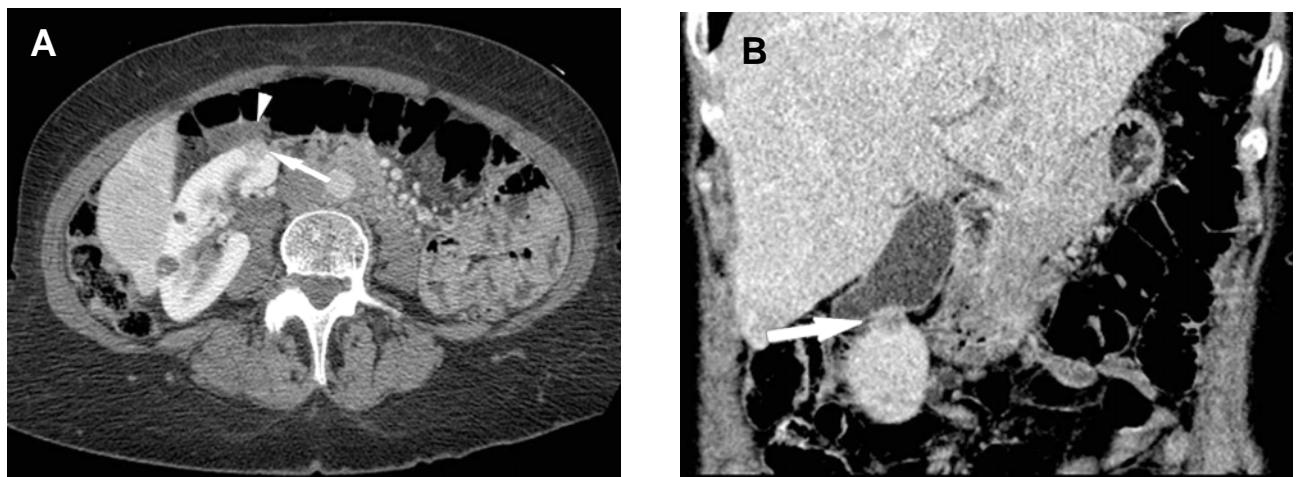


Figure 2 – The axial sections in this case failed to show the gallbladder involvement as clearly as the sagittal reformatted image did. A) Axial section through the abdomen showing the small renal cell carcinoma (white arrow) and the gallbladder adjacent to it (arrowhead). B) Coronal image showing involvement of the gallbladder seen as the loss of fat plane and thickening in the gallbladder wall (white arrow). The gallbladder had to be resected during surgery as it was adherent to the tumor and histopathology showed extension of the tumor into the gallbladder.

Table 2 – The mAs is regulated according to the body thickness as per the table illustrated below.

Patient Size (AP diameter from lateral scanogram)	Auto mA™ Range	Upper Limit of mAs
Measured width < 28 cm	100 - 550	220
Measured width 29 - 34 cm	100 - 700	200
Measured width 35 - 41 cm	100 - 750	375
Measured width > 41 cm	350 - 660	528

the renal collecting system and renal vessels; presence of fat planes between the tumor and other structures (for e.g., liver, colon and posterior abdominal wall

muscles); tumor extension into the renal vein or IVC and the level of this extension. The presence of intrabdominal metastasis, the function of the

Table 3 – Tumor.

Renal hilum	Vessel anomalies, lymph nodes wrapped around vessels
Close proximity to adjacent organs	Left side: pancreas, spleen, aorta/branches, iliacs, psoas, colon Right side: liver/gallbladder, IVC, colon, duodenum, iliacs
Metastases	Liver, LN, adrenals, opposite kidney
Size of mass	Staging Possible radiofrequency ablation (laparoscopic or percutaneous, partial nephrectomy Upper, mid or lower
Location on kidney	Anterior, posterior or lateral Involvement of collecting system Possible radiofrequency ablation (laparoscopic or percutaneous, partial nephrectomy
Collateral vessels	Arteries, veins

Table 4 – Inferior vena cava (IVC).

Level of thrombus Possible invasion of IVC wall	Infrahepatic, intrahepatic, hepatic veins, IVC above diaphragm, atrium.
Distension of IVC Invasion of IVC branches and extent.	Obstruction, extent of bland thrombus above and below IVC tumor thrombus

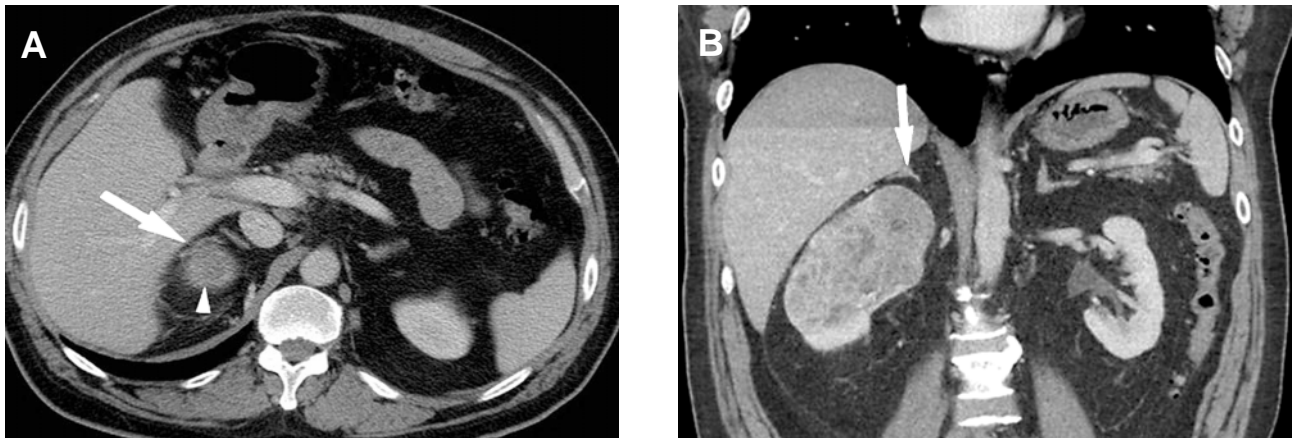


Figure 3 – Noninvolvement of the adrenal shown more clearly on the coronal reformat. A) Axial image through the superior portion of the right kidney illustrating the tumor (arrowhead) in close proximity to the right adrenal gland (arrow). Fat plane between the tumor and the adrenal is not well seen. B) Note that the fat plane is much better seen on this coronal reformatted image confirming non-involvement of right adrenal gland.

contralateral kidney, and the appearance of the adrenal glands are also reliably assessed (12), Tables-3 and 4.

CONCLUSION

64 slice CT imaging provides an improvement in the preoperative analysis of renal masses. The

reformatted images in multiple planes and cardiac-gated sequences can offer additional help in surgical planning and reformatted images provide detailed information about arterial and venous collaterals and invasion of adjacent organs.

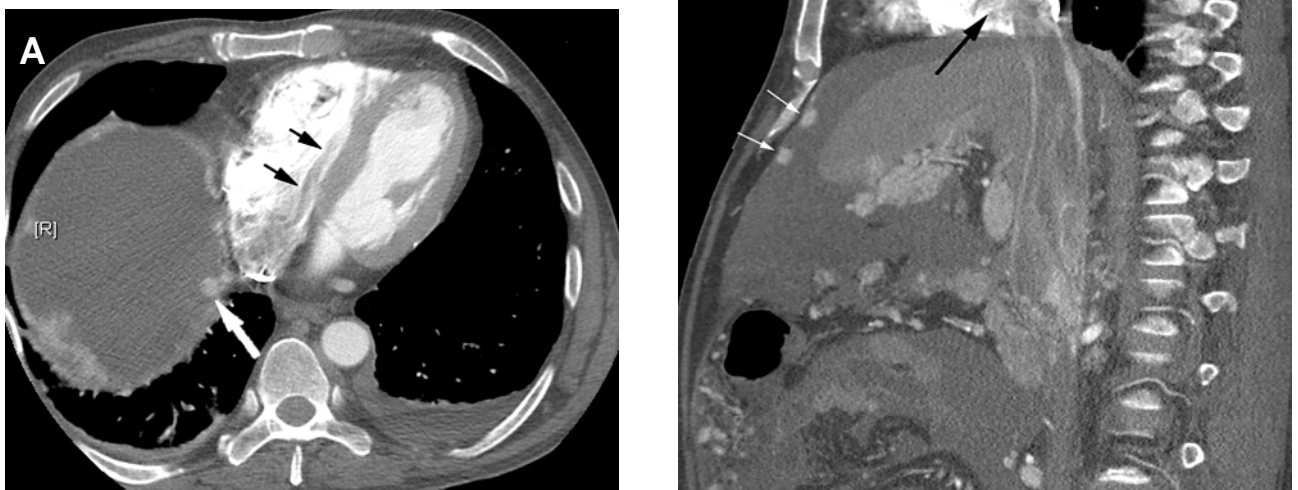


Figure 4 – Tumor thrombus extent shown much better on cardiac-gated reformats. This study was performed by cardiac gating to assess the extent of tumor extension into the inferior vena cava. A) Axial image - tumor is seen to extend into the right atrium and into the right ventricle as well (black arrows). B) Sagittal reformat - note peritoneal metastasis (white arrow) and extend into the right atrium and into the right ventricle well (black arrow).

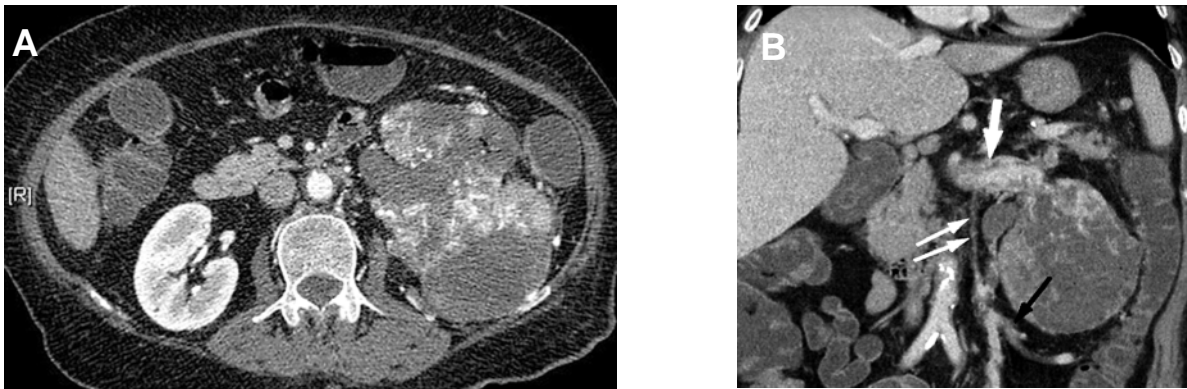


Figure 5 – Ovarian vein thrombosis seen much better on the coronal reformat. A) Axial section demonstrates the large mass in the left kidney with multiple venous collaterals around it. B) Coronal reformatted image illustrates ovarian vein thrombosis (small double white arrows), which was missed on the axial section. Note the large thrombus in the left renal vein (large white arrow); the collaterals (black arrow) drain retrograde through the patent proximal ovarian vein.

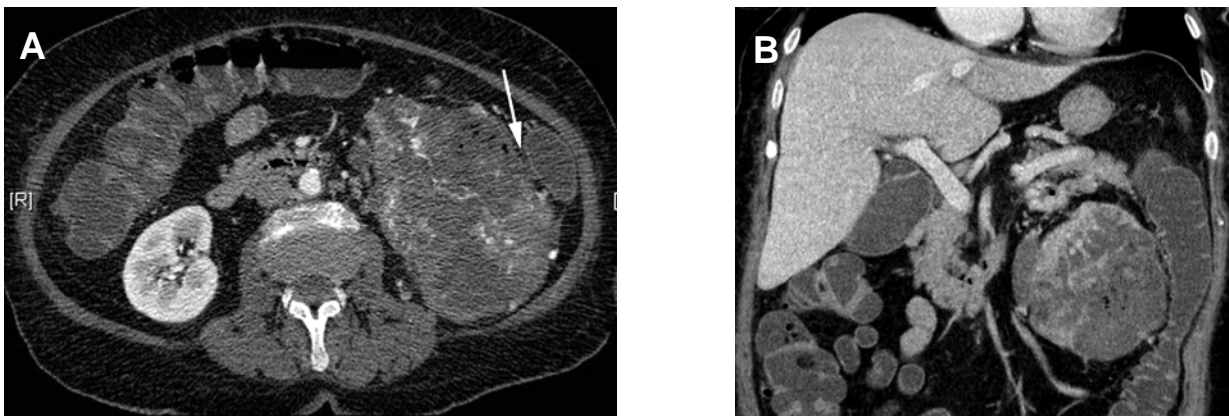


Figure 6 – Relationship to the colon seen better on coronal reformat. A) Axial section through the left renal mass showing fat stranding (white arrow) suggesting extension of the mass into the colon. B) Coronal reformatted image illustrating the extent of contact of the mass with the colon but not confirming invasion. The colon was not involved at surgery.

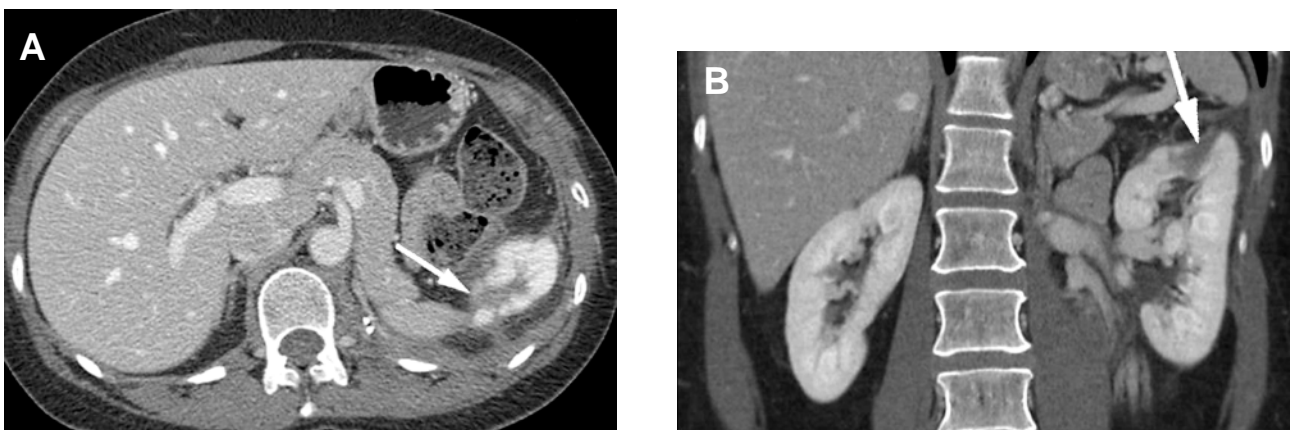


Figure 7– Postoperative CT showing scar tissue without recurrence of tumor. A) Axial section shows irregularly enhancing area in the upper pole of the left kidney (white arrow). B) Coronal reformats through the same area showed this to be only scar tissue (white arrow).

CONFLICT OF INTEREST

None declared.

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Randomized Prospective Evaluation of Nephrostomy Tube Configuration: Impact on Postoperative Pain

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ABSTRACT

Objective: Conduct a prospective randomized single-blind comparison of two nephrostomy catheter designs, evaluating specifically intraoperative placement and postoperative comfort.

Materials and Methods: The single-blind, prospective randomized trial was conducted with institutional review board approval. All patients undergoing percutaneous nephrolithotomy who gave informed consent were randomized to placement of either a Boston Scientific Flexima 8.3F pigtail nephrostomy tube #27-180 (PIG) or a Boston Scientific 8.2F nephroureteral stent #410-126 (NUS). Randomization was concealed from the surgeon until time of placement. Subjective intraoperative placement characteristics were rated by the surgeon on a scale of 1 = excellent, 2 = fair, 3 = good and 4 = poor. The patient's postoperative pain intensity was evaluated with a Visual Analog Pain Score (0 = no pain to 10 = worst pain).

Results: Nine patients were randomized to each group. The PIG group was rated significantly better than the NUS group with regards to ease of placement ($p = 0.007$) and radiopacity of the tube ($p = 0.007$) by surgeon. Visual analog pain scores on postoperative day one, was significantly lower in the PIG group (mean = 2 ± 2) than the NUS group (mean = 5 ± 1) ($p = 0.004$). The mean amount of intra-venous morphine equivalent given in the PIG group (mean = 1 ± 4 Eq morphine) was less on average compared to the NUS group (mean = 6 ± 13 Eq morphine), but the differences did not reach statistical significance ($p = 0.06$).

Conclusions: Following percutaneous nephrolithotomy, use of a small pig-tail nephrostomy tube results in greater ease of placement and less postoperative pain than a nephroureteral catheter.

Key words: percutaneous nephrolithotomy; postoperative pain; nephrostomy; stent; randomized controlled trial
Int Braz J Urol. 2007; 33: 313-22

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) has been the standard of care for large renal calculi since its introduction in 1976 (1). It has been reported that patients will require up to 6.5 doses of narcotics postoperative, and the time to complete recuperation and resumption of full activities is over 9 days (2,3).

It has been proposed that the degree of postoperative discomfort corresponds to the size of percutaneous nephrostomy tube left at the conclusion of the procedure (4). However, while catheter size may impact patient discomfort, the impact of catheter configuration on postoperative pain has not been evaluated in a prospective study.

The purpose of this study is to compare patient discomfort, morbidity and efficacy with two 8F catheters: a pigtail (Flexima) versus an open-ended nephroureteral catheter for postoperative renal drainage following PCNL. This study will specifically evaluate the impact of nephrostomy tube design.

MATERIALS AND METHODS

This single-blind, prospective randomized trial was conducted with institutional review board approval. All patients undergoing percutaneous nephrolithotomy from January 2005 to March 2006 who gave informed consent were randomized to placement of either a Boston Scientific Flexima 8.3F pigtail nephrostomy tube (Flexima copolymers, #27-180) (PIG) or a Boston Scientific 8.2F nephroureteral stent (Percuflex durometer, #410-126) (NUS). Patients were blinded to the stent placed for the duration of the study. Simple randomization was performed using a computer-generated number sequence and was concealed from the surgeon until time of placement.

All patients undergoing percutaneous nephrolithotomy during the study period were approached for informed consent to participate. Patients were excluded if an antegrade endopyelotomy was performed concurrently. Patients were counseled that if a ureteral injury occurred during the procedure a nephroureteral stent would be left in place, however this did not occur during our study.

Placement of each catheter was performed over the working super-stiff guide-wire, through the lumen of the 30F Amplatz nephrostomy sheath at the completion of the procedure. The position of the catheter was confirmed fluoroscopically with the pigtail nephrostomy catheter positioned in the renal pelvis, while the nephroureteral stent traversed the ureter with coiling in the bladder. The coils for each catheter were formed by gentle tension on the retention suture. The catheters were secured at the skin level with 2-0 silk sutures.

Subjective intraoperative placement characteristics were rated by the surgeon on a scale of 1 = excellent, 2 = fair, 3 = good and 4 = poor. The patient's postoperative pain intensity was evaluated

with a Visual Analog Pain Score (0 = no pain to 10 = worst pain). Narcotic diaries were maintained and all opioid drugs were converted to a morphine equivalent (Eq morphine), Table-1.

The present study was powered based on prior studies of percutaneous nephrostomy size and technique, which have demonstrated significant differences with sample sizes of 10 patients per arm (4-6).

Student t-test was also used to study the impact of catheter configuration on pulmonary function (FEV1), blood loss (Hgb), serum creatinine level (Cr), length of stay, and time to ambulation and oral food intake (hours). It is relevant to mention that oral fluid intake was encouraged to commence in the immediate peri-operative recovery period, and time to oral intake was defined as tolerating oral liquids. P values < 0.05 were considered significant.

Nephrostomy catheters were clamped on postoperative day 1 if there were no concerns regarding fever, pain, hematuria or residual stone fragments. If the patient did not experience pain within 3 hours of clamping, the catheter was removed by transecting the catheter at the skin level to release the retention coil.

RESULTS

Nine patients were randomized to each group. Demographic features of both groups (gender, stone size, laterality) were comparable except mean age, which was significantly lower in the NUS than PIG (54 ± 11 versus 65 ± 11 years, respectively) ($p = 0.004$) (Table-2).

Table 1 – Calculating morphine equivalent dose: $\text{Total EDU} \times \text{morphine } 30 \text{ mg} = \text{morphine equivalent dose}$.

Opioid	Equianalgesic Dose ED (mg)
Oxycodone	20
Hydrocodone	30
Codeine	200
Meperidine	300

Table 2 – Demographic features of the 8.3F pigtail nephrostomy tube (PIG) and the 8.2F nephroureteral stent (NUS) groups.

	PIG (range)	NUS (range)	p Value
Age (years)	65 ± 11 (51-78)	54 ± 11 (36-69)	0.04*
Male / Female	6 / 2	6 / 5	0.34
Stone size (cm ²)	6.7 ± 1.2 (2.5 - 7.5)	3.2 ± 1.3 (1.6 - 6.0)	0.15
Left / Right Side	3 / 5	8 / 3	0.14
BMI (kg/m ²)	30 ± 7 (21.2-42.9)	29 ± 6 (19.1 - 40.1)	0.40
Previous PCNL	4	4	0.58

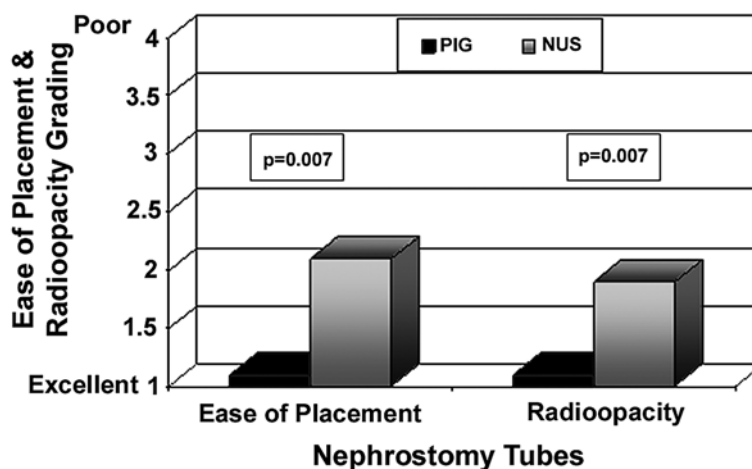
The PIG group was rated significantly better than the NUS group with regards to ease of placement ($p = 0.007$) and radiopacity of the tube ($p = 0.007$) by surgeon (Figure-1).

Visual analog pain scores on postoperative day one, was significantly lower in the PIG group (mean = 2 ± 2) than the NUS group (mean = 5 ± 1) ($p = 0.004$) (Figure-2). The mean amount of intra-venous morphine equivalent given in the PIG group (mean = 1, Standard Deviation = 4 Eq morphine) was less on average compared to the NUS group (mean = 6, Standard Deviation = 13 Eq morphine), but the differences did not reach statistical significance ($p = 0.06$). In the PIG group five of eight patients (62.5%)

had their catheters placed supra-costal versus only 3 of eleven (27.7%) in the NUS group. There was no significant difference in calyx selected for puncture in the PIG (2 upper, 4 middle and 2 lower) and NUS (3 upper, 2 middle, 6 lower) groups. The location of puncture did not influence the ease of placement in both groups.

One patient of NUS group was excluded from the time to ambulation and PO intake statistical analysis because of a pulmonary embolus that required rest and fasting for a longer period of time (120 hours).

PIG group had significant less time ($p = 0.005$) to PO intake than NUS group (3.7 ± 2.8 hours PIG -

**Figure 1** – Surgeon's rating of nephrostomy tube ease of placement and radiopacity.

Evaluation of Nephrostomy Tube Configuration

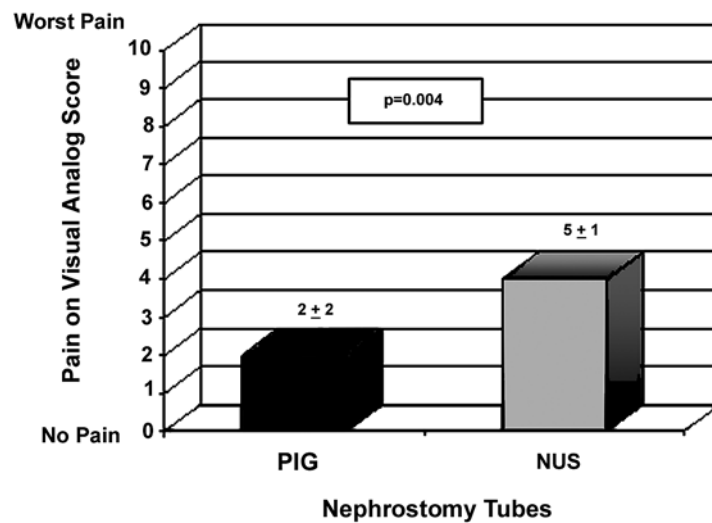


Figure 2 – Postoperative day-1 pain.

10.88 ± 6.19 hours NUS). Neither catheter was superior in regards to change in Hgb (0.96 ± 0.53 mg/dL NUS, 2.16 ± 0.53 mg/dL PIG) (p = 0.15); change in Crt (0.047 ± 0.57 mg/dL NUS, 0.14 ± 0.22 mg/dL PIG) (p = 0.20); change in FEV1 (88.9 ± 32.02 mL NUS - 243.6 ± 119.89 mL PIG) (p = 0.60); length of stay (2.81 ± 1.82 days NUS - 3.15 ± 3.44 days PIG) (p = 0.80); dressing changes (6.8 ± 5.90 NUS - 3.75 ±

2.90 PIG) (p=0.38), or ambulation (17.50 ± 10.53 hours NUS - 9.7 ± 6.0 hours PIG) (p = 0.11) (Table-3).

COMMENTS

Percutaneous nephrostomy tubes are associated with postoperative pain and long hospital

Table 3 – Pre and postoperative data for the 8.3F pigtail nephrostomy tube (PIG) and the 8.2F nephroureteral stent (NUS) groups.

	PIG (range)		NUS (range)		Postop Change		pValue
Average	Preop	Postop	Preop	Postop	NUS	PIG	-
Hgb (mg/dL)	12.97	10.35	12.36	11.41	0.96	2.16	0.15
	(10.1 - 14.8)	(8.9 - 14.8)	(10.4 - 14.7)	(8 - 15)			
Crt (mg/dL)	1.09	1.24	1.19	1.14	0.05	0.14	0.20
	(0.7 - 1.4)	(1.0 - 1.6)	(0.6 - 2.6)	(0.7 - 2.6)			
FEV1 (mL)	1978.0	1734.3	1445.0	1361.1	88.9	243.6	0.60
	(700 - 3500)	(700 - 3500)	(800 - 2000)	(800 - 2000)			
Ambulation (h)	9.7	(4 - 21)	17.5	(2 - 120)	-		0.11
Hospital stay (d)	3.15	(1 - 10)	2.81	(1 - 7)	-		0.80
PO intake (h)	3.7	(1 - 8)	6.19	(2 - 18)	-		0.05*
Dressings (n)	3.75	(2 - 8)	6.80	(1 - 15)	-		0.38

Hgb = hemoglobin; Crt = creatinine; FEV = forced expiratory volume.

stays. The intensity of distress is related to the size of the nephrostomy catheters. It has been reported that smaller catheters reduce patient discomfort without increasing procedure morbidity (5).

The issue of stent size (8F vs. 20F or larger) has already been addressed clearly in the literature (5,6) and currently our practice is to utilize exclusively an 8F drainage tube after PCNL. Tubeless PCNL has been shown to be an effective alternative in select patients (6), though one might debate the relative quality of life issues related to a PNT vs. ureteral stent left following a tubeless procedure. Recently, Choi et al. demonstrated in a randomized trial that the post operative discomfort is similar between small bore nephrostomy tubes and tubeless PCNL (7). Though convalescence was shorter for the tubeless cohort in this study, the nephrostomy tube was left in place for 3-5 days, which exceeds our practice of removing the tube within the first 48 hours if possible.

In our minds, the remaining issue to resolve was to determine the optimal configuration of the percutaneous nephrostomy catheter. Though one might intuitively predict a pigtail catheter would cause less discomfort, lacking the ureteral and bladder segments, an alternative view would be that the nephroureteral stent promotes drainage, particularly in the face of clot or residual stone fragments. Nephrostomy catheter configuration has previously been demonstrated to impact drainage properties and retention strength (8).

Whereas scientific reports have analyzed specifically the size of the PNT and its relationship to postoperative pain, no study has prospectively compared different types of mini-tubes of the same size with regards to patient discomfort.

In this study, 18 patients were randomized and prospectively analyzed regarding severity of pain and opioid intake after placement of two different 8.3F. Catheters; a pigtail (PIG) and nephroureteral (NUS) for nephrostomy drainage. Visual analog pain scores demonstrated that the PIG group had significantly less postoperative pain than the NUS group ($p = 0.04$). The same trend was noted with regards to intra-venous morphine equivalent required by PIG group, which was less on average than NUS ($p = 0.06$). Surprisingly, PIG group had a higher incidence of supra-costal

punctures, which would predispose to more pain, therefore the differences between NUS and PIG may be even more pronounced than noted in our results.

None of the groups showed significant differences in blood loss, length of hospital stay, pulmonary function and time to ambulation; these data are supported by recent reports that present small bore catheters as a safe and comfortable choice for nephrostomy drainage (5, 6). Time to PO intake was significantly lower in the PIG group than the NUS ($p = 0.05$), which may be linked to the difference in pain described above.

In addition, both catheters were evaluated by the urologic surgeons according to the ease of placement and radiopacity. Although both catheters demanded no great effort in their insertion, the PIG catheters were found to be easier to manipulate and easier to be visualized under fluoroscopy than NUS ($p = 0.007$).

In a different patient population, Mokhmalji et al. presented a prospective randomized clinical trial comparing quality of live (QoL) after ureteral (JJ) stent or nephrostomy tube placement for relief of ureteral obstruction. They demonstrated that reduction in QoL was moderate but more pronounced in patients with ureteral stents than in those who underwent percutaneous nephrostomy (9). This study supports our observation that patient discomfort increases when the drainage catheter traverses the ureter and bladder; for this reason, we currently use a nephroureteral stent only in the face of endopyelotomy or ureteral perforation.

In contrast, Karger et al. stated that the 8.5F NUS spared patients of post operative pain compared to a historical control group comprised of patients with a 24F Malecot nephrostomy tube (10). This study, however, was not randomized and used catheters of greatly differing calibers for their comparison; such that the observed differences could be attributable to catheter size rather than configuration.

One limitation of the present study is that we did not assess other urinary tract symptoms such as urgency and frequency, nor did we localize the site of the pain. Nevertheless, as our study evaluates the impact on post operative pain and morbidity of two catheters of the same size, the findings suggest that

nephrostomy catheter design may play an important role in patient postoperative comfort.

CONCLUSION

Following percutaneous nephrolithotomy, use of a small pig-tail nephrostomy tube results in greater ease of placement and less postoperative pain than a nephroureteral catheter.

CONFLICT OF INTEREST

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EDITORIAL COMMENT

The era of open stone surgery and plastic surgical correction of the renal pelvis, beside the unavoidable trauma of open surgical access had already been dominated by postoperative problems regarding drainage systems and urinary reduction.

Postoperative problems due to different percutaneous and/or intraluminal catheters basically are induced by the following factors: affection of the respiratory system caused by transpassing catheters, affection of the percutaneous stent location because of the renal mobility, suppression of the peristaltic activity inside the collecting system caused by the "foreign bodies", decline in reflux – protection caused by ureteral stents entering the bladder and passing Waldeyers sheet.

The effect on patients postoperative condition means additional multiple branch therapy, i.e. analgesic regimen, treatment of ascending infections,

prolongation of the hospital stay and an increase in costs as well.

The urological progress of the last decade especially with minimally invasive procedures and also minimal percutaneous nephrolithotripsy (PCNL) induced effective research and investigations to minimize the postoperative drainage related trauma, what has also been demonstrated by the present article, culminating in the tubeless postoperative nephrostomy using the pouring effect of gelatine to perform a watertight closure of the working channel.

The very actual status of the investigations demands for obligatory strategies and routes also for drainage systems after PCNL dependant on residual clearance function, stone history (number, size, consistency), infectious conditions, duration of the surgical procedure and patients complication level value.

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EDITORIAL COMMENT

One of the most significant areas of investigation with regards to percutaneous nephrolithotomy (PCNL) involves the need for, and type of drainage of the collecting system with a percutaneous nephrostomy catheter. Postoperative discomfort from a percutaneous catheter placed at the conclusion of the procedure has been attributed to a number of factors including catheter diameter, access location, and number of catheters. Many surgeons have been revising their technique in favor of placing smaller catheters or performing tubeless PCNL, with the intention of reducing patient discomfort without compromising procedural outcomes or increasing complications.

The purpose of this study was to prospectively examine the impact of percutaneous catheter design on postoperative pain following PCNL. Specifically, an 8.3F pigtail nephrostomy catheter (PIG) was compared to an 8.2F open-ended nephroureteral catheter (NUS). The authors conclude that the PIG was less painful than the NUS, based on lower visual analog pain scores and lower analgesic requirements. Increased pain in the NUS group was thought to be due to the catheter traversing the ureter and bladder. This idea has been previously proposed in studies comparing the discomfort associated with a percutaneous nephrostomy catheter as compared to an indwelling ureteral stent in the setting of obstruction.

The authors should be applauded on their efforts in conducting this evaluation, however several limitations are apparent. There is a statistically significant difference in ages between the two groups, as the mean age of the NUS group was 11 years younger than the PIG group. Pain thresholds between individuals of different ages can vary considerably and may impact reporting of pain scores. The authors state that both catheters demanded no great effort in their insertion, although the PIG group was subjectively rated better in terms of ease of catheter placement. The authors did not cite a reason for this observation. If this is the case, then one might conclude that more difficult catheter insertion in the NUS group may translate into greater postoperative discomfort.

While there was no significant difference in selection of calyceal puncture between the groups, 62.5% of catheters in the PIG group were supracostal,

compared to only 27.7% in the NUS group. It is surprising to note that despite a higher number of supracostal catheter placements in the PIG group, the pain scores were lower than in the NUS group. This would suggest that the location of the access does not correlate with the amount of discomfort. The authors appropriately acknowledge that they did not localize the location of pain in either group. This point is extremely important, since pain in the NUS group may be compounded by ureteral and bladder irritation. Without this information, it may be conceivable that even the suture securing each catheter to the skin, may somewhat contribute to the degree of discomfort.

In summary, nephrostomy tube configuration does appear to directly impact postoperative pain. Based on the results provided by the authors, additional studies with larger matched cohorts would serve to validate the conclusions of this study.

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EDITORIAL COMMENT

In this prospective randomized trial, the authors evaluated the impact of percutaneous tube configuration (8.3F pigtail nephrostomy tube vs. 8.2F nephroureteral stent) on pain scores at postoperative day-1 and the ease of intraoperative tube placement following percutaneous nephrolithotomy (PCNL) in a total of 18 patients. There were nine patients in each arm. The pigtail group was associated with easier tube placement and better visualization on fluoroscopy (subjective evaluation by the surgeon). Furthermore, patients who received pigtail nephrostomy tubes had marginally less analgesia requirements (morphine equivalent) and their pain scores were significantly lower. There was no statistical difference between

the two groups regarding the change in hemoglobin and creatinine levels, change in pulmonary function, time to ambulation, and hospital stay. However, patients in the pigtail group resumed oral intake earlier. On the basis of their findings, the authors concluded that the use of an 8.3F pigtail nephrostomy tube following PCNL resulted in greater ease of placement and less postoperative pain than an 8.2F nephroureteral catheter.

The efficacy and safety of PCNL for the treatment of kidney stones greater than 2 cm in diameter in upper and middle calices, and greater than 1 cm in diameter in lower calices, is well established. The ideal drainage method following PCNL is of

interest, because it is intimately related to the patients' quality of life and length of hospital stay. Currently, there is a trend towards the use of the "tubeless" technique (involving the placement of a ureteral stent instead of a nephrostomy tube) or the use of small bore nephrostomy tubes. Several points relating to the complexity of the procedure, status of the affected kidney, and body habitus of the patient need to be considered before choosing the ideal tube following PCNL. The "tubeless" technique may be appropriate in select patients, such as those with small stone burdens, no significant intraoperative complications and no significant residual stones (1). As such, presence of an intraoperative complication such as significant hemorrhage or perforation, or residual stones mandates placement of a nephrostomy tube. The "tubeless" technique raises concerns that the risk of bleeding and urinary extravasation may be increased. Moreover, the concurrent morbidity of stents should not be underestimated. Additionally, patients with severe hydronephrosis are likely to benefit from the nephrostomy tubes. Lastly, obese patients may suffer from dislodging of the pigtail tubes resulting from pannus movement.

However, "tubeless" PCNL appears to reduce postoperative morbidity. Therefore, it would be useful to examine adjunctive methods that would augment the efficacy and safety of this technique. For example, gelatin matrix thrombin has been used to seal PCNL tracts in small patient series with favorable preliminary results. Lee et al. (2) first described the use of gelatin matrix thrombin in PCNL tracts. However, to date, a prospective randomized trial does not exist in the published literature assessing the true role of hemostatic agents and/or urinary sealants for PCNL tract closure.

As the authors stated, nephroureteral stents may promote more efficient urinary drainage compared to pigtail tubes. Traditionally, drainage after PCNL has been achieved with large bore re-entry tubes to provide effective pelvi-ureteric junction stenting, tamponade of the PCNL tract, preservation of ureteric access, and allow repeat access for a "second look" PCNL if required. However, the current data supports the use of small bore tubes following uncomplicated PCNL (references 4 - 6 in the article). Desai et al. proposed

an algorithm for nephrostomy drainage after PCNL based on their large experience and findings of their prospective randomized trial comparing the three different drainage methods (reference 6 in the article). In brief, the authors recommend the use of a large bore (20F) nephrostomy tube following complicated PCNL, and either a 6F double-J stent (if stone-free) or a small bore (9F) nephrostomy tube (if residual stones) following uncomplicated PCNL. Another drainage strategy was proposed by Kim et al. after PCNL for large or complex stones (3). In the presence of pyonephrosis, large residual stones and/or difficult renal anatomy, a 20F re-entry tube was recommended. If multiple accesses were required then a 20F circle loop was suggested and an 8.5/10F cope loop was recommended after a standard PCNL.

The authors should be commended for conducting a prospective randomized trial. However, some pertinent issues deserve attention. Ideally, it would be natural to expect a detailed inclusion and exclusion criteria from a prospective study protocol. Secondly, the impact of nephrostomy tube size on stone-free rates with small residual stones after PCNL is not well addressed. From this perspective, it would be useful to know the stone-free rates after PCNL in the current study as well as in future studies on this topic. More importantly, evaluation of the impact of stent/tube diameter or configuration on the patients' quality of life, as assessed by validated questionnaires, would undoubtedly provide more objective and structured analysis. For instance, Joshi et al. developed and validated the ureteral stent symptom questionnaire (USSQ) for symptom and quality of life evaluation to assess the impact of different types of stents (4). Finally, the sample size estimation for this study does not appear to be based on the primary outcome of interest and the method of power calculation has not been thoroughly described. The only prior study of the three referenced by the authors for power calculation, that has assessed pain as a primary endpoint, recruited 30 patients. Therefore, it is likely that this current study in which 18 patients were recruited was under-powered. Fortunately, the authors found some significant results. The authors reported, for most variables, the means and standard deviations, and used t-tests for data analysis. Medians and inter-

quartile ranges (IQR) are more appropriate to avoid small means with meaningless negative standard deviations, e.g., IV morphine equivalent with mean = 1 and SD = 4. For a study with only 9 patients in each of the two arms, it is important to check assumptions by using t-tests primarily assessing the normality assumption for the continuous variables. Alternatively, nonparametric methods, such as a Wilcoxon test, can be used. Even though this is a randomized study, patient age was different between the two arms. That alone may render the significant difference in the primary outcome artificial.

Notwithstanding these caveats, the current study adds information to the literature with some objective evidence to support the role of small bore pigtail nephrostomy tubes after percutaneous nephrolithotomy in order to reduce operative morbidity.

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REPLY BY THE AUTHORS

We appreciate the constructive editorial comments of the expert reviews, and would like to clarify the following points. All patients undergoing single access PCNL were offered informed consent - there were no exclusion or inclusion criteria. The USSQ is validated specifically for ureteral stents; it

has not been validated for percutaneous nephrostomy tubes. All studies referenced for the power analysis used postoperative pain as a primary endpoint. The one study that randomized 30 patients (ref. 6 in the article) had 10 patients in each arm (large-bore, small-bore, tubeless).

Management of Diaphragmatic Injury during Transperitoneal Laparoscopic Urological Procedures

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ABSTRACT

Introduction: Carbon dioxide pneumothorax is a rare complication in laparoscopic urology, but with the widespread use of laparoscopy and the increasing surgical pathologies managed by this technique this infrequent complication has become a potential risk.

Materials and Methods: A total of 786 laparoscopic transperitoneal urologic operations were reviewed at our institution. All procedures were performed by the same surgeon and included 213 adrenalectomies, 181 simple nephrectomies, 143 lymphadenectomies, 118 radical nephrectomies, 107 partial nephrectomies and 24 nephroureterectomies. Mean patient age was 53.2 years (range 24 to 70). Mean BMI was 28.15 Kg/m² (range 20 to 48.9).

Results: A total of 6 cases (0.7%) of diaphragmatic injury were found. All reported patients had additional factors that may have contributed to diaphragmatic injury. Diaphragmatic repair was always carried out by intracorporeal suturing and only one case required chest tube placement. All patients evolved uneventfully.

Conclusions: Repair of diaphragmatic injuries should always be attempted with intracorporeal suture since this is a feasible, reproducible and reliable technique.

Key words: *pneumothorax; diaphragm; intraoperative complications; laparoscopy*

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INTRODUCTION

The clear advantages that laparoscopy provides over open surgery have made this technique very popular in the last decade. However, for urologist laparoscopy has gained wide acceptance only in recent years. Inadvertent diaphragmatic injury during transperitoneal laparoscopic surgery in urology is a rare occurrence (1). Yet, with the widespread use of laparoscopy and the increasing surgical pathologies managed with this technique, there is a potential for an increased risk of carbon dioxide pneumothorax due

to diaphragmatic injury. Capnothorax associated with laparoscopic surgery is different from air pneumothorax and may call for a different treatment.

We report the laparoscopic management of six cases with iatrogenic diaphragmatic injury during laparoscopic urologic surgery.

MATERIALS AND METHODS

The records of 786 laparoscopic transperitoneal urologic operations were reviewed. All

procedures were performed by the same surgeon (OAC) and included: 213 adrenalectomies, 181 simple nephrectomies, 143 retroperitoneal lymphadenectomies, 118 radical nephrectomies, 107 partial nephrectomies for cancer and 24 radical nephroureterectomies. A total of 6 cases of diaphragmatic injury were found. Mean patient age was 53.2 years (range 24 to 70). Mean BMI was 28.15 (range 20 to 48.9). Operative and clinical records were reviewed and patient outcome evaluated. Details of injury identification and operative management are specified (Table-1).

For diaphragmatic repair, no additional trocars were needed. In most cases, usual working port configuration for adrenalectomy and nephrectomy allowed intracorporeal suturing. However, if necessary an additional 5 mm port was placed on left or right flank respectively. The defect was repaired with separate 0-poliglacline sutures while pneumoperitoneum was decreased in 12 mmHg. Before the stitches were secured, the anesthesiologist administered a large inspiratory breath (Figures-1 and 2).

Criteria used for chest tube placement was pneumothorax greater than 20% of lung volume or associated with hemodynamic or ventilatory changes.

RESULTS

A total of 6 cases of diaphragmatic injury were recorded during three adrenalectomies, one partial nephrectomy, one radical nephrectomy and one left retroperitoneal lymph node dissection respectively. In all cases, the cause of pleural lesion was iatrogenic injury to the diaphragm.

Case 1 - A 24-year-old woman (BMI 21) with a history of ulcerative colitis and an incidental 12 cm left adrenal cyst underwent laparoscopic adrenalectomy. During surgery an increase in end inspiratory pressure and end tidal carbon dioxide levels was noted. This prompted the inspection of the operative field. A 2 cm lesion was found on the left diaphragm, no pulmonary parenchyma was evident. The defect was repaired with 0-poliglacline sutures while pneumoperitoneum was decreased in 12 mmHg with the anesthesiologist administering a large inspiratory breath before securing the stitches. Adrenalectomy was com-

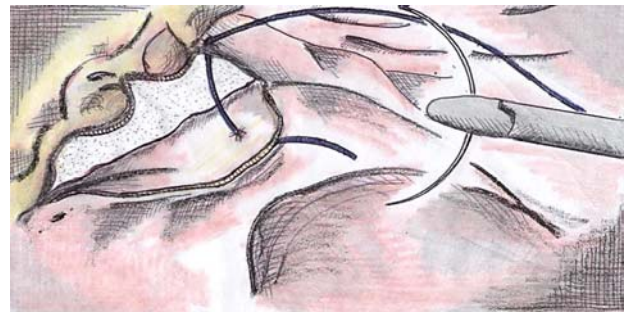


Figure 1 – Diaphragmatic lesion repaired with intracorporeal suturing.

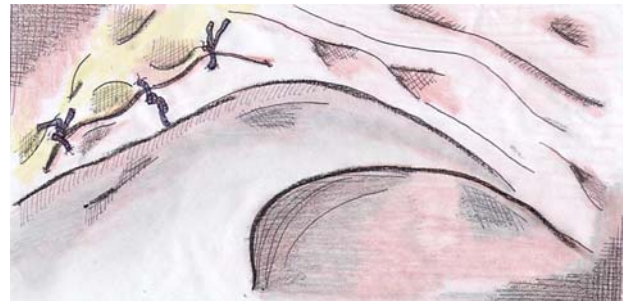


Figure 2 – Diaphragmatic repair completed.

pleted with a total time of 135 minutes. A chest tube was placed and left for 12 hours. Follow-up chest x-ray showed no residual pneumothorax. The patient was discharged home after 48 hours.

Case 2 - A 40-year-old woman (BMI 24.5) underwent a right adrenalectomy for an incidental 7 cm right adrenal mass. During adrenal dissection a 3 cm iatrogenic injury was identified on the right diaphragm with pulmonary parenchyma exposure. The pleural cavity was inspected with the laparoscope and a pleural mass was observed. A biopsy specimen was taken and the diaphragmatic defect was repaired using the technique previously described. The procedure was finished in a total of 60 minutes. Follow-up x-rays showed no residual pneumothorax. Final histologic examination revealed an adrenal adenoma and a pleural teratoma. The patient was discharged home after 48 hours.

Case 3 - A 70-year-old female patient (BMI 48.9) with a 3 cm lateral right mid pole renal tumor underwent a partial nephrectomy. The partial nephrectomy was carried out under warm ischemia of 25 min-

Table 1 – Patient data, injury specifications and operative management.

Case	Age	Sex	BMI	Date of Injury	Surgery	Tumor Size (cm)	Operative Time (min)	Blood Loss (mL)	Floppy Diaphragm Sign	Repair Method	Chest Tube	Previous Surgery	Associated Pathologies
1	24	F	21	04/18/96	Left adrenalectomy	12	135	0	No	Intracorporeal suture	Yes	No	Ulcerative colitis
2	40	F	24.5	02/14/99	Right adrenalectomy	7	60	0	No	Intracorporeal suture	No	No	No
3	70	F	48.9	07/11/03	Right partial nephrectomy	3.5	120	100	Yes	Intracorporeal suture	No	Cholecystectomy	No
4	52	M	32	11/15/04	Left radical nephrectomy	5	150	400	No	Intracorporeal suture	No	Open partial nephrectomy	No
5	68	M	20	08/20/05	Para-aortic lymph node dissection	7	120	200	Yes	Intracorporeal suture	No	Laparoscopic radical nephroureterectomy	Previous chemotherapy
6	65	F	22.5	12/28/05	Left adrenalectomy	5	60	0	Yes	Intracorporeal suture	No	No	No

utes with a total operative time of 120 minutes. While the upper pole of the right kidney was being dissected the “floppy diaphragm” sign was observed. After inspection a 1 cm diaphragmatic lesion was evident. No pulmonary parenchyma was seen. The defect was repaired with the technique described above. There was no need for tube thoracostomy and follow-up x-rays revealed complete resolution of the pneumothorax. The patient was discharged after 48 hours.

Case 4 - A 52-year-old man (BMI 32) that underwent a previous open left partial nephrectomy for renal carcinoma was submitted to a laparoscopic left radical nephrectomy for a 5 cm recurrent tumor. During surgery a 4 cm diaphragmatic injury was observed and repaired laparoscopically as described before. The procedure was finished in 150 minutes. There was no need for chest tube and the patient was discharged on postoperative day 5.

Case 5 - A 68-year-old male patient (BMI 20) with a history of laparoscopic left radical nephroureterectomy and previous chemotherapy underwent a left retroperitoneal lymph node dissection for a 7 cm left para-aortic mass. During surgery a 3 cm diaphragmatic defect was evidenced in association with the sudden inferior billowing of the diaphragmatic wall. The defect was repaired as previously described. The procedure was completed in 120 minutes. There was no need for tube thoracostomy and follow-up x-rays showed no residual pneumothorax. The patient was discharged on postoperative day 3.

Case 6 - A 65-year-old woman (BMI 22.5) underwent a left adrenalectomy for an incidental 5 cm left adrenal mass diagnosed during lung cancer staging. During the procedure two 1 cm diaphragmatic lesions were produced while the peritoneum was dissected over the colon. The “floppy diaphragm” sign was unmistakable in this case. The lesions were repaired and the procedure was finished in a total of 60 minutes. No chest tube was put in place and follow-up x-rays showed no residual pneumothorax. The patient was discharged on postoperative day 3.

COMMENTS

Iatrogenic injury of the diaphragm during general laparoscopy is unusual. In laparoscopic renal and

adrenal surgery this complication does not exceed 0.6% in the largest series (2). The occasional occurrence of this complication is due to the clear separation that exists between the kidneys and the diaphragm (1). However, with the advances made in laparoscopic renal and adrenal surgery, more surgeons are expanding the limits for laparoscopy by attempting very demanding procedures. This may sustain or even increase the incidence of iatrogenic diaphragmatic injuries. It is noteworthy that this series reflects the experience of a single surgeon that has surpassed the learning curve of standardized techniques (OAC).

All of the patients that we report have additional factors that may have lead to diaphragmatic injury. Morbid obesity, large tumors, inflammatory intestinal pathologies, previous surgeries and chemotherapy are some of the factors that can facilitate the occurrence of diaphragmatic lesions. However, adrenal surgery by itself has an inherent risk for diaphragmatic injury because the adrenal gland is juxtaposed against the diaphragm. Table-1 summarizes patient data, injury specifications and operative management.

Diaphragmatic injury can originate from improper trocar placement or direct contact with monopolar electrocautery or harmonic scalpel (2). When the retroperitoneal approach is preferred for renal or adrenal surgery improper trocar placement can easily lead to diaphragm injury (2).

The lesion can appear as an evident tear of the diaphragm or be invisible to the surgeon's inspection and be alerted by changes in patient cardiopulmonary status. Pneumothorax may produce changes in auscultation, end inspiratory pressure, blood pressure and arterial blood gasses (3). In addition, an undetected injury may become evident by the floppy diaphragm sign, in which the diaphragm billows inferior with any degree of abdominal desufflation, reflecting the loss of negative pressure within the diaphragm (4). In our series, this sign was evident in 3 out of the 6 patients and prompted the rapid diagnosis of the diaphragmatic injury. We also report a case in which pleural cavity inspection was done with the laparoscope through the diaphragmatic lesion in order to perform a biopsy of a suspicious pleural area that was evident after the injury took place. This suspicious area later proved to be pleural teratoma.

The anesthesiologist involvement is decisive in the diagnosis and timing of repair. Carbon dioxide pneumothorax may go undetected intraoperatively and close monitoring of cardiopulmonary status may alert of the injury.

In order to avoid diaphragmatic injury, care must be taken when large adrenal masses are dissected and during the mobilization of intra-abdominal structures for kidney exposure.

Our report is the largest series after the multicentric work published by Del Pizzo et al. of the New York Presbyterian Hospital (2). Similar to what was described by Del Pizzo we also chose interrupted polyglactin sutures for the laparoscopic repair regardless of lesion size and location. Previous reports show that multiple techniques can be used to repair the diaphragm. In one specific case of a hand-assisted nephrectomy, the author chose to leave a dual layer mesh of polypropylene and polyglactin for a 1 cm lesion. The mesh was secured to the diaphragmatic rent by aid of a laparoscopic stapler and the surgeon's hand (5). Several reports confirm the feasibility of diaphragmatic repair by means of intracorporeal suturing (2,3,6). We believe that diaphragm suturing must always be attempted due to the simplicity and reliability of this technique. Nevertheless there has been one successful report of diaphragmatic injury repair without the use of stitches (7). This was achieved by employing a matrix gel and a thrombin solution (Floseal®) with interposition of the omentum over a 1 cm diaphragmatic lesion. The authors refer to their technique as a suitable option for small lesions. To reach an effective repair of the diaphragm, air must be evacuated before the stitches are secured by means of either a suction device or the administration of a long forced inspiratory breath. In addition, repair of diaphragmatic injury has to be timed according to patient parameters and feasibility of repair. When the patient is in stable condition surgery can continue and the injury may be addressed at the end of the procedure. In cases of large tumors that may obstruct the surgeon's direct access to the lesion, surgical specimen should be removed first in order to ease repair. Nevertheless we think that if possible, the diaphragm injury should be repaired without delay. This was the case

in all of our patients in which early recognition of diaphragmatic injury allowed for a prompt repair without the interference of the surgery. Pneumothorax greater than 20% of lung volume or associated with hemodynamic or ventilatory changes is managed with thoracostomy (6). Pleural lesions produced by trocar placement or important residual capnothorax may also warrant thoracostomy. Compared to air, carbon dioxide has higher solubility and increased diffusion coefficient, this allows a greater amount of molecules to diffuse across a membrane in a given time. This explains why capnothorax usually resolves spontaneously and allows for expectant management in stable patients (6).

In case n° 1 ventilatory changes were evident with carbon dioxide retention, but the patient remained hemodynamically stable, the lack of experience in the management of capnothorax prompted a chest tube placement. Retrospectively we think this could have been avoided. Abreu et al., reported a higher incidence of gas collections associated with the retroperitoneal over the transperitoneal approach (6.6% vs. 0.7%) (8). However, they concluded that asymptomatic, subclinical, spontaneously resolving gas collections in the chest are more common with retroperitoneoscopy but the incidence of symptomatic or serious thoracic complications is similar between transperitoneal and retroperitoneal laparoscopy (9). We did not observe injuries from direct trocar entry in our series; this can be explained by the fact that we prefer the transperitoneal to the retroperitoneal approach for renal or adrenal surgery.

CONCLUSIONS

While uncommon, iatrogenic injury of the diaphragm is a possible complication of laparoscopic transperitoneal urologic procedures. Patient characteristics, adrenal surgery and tumor size may be associated with a higher risk of injury. Care must be taken to prevent it and surgeons need to be trained to resolve it. Repair of diaphragmatic injuries should always be attempted with intracorporeal suture since this is a feasible, reproducible and reliable technique.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Inadvertent diaphragmatic injury is a rare, but a serious matter for laparoscopic surgery of the upper urinary tract. On the one hand, as stated by the authors, aggravating circumstances such as obesity, large tumors, or previous surgery may increase the risk of an inadvertent injury; on the other hand, lack of experience and technical errors can enforce this complication. Whereas major surgical difficulties are

best managed by extensive experience of the surgeon, technical errors can be avoided by paying attention to a few guidelines.

During retroperitoneoscopy, a diaphragmatic injury (caused by improper trocar placement) is usually avoided by an initial lumbodorsal incision within the muscle-free triangle between latissimus dorsi muscle and oblique external muscle. Using this ac-

cess technique the following trocars, in particular the upper ones, are placed under palpatory control, therefore usually avoiding injuries to the diaphragm (1).

Due to the increasing numbers of laparoscopic centers worldwide, special care has to be taken to train the individual surgeon. In our opinion and as stated previously, every surgeon should run through a training program prior to the clinical setting, which imparts the basics of laparoscopic intracorporeal suturing and knotting techniques. Only thereafter is it possible to ensure that a quick and safe management of complications can be provided (2,3).

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Adverse Events and Readmissions after Day-Case Urological Surgery

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ABSTRACT

Objective: The literature lacks of studies on postoperative outcomes after urological ambulatory surgery. Our study aims to identify parameters associated with postoperative complications within 30 days after ambulatory urological surgery.

Materials and Methods: Adjusted and unadjusted comparisons between clinical features and postoperative outcome (complicated and uncomplicated).

Results: Postoperative course was complicated in 5% of the patients. Discharge schedule was not completed in 1.1% while unplanned visits resulted in admission in 0.5%. Multivariate analyses could only confirm the independent effect of type of anesthesia and diagnosis-related group (DRG) relative weight.

Conclusions: Ambulatory urological surgery can be safe in terms of postoperative complications. In the present study surgery under general anesthesia, or a higher DRG relative weight procedure, increased the risk of complications compared to surgery under regional or local anesthesia or lower DRG relative weight operations. Patients scheduled for general anesthesia or undergoing complex urological procedures should be warned about an increased risk of postoperative incidents and/or readmission.

Key words: ambulatory surgical procedures; anesthesia; treatment outcome

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INTRODUCTION

Ambulatory surgery represents more than 60-70% of all surgical procedures performed in the United States (1). Considering the extraordinary progress experienced in minimally invasive techniques, this trend will increase during the next years and will probably spread to most surgical specialties. Among modern urologists, there is a growing recognition that many well-established urological procedures may be performed in an ambulatory setting (2). Nevertheless,

urological procedures - particularly low-complexity interventions like varicocelectomy and hydrocelectomy - have been identified as an independent risk factor for postoperative complications (3).

Most publications addressing the outcomes of ambulatory surgery reflect observations during patients' stay or within the first 2-3 days after hospital discharge (4,5). This retrospective study aims to identify parameters associated to postoperative complications within 30 days after ambulatory urological surgery.

MATERIALS AND METHODS

For this study, the files of all patients undergoing elective ambulatory urological surgery throughout a 16-month period in a single public centre were reviewed. After the pre-operative urological work-up, and once the type of procedure was agreed with the patient, the discharge terms were clarified, paying special attention to those operations requesting an indwelling catheter at discharge (internal urethrotomy for urethral stenosis and resection of female para-urethral cyst).

All patients scheduled for major procedures underwent a pre-anesthesia visit preoperatively. Peripheral blood samples were obtained for cell count and determination of serum concentrations of glucose, total protein, creatinine, sodium, and potassium. Coagulation status was not routinely tested. An electrocardiogram was performed in patients over 45 years-old. Type of anesthesia was planned in this visit and informed consent was obtained for the procedure.

Only poor-risk cases (ASA 3 or higher) were excluded and operated as inpatients. No age limits were applied. All pediatric patients (< 11 years) were operated under general anesthesia (GA); a minimum weight of 15 kg was used as inclusion criterion in these cases.

General intravenous anesthesia with propofol and remifentanyl was the preferred technique also for adult patients undergoing major procedures; drugs were delivered via a TCI (Target Controlled Infusion) pump with target effect in the range of 2-6 mcg/mL for propofol and 5-10 ng/mL for remifentanyl. Airway was secured with a laryngeal mask. In pediatric patients, an inhalational technique supplemented with fentanyl was chosen.

Regional anesthesia was performed by the intrathecal route with small gauge (25-27) pencil point needles in the sitting position and an average of 1.5 mg per dermatome of hyperbaric bupivacaine. Fentanyl \leq 20 mcg was added for transurethral procedures.

Typically, patients were sequentially admitted early in the morning, operated and discharged when pain was controlled, and micturition and ambulation confirmed. Perioperative pain was evalu-

ated using a visual analog scale (VAS 0 to 10) at arrival in the recovery unit and every 30 minutes. Low-intensity pain (VAS < 3) deserved no analgesia. The standardized treatment for moderate pain (VAS 4-6) was the endovenous administration of a non-steroidal anti-inflammatory drug (NSAID): metamizole 2 g or ketorololac 30 mg or propacetamol 2 g. Severe perioperative pain (VAS > 7) included the association of endovenous major opioids (fentanyl 0.5-1 μ g/kg or morphine 0.03-0.05 mg/kg or alfentanil 3-5 μ g/kg). Standard analgesic treatment at discharge was oral metamizole (500 mg qd), paracetamol (500 mg qd) or ibuprofen (400-600 mg qd). Management of low to moderate perioperative pediatric pain deserved endorectal metamizole (40 mg/kg qd), oral (15 mg/kg qd) or endorectal paracetamol (25 mg/kg qd), or oral ibuprofen (5-10 mg/kg qd). For severe pain, oral tramadol (0.5-1 mg/kg qd) was associated.

For a safer discharge, pigtail catheters (double J) were routinely inserted after ureteroscopy and removed one week later under local anesthesia in the outpatient clinic. Female stress urinary incontinence was treated using retropubic tension-free vaginal tapes. As a general policy, and irrespectively of the procedures, drainages were removed before discharge. When needed patients were instructed about wound and/or sound care. Staff urologists and anesthesiologists were permanently available (round-the-clock).

For the present study, clinical data (age and gender, type of surgery and anesthesia) were downloaded from the electronic patient record (EPR, Selene, Siemens®). For mathematical analysis, all 21 different types of surgery (Table-1) were grouped into four major surgical categories (testicle/scrotum, penis, bladder and ureteroscopy). Diagnosis-Related Group (DRG) relative-weight was used as index of clinical complexity. The DRG system (6) classifies hospital cases into one of approximately 500 groups expected to have similar hospital resource use. DRG relative weights translate the case-mix of patients treated across hospitals.

Postoperative course was the primary outcome measure; for analysis it was considered either uncomplicated (discharge before 10 pm and absence

Table 1 – Type of surgery and groups for mathematical analysis. Twenty-one different types of surgery were classified into 4 major categories.

Type of Surgery	N	Group for Analysis	N
Testicular prosthesis implant	1	Scrotal / Testicular surgery	657 / 1,189 (55.3%)
Vaso-vasostomy for vasectomy reversal	2		
Testicle biopsy for subfertility	3		
Resection of epididymal cyst	5		
Inguinal orchidectomy for scrotal mass	8		
Varicocelectomy	16		
Orchidopexy	17		
Resection of scrotal cyst	17		
Hidrocelectomy	28		
Vasectomy	560		
Resection of post-circumcision scar	1	Penile surgery	417 / 1,189 (35.1%)
Penile biopsy for suspicious lesions	5		
Meatotomy	6		
Nesbit operation for penile curvature	6		
Frenulectomy for painful erection	130		
Circumcision for phimosis	269		
Internal urethrotomy for urethral stenosis	1	Bladder / Urethral surgery	54 / 1,189 (4.5%)
Resection of para-urethral cyst	1		
Resection of urethral caruncle	1		
Randomized bladder biopsy	2		
Transurethral resection of bladder tumor	10		
Pigtail insertion	15		
Insertion of retropubic tension-free vaginal tape	24		
Ureteroscopy for ureteral lithiasis	61	Ureteroscopy	61 / 1,189 (5.1%)
Total	1,189		1,189

of unplanned visits to outpatients clinic or emergency ward) or complicated (failure to complete the discharge schedule and/or unplanned visits).

An algorithm was created in the EPR to identify the reasons for delaying hospital discharge or warranting unexpected visits to the emergency ward or outpatient clinic within 30 days after surgery.

To identify patients more prone to suffer postoperative complications, univariate comparisons be-

tween clinical features and postoperative outcome (uncomplicated or complicated) were performed using the Pearson's chi square and Mann-Whitney U tests. Relative risks (RR) for complicated postoperative course were calculated adjusted to every prognostic factor.

To further approach the effect of every variable in the presence of the rest of covariates, logistic regression models were used, taking the postoperative outcome (uncomplicated or complicated) as the

dependent variable. Additionally, all inpatient admissions were recorded.

Statistical analyses were performed using the SPSS v11.5 statistical software.

A level of significance of 95% ($p < 0.05$) was used for all comparisons.

RESULTS

Throughout the study period, 1,420 consecutive patients were operated on an outpatient basis. Since structured electronic databases were implemented some months after the implementation of day-case urological surgery, only 1,189 cases (95.1% men, 4.9% women, mean age 35.3 years, SD 13.1) were available for analysis. Procedures on testicle/scrotum represented 55.3% (657/1,189) of the total number of interventions, while penile surgery accounted for 35.1% (417/1,189) of all ambulatory operations; ureteroscopy and bladder surgery accounted for 5.1%

(61/1,189) and 4.5% (54/1,189) of all ambulatory procedures, respectively (Table-1). We used age as a categorical rather than a continuous variable since the association between age and outcome was not linear but bimodal, thus resulting in two risk groups: low risk (13-59 years) and high risk (older than 59 years + younger than 13 years).

Table-2 shows patient characteristics, type of surgery, anesthesia and average DRG relative-weight for every category.

Postoperative course was complicated in 59 patients (59/1,189, 5%). Admission of outpatients was decided in 0.5% (6/1,189) and discharge postponed in 1.1% (13/1,189). The remaining 3.4% presented to the outpatient clinic or emergency ward and could be immediately discharged. Median time to the unplanned visit was 9 days. Post-surgical pain and bleeding or hematuria accounted for the vast majority of complications (40/59, 67.8%). Table-3 shows the distribution of complications.

Table 2 – Distribution of age, gender, type of surgery, type of anesthesia and diagnosis-related group (DRG) relative weight for every category.

		N (%)	DRG Relative Weight (mean, SD)
Age group	< 13 y	41 (3.5)	0.38, 0.12
	13-29 y	297 (25)	0.56, 0.14
	30-49 y	719 (60.4)	0.46, 0.15
	50-59 y	75 (6.3)	0.73, 0.28
	60-70 y	36 (3)	0.81, 0.33
	> 70 y	21 (1.8)	0.71, 0.18
Gender	male	1,131 (95.1)	0.50, 0.18
	female	58 (4.9)	0.85, 0.17
Type of surgery	Scrotal / Testicular surgery	657 (55.3)	0.42, 0.10
	Penile surgery	417 (35.1)	0.56, 0.16
	Bladder surgery	54 (4.5)	1.00, 0.29
	Ureteroscopy	61 (5.1)	0.73, 0.0001
Type of anesthesia	Local	963 (81)	0.46, 0.10
	Regional	108 (9.1)	0.88, 0.29
	General	118 (9.9)	0.65, 0.20

SD = standard deviation; y = years.

Table 3 – Distribution of complications.

Complication	N (%)
None	1,130 (95%)
Post-surgical pain	23 (1.9%)
Local bleeding / Hematuria	17 (1.4%)
Stranguria / Urinary retention	7 (0.6%)
Fever (> 38° C)	6 (0.5%)
Local infection / Wound dehiscence	5 (0.4%)
Bladder perforation	1 (0.2%)
Total	1,189 (100%)

Age acted as a prognostic factor, with patients < 13 and > 60 years old being more exposed to complicated postoperative courses (chi square < 0.001). RR for this category was 3.4 (95% CI 1.8-6.6, $p < 0.001$); in other words, the probability of suffering a complicated postoperative course was almost 3.5 times higher for patients < 13 and > 60 years old when compared with patients aged 13-59 years (reference category).

A clear although non-significant trend towards more complicated postoperative courses was detected among women operated as day cases (chi square = 0.053, RR 2.34, 95% CI .95-5.7, $p = 0.06$).

A clear grading in terms of procedure-related postoperative complications was evident, being testis/scrotum surgery (reference category) associated with the lowest rate of adverse events (22/657, 3.3%), whereas increased rates were observed for penile surgery (19/417, 4.6%, RR 1.37, 95% CI .73-2.57, $p = 0.31$), bladder surgery (7/54, 13%, RR 4.29, 95% CI 1.74-10.58, $p = 0.002$) and ureteroscopy (11/61, 18%, RR 6.35, 95% CI 2.91-13.83, $p < 0.001$).

GA resulted in the highest proportion of complicated postoperative courses when compared to regional or local anesthesia (chi square < 0.001). The risk of postoperative complications following regional anesthesia was 6.89-fold (RR 6.89, 95% CI 3.46-13.75, $p < 0.001$) that of local anesthesia (reference category). Surgery under GA had a risk of postoperative complications almost 10-fold higher than surgery using local anesthesia (RR 9.8, 95% CI 5.23-18.35, $p < 0.001$).

Table 4 – Results of the univariate risk factor analysis.

Patient Variable		Clinical Outcome					
		Uncomplicated	Complicated	p Value	RR	95% CI	p Value
Age group dichotomized	13 - 59	1,045 (95.8%)	46 (4.2%)	<0.001	3.4	1.8 - 6.6	<0.001
	< 13 + > 59	85 (86.7%)	13 (13.3%)				
Gender	male	1,078 (95.3%)	53 (4.7%)	0.053	2.34	0.95 - 5.7	0.06
	female	52 (89.7%)	6 (10.3%)				
Type of surgery	Scrotal /	635 (96.7%)	22 (3.3%)	<0.001	1.37	0.73 - 2.57	0.31
	Testicular surgery		19 (4.6%)				
	Penile surgery		7 (13%)				
	Bladder surgery		11 (18%)				
	Ureteroscopy						
Type of anesthesia	Local	941 (97.7%)	22 (2.3%)	<0.001	6.89	3.46 - 13.75	<0.001
	Regional	93 (86.1%)	15 (13.9%)				
	General	96 (81.4%)	22 (18.6%)				
DRG relative-weight		0.51	0.69	<0.001	14.5	6.2 - 34.3	<0.001

CI = confidence interval; DRG = disease-related groups; RR = relative risk; Referent = reference category.

Complicated postoperative courses had an average DRG relative-weight of 0.69 while uncomplicated cases averaged 0.50 (Mann-Whitney U test < 0.001). During the univariate analysis, every DRG relative-weight unit multiplied times-14.5 (RR 14.5, 95% CI 6.2-34.3, $p < 0.001$) the risk of a complicated postoperative course. Table-4 summarizes this phase of the study.

Multivariate analyses could only confirm the independent effect of type of anesthesia and DRG relative-weight. The final model revealed that a hierarchy existed in terms of anesthesia-related complications, with GA resulting in the highest rate of complications (RR 7.6, 95% CI 3.8-15, $p = 0.003$) when compared to the reference category (local anesthesia). Also, DRG relative-weight acted as an independent prognostic factor: every DRG relative-weight unit multiplied times-3.3 (RR 3.3, 95% CI 1.003-11.4, $p = 0.049$) the risk of a complicated postoperative course. Predictive regression models are presented in Table-5.

In 19 cases inpatient admission was eventually decided (6/1,189, 0.5%) or discharge was postponed (13/1,189, 1.1%).

COMMENTS

Although there may be the misconception that ambulatory surgery only deals with minor procedures, the reality is that a wide variety of procedures is commonly performed: in the authors' institution more than 20 different open surgical and endoscopic urologic

procedures are routinely performed as day-surgery cases with an average case-mix (mean DRG relative-weight) of 0.52. Overall, ambulatory surgery represents more than 80% of the surgical activity in this department where the global DRG relative-weight is 1.38.

So far, the results can be considered satisfactory with 95% of patients completing the discharge schedule and not needing any unplanned visit. Similarly, 1.1% of the patients could not be discharged while 0.5% had to be readmitted as a result of complications. These rates are consistent with other studies (7-9). The rate of mortality associated with anesthesia and surgery in the outpatient setting has been estimated to be 0.25 to 0.50 per 100,000 outpatient procedures (7,9). As expected, no deaths were identified in the present study (mean patients age 35 yrs). This finding is also comparable with results published elsewhere (8-12), and translate the levels of safety achieved in ambulatory surgery (4,13).

This study identified two factors affecting the complication rate related to ambulatory urologic surgery: the rate of postoperative complications was strongly dependent on DRG relative-weight and type of anesthesia. Patient-specific factors have been previously identified as important predictors of adverse events: advanced age (> 85 years) and comorbidity have been associated with increased risk of inpatient hospital admission (12,14). Also, type of surgery (urological surgery, among others) has been confirmed as a risk factor elsewhere (3,15). In our study, age, while acting as a risk factor during the univariate analysis, could not be confirmed as inde-

Table 5 – Significant results of the multivariate logistic regression model for independent predictors of complicated postoperative course.

Patient Variable		Relative Risk of Complicated Postoperative Course		
		RR	95% CI	p Value
Type of anesthesia	Local		Referent	
	Regional	3.97	1.59 - 9.88	0.003
	General	7.63	3.86 - 15.07	< 0.001
DRG relative-weight		3.39	1.003 - 11.48	0.049

CI = confidence interval; DRG = disease-related groups; RR = relative risk; Referent = reference category.

pendent risk factor during the multivariate analysis. Nevertheless, it is remarkable that a bimodal curve of risk was identified, with younger (< 13 yrs) and elder patients (> 60 yrs) being markedly exposed to postoperative complications. In spite of accounting for the lowest clinical complexity (mean DRG relative-weight 0.38, SD 0.12) younger patients experienced the vast majority of complicated postoperative courses. We hypothesize that parents' expectations can sometimes exceed the performance of ambulatory surgery in the pediatric setting thus resulting in an elevated number of delayed discharges and unplanned visits to the hospital. Anyway, children are considered to be excellent candidates for day-case surgery. Pediatric outpatient surgery has been proposed from the age of 4 months (16), and the benefits of a short hospitalization probably justify the modest risk of postoperative incidents and/or hospitalization (17).

Type of surgery (testicle/scrotum, penis, bladder and ureteroscopy, in this study), while a friendly parameter to clinicians, could not be confirmed as a prognostic variable. In other words, the grouping of surgical procedures used in this study could be sensible for surgical planning but was not helpful to foresee risky operations (in terms of postoperative incidents). On the contrary, we observed an increased risk of postoperative complications associated to clinical complexity as defined by the DRG relative-weight system. It is conceivable that technically demanding procedures can result in postoperative complications but post-surgical outcome is multifactorial with many variables involved. This is the reason why we decided to test the ability of DRG relative-weight to discriminate between patients at risk and not at risk. So far it has been proved that the use of the DRG-system positively affects length of stay (LOS), operative blood loss, transfusion rates, operative margins and postoperative complications, resulting in a higher efficiency (18,19). As far as we know, the DRG relative-weight system has not been used as a prognostic factor for postoperative complications.

The effect of anesthesia on postoperative outcome has been widely studied (20). In a vast study of 17,638 patients, there were no anesthesia-related ad-

missions or deaths (10). The type of surgery plays a major role in increasing the postoperative LOS; clearly, urologic patients have longer LOS than those undergoing ophthalmologic surgery (21). In the present study, type of anesthesia (GA) acted as a risk factor for postoperative complications (in terms of discharge and readmission rates) after ambulatory surgery. It is of interest the fact that the level of surgical complexity (in terms of DRG relative-weight) was higher for the group operated under regional anesthesia while patients undergoing GA suffered the vast majority of complications. GA-related side effects probably explain such effect. It is intriguing since a recent experience in healthy men undergoing minor genitourinary procedures proved that GA with remifentanyl and propofol was as safe and effective anesthesia as spinal block with the advantage of a faster discharge (22).

Our study has several limitations: the accuracy of our analysis might be biased by its retrospective nature. In addition postoperative complications could be underestimated given no information on visits to general practitioners is available. Other limitations include small sample sizes for ureteroscopy and bladder surgery, and an uneven gender distribution (markedly biased towards male surgery). Also, a number of different procedures was grouped thus making impossible a detailed procedure-specific analysis. From the procedural point of view, we accept that the use of pigtail catheters after uncomplicated ureteroscopy can be arguable (23,24). Nevertheless, our standard is ureteral dilation before the ureteroscope insertion. In this particular setting pig-tails can be warranted (23).

Now, let us be practical. What can be done to improve the performance of day-case urology? Unfortunately, the type of surgery and surgical complexity are factors that cannot be altered preoperatively, while the need for GA cannot be easily modified. Nevertheless patient and staff education offer a window of opportunity for improving the success rate of day-surgery. It has been suggested that the success of ambulatory surgery depends on how attractive it can be for the patient (25). We believe that it also has to be appealing for health-professionals; in the authors' experience upfront procedural informa-

tion to medical-staff (surgeons, anesthesiologists, nurses and ancillary staff) and patients is vital: the terms of discharge must be clear before patients are included in the waiting list. Otherwise, reasons for delayed discharge can always be identified.

CONCLUSIONS

Ambulatory urological surgery can be safe in terms of postoperative complications and readmissions. Independently of other clinical factors (age, gender, type of surgery and surgical complexity), surgery under general anesthesia represents a risk factor for postoperative complications and readmission. Similarly, complex procedures (in terms of DRG relative weight) increase the risk of complications compared to low complexity operations. Whenever possible, surgery under regional and/or local anesthesia should be encouraged.

CONFLICT OF INTEREST

None declared.

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The Role of Squamous Differentiation in Patients with Transitional Cell Carcinoma of the Bladder Treated with Radical Cystectomy

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ABSTRACT

Objective: We aim at determining the prognostic value of squamous differentiation in patients with transitional cell carcinoma (TCC) of the bladder that were treated with radical cystectomy.

Materials and Methods: From January 1993 to January 2005, we retrospectively selected 113 patients. Correlations among squamous differentiation with other clinical and pathological features were assessed by both chi-square and Fisher tests. The Kaplan-Meier method was used to evaluate survival curves and statistical significance was determined by the log-rank test. Multivariate analysis was performed through a Cox proportional hazards regression model.

Results: Squamous differentiation was observed in 25 (22.1%) of the 113 patients. This finding was significantly related only to the pathological stage. Mean follow-up after cystectomy was 31.7 ± 28.5 months. Disease recurrence occurred in 16 (64%) and 30 (34%) patients with and without squamous differentiation (log-rank test, $p = 0.001$), and mortality occurred in 10 (40%) and 14 (16%) of the patients with and without squamous differentiation respectively. Univariate analysis revealed that pathological stage, squamous differentiation, tumor size and lymph node involvement were significant predictors of cancer-specific survival. However, only squamous differentiation and tumor size were independent prognostic variables on multivariate analysis.

Conclusions: Squamous differentiation was an independent prognostic factor for cancer specific survival in patients with bladder cancer treated with radical cystectomy. Further studies with a larger number of patients are necessary to confirm these results.

Key words: carcinoma, transitional cell; squamous cell neoplasms; cystectomy; prognosis

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INTRODUCTION

Bladder cancer is the fourth leading cause of cancer in American men. It is estimated that 61,420 new cases will be diagnosed in 2006 and approximately

20% to 30% of these patients will present muscle infiltrative tumors (1). The high mortality rates of 50% in 5 years (2) even in patients who undergo aggressive treatment with radical cystectomy has motivated the finding of new clinical or pathologic prognostic factors

that could help selecting patients for adjuvant treatment.

Although pure squamous cell carcinoma of the bladder is found in only 5% of all bladder cancers (3,4), the incidence of squamous differentiation in transitional cell carcinoma (TCC) of the bladder is higher and ranges from 11% to 60% of the cases (5,6). The prognostic value of squamous differentiation in patients with bladder transitional cell carcinoma is controversial. While some authors have shown relation of this finding to adverse pathologic features (7,), to a higher resistance to radiotherapy (8), or to a disease-free period shorter than pure TCC (4,9), most studies could not show the independent statistical value of this variable on multivariate analysis (5,6,10).

In the present study, we sought to determine the prognostic relevance of squamous differentiation in patients with TCC of the bladder treated with radical cystectomy.

MATERIALS AND METHODS

The study comprised a retrospective analysis of 113 patients who underwent radical cystectomy and urinary diversion for bladder cancer during the period of January 1993 to January 2005. All patients who had been treated with neoadjuvant chemotherapy, who had incompletely documented procedures, who had presented other malignant bladder tumors, and who had no available follow-up were excluded from the study. This represented 37 cases. Among the excluded cases, there were 3 squamous cell carcinomas and 3 adenocarcinomas of the bladder. All the others presented TCC of the bladder and were included in the study.

Preoperative diagnosis was made by transurethral resection. All patients underwent physical examination, chest radiography and computed tomography of the abdomen and pelvis. The majority of patients underwent surgery for muscle infiltrative tumors (T2). Other indications included superficial bladder cancer refractory to intravesical therapy and multifocal stage T1, grade 3, disease. Fifteen patients with extravesical disease (T3b or T4) and / or positive lymph nodes were submitted to adjuvant

chemotherapy. The methotrexate, vinblastine, doxorubicin and cisplatin protocol was used for at least three cycles.

The variables evaluated were patient age, gender, pathological stage, tumor grade, tumor size, presence of carcinoma in situ (CIS), lymph node involvement and the presence of squamous differentiation. Staging and grading were performed according to the TNM classification and to the World Health Organization System respectively (11,12). Tumor size was considered as the greater diameter on macroscopic analysis of the surgical specimen. For analysis of pathological stage patients were grouped as follows: T0, T1 (T1 + Tis), T2 (T2a + T2b), T3 (T3a + T3b) and T4. A tumor component was considered to be squamous when intercellular bridges and/or keratinization were evident (Figure-1). Follow-up consisted of a visit two months after surgery, then another visit every 4 months for 1 year. After this period they were seen every 6 months until disease progression or death.

Main postoperative end-points were recurrence-free survival and cancer-specific survival. The recurrence-free survival period was estimated from the time of surgery to the date of the first documented clinical recurrence or until the last follow-up if the disease had not recurred. Bladder cancer recurrences in the pelvis were considered as local

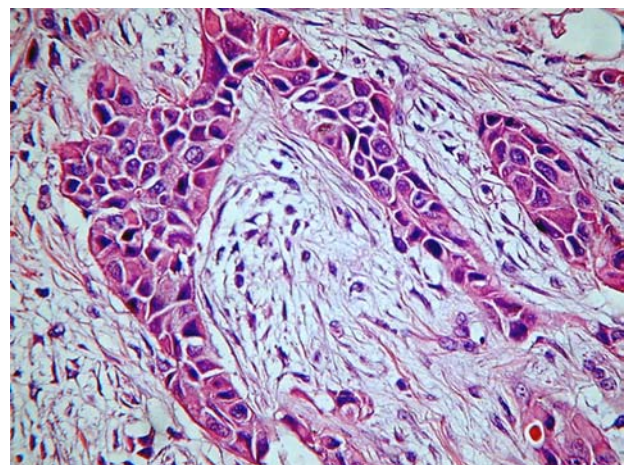


Figure 1 – Transitional cell carcinoma of the bladder with areas of squamous differentiation (HE).

recurrences, outside the pelvis as distant metastases and in the urinary tract as urothelial recurrences. Patients who died from other causes were censored at the time of death. Correlations among squamous differentiation with other pathologic features were assessed by the Chi-square or Fisher's exact tests. The Kaplan-Meier method was used to evaluate survival curves and statistical significance was determined by the log-rank test. Statistical significance was set as a p value of 0.05 or less. Statistical analysis was performed using the SPSS 12.0 for Windows software.

RESULTS

Patient characteristics are shown in Table-1. Mean patient age was 65.9 years (range 42 to 90 years) and most patients (85.8%) were male. Forty nine percent presented organ-confined disease (Tis, T1 and T2) and the great majority (86.9%) were high graded. Concomitant CIS was observed in 40.7% of patients and lymph nodes were involved in 15.7% of cases. Twenty nine patients had no information regarding tumor grade and 43 regarding lymph node status. These last patients were treated in the beginning of the study period when routine pelvic lymphadenectomy was not performed. The remaining 70 patients underwent systematic lymphadenectomy that consisted in the removal of lymph nodes from the obturator fossa to common iliac arteries. As many patients had several transurethral resections before cystectomy, in 20 reports tumor size could not be precisely described. Forty six (49%) presented tumors measuring less than 3 cm and 47 (51%) tumors measuring 3 cm or more. This cut-off point was based on the median size.

Squamous differentiation was observed in 25 (22.1%) of the 113 patients. This finding was significantly related only to pathologic stage (Table-2). Patients with squamous differentiation presented stage T0, T1, T2 and T3 in 0%, 16%, 20% and 52% of the cases respectively ($p = 0.031$).

Mean follow up after cystectomy was 31.7 ± 28.5 months (median 24.0 months). By the end of follow-up, 46 (40.7%) tumors had recurred. Twenty

four (21.2%) patients died of bladder cancer. We noted important differences in recurrence-free and cancer-specific survival rates between patients with squamous differentiation and without squamous differentiation (Figures-2 and 3). Disease recurrence occurred in 16 (64%) and in 30 (34%) patients with and without squamous differentiation respectively (Log-Rank test; $p = 0.001$), and mortality occurred in 10 (40%) and 14 (16%) of patients with and without squamous differentiation respectively (Log-Rank test; $p = 0.002$). On univariate Cox regression analysis, an advanced pathologic stage, lymph node involvement, higher tumor size and the presence of squamous differentiation were significantly associated to cancer-specific survival (Table-3). The Hazards ratios for tumor stage was not determined since no patient with T0 disease died

Table 1 – Patients characteristics.

	N (%)
Age	
Mean \pm SD / median	65.9 \pm 9.7 / 67.0
Range	42 to 90
Gender	
Men	97 (85.8)
Women	16 (14.2)
Tumor stage	
T0	13 (11.5)
Tis	9 (8.0)
T1	18 (15.7)
T2a	18 (15.7)
T2b	11 (9.7)
T3a	12 (10.6)
T3b	23 (20.4)
T4	9 (8.0)
Grade	
Low	11 (13.1)
High	73 (86.9)
Carcinoma in situ	
Yes	46 (40.7)
No	67 (59.3)
Tumor size (cm)	
Mean \pm SD / median	3.2 \pm 2.2 / 3.0
Range	0.8 to 10.0
Lymph node involvement	
Yes	11 (15.7%)
No	59 (84.3%)

Squamous Differentiation in Bladder Cancer

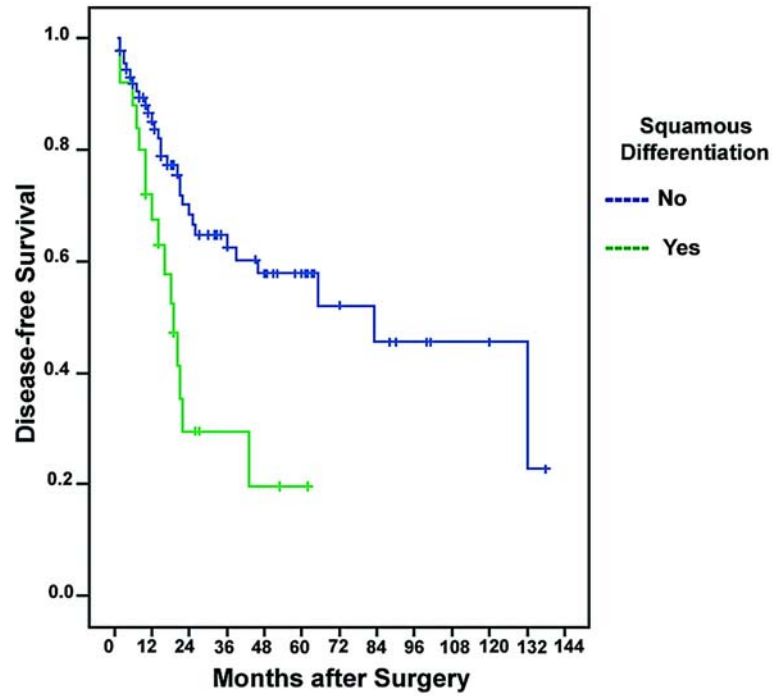


Figure 2 – Disease-free survival among patients with and without squamous differentiation (log-rank test; $p = 0.001$).

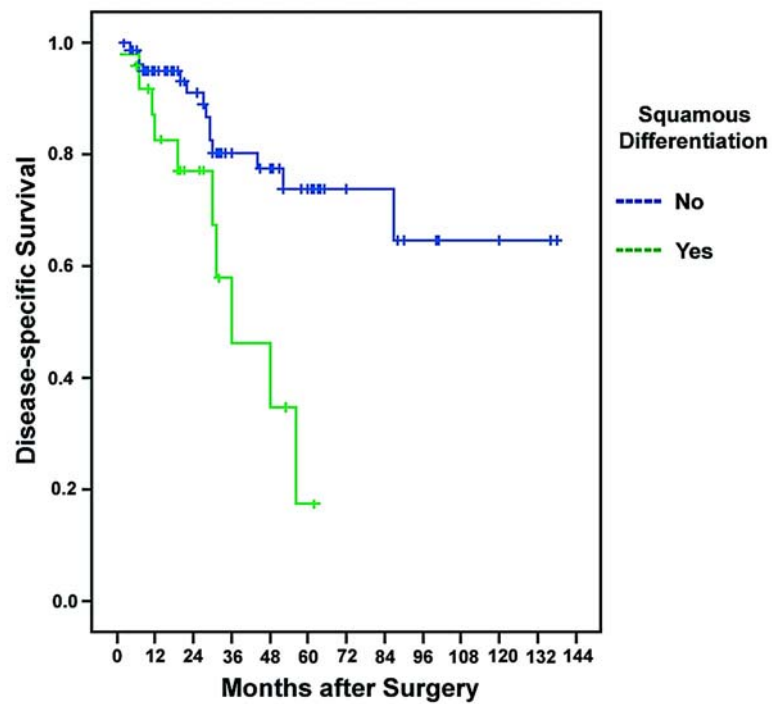


Figure 3 – Cancer-specific survival among patients with and without squamous differentiation (log-rank test; $p = 0.001$).

during the follow-up period. However, on multivariate analysis, only tumor size and the presence of squamous differentiation remained as independent significant variables (Table-4).

COMMENTS

In the present study we found a 22.1% rate of squamous differentiation in patients with TTC of the bladder. This feature was significantly related to the pathological stage. Among patients with squamous differentiation 16%, 20% and 52% of the patients had pT1, pT2 and pT3 stage respectively. The fact that only 12% of patients had pT4 disease can be explained by the small number of patients with this stage. Disease recurrence occurred in 64% and in 34% patients with and without squamous differentiation respectively (Log-Rank test; $p = 0.001$), and mortality occurred in 40% and 14 16% of patients with and without squamous differentiation respectively (Log-Rank test; $p = 0.002$). The presence of squamous differentiation was a significant prognostic variable for cancer-specific survival in either uni or multivariate analysis.

Billis et al. (7), reviewed specimens of bladder TCC transurethral resections (TUR) from 165 patients and found 12 (7.27%) cases with squamous and/or glandular differentiation. As in the present series, they showed that tumors with squamous and/or glandular differentiation had a significant statistical correlation with higher stage at clinical presentation, suggesting that tumors with this features are more aggressive neoplasms. Martin et al. (8), also analyzed TUR specimens from 100 patients with bladder tumor and reported that while 78% of patients with squamous metaplasia failed to respond to radiotherapy while a 90% response rate was seen among patients without this finding. The authors concluded that alternative methods should be sought to the former group since they may have radiotherapy resistant tumors. Vecchioli et al. (9), reported that the presence of extensive areas of squamous metaplasia (metaplastic areas = or greater than 50% of neoplastic surface) was always found in association with high grade neoplasms and with a disease-free period shorter than pure TCC.

Table 2 – Distribution of variables according to the presence of squamous differentiation.

	Squamous Differentiation		p Value
	No	Yes	
Age			0.939 ⁺
< 67 years	43 (48.9%)	12 (48.0%)	
≥ 67 years	45 (51.1%)	13 (52.0%)	
Gender			0.751 ⁺⁺
Female	12 (13.6%)	4 (16.0%)	
Male	76 (86.4%)	21 (84.0%)	
Grade			0.277 ⁺⁺
Low	10 (15.9%)	1 (4.8%)	
High	53 (84.1%)	20 (95.2%)	
Tumor size			0.959 ⁺
< 3.0 cm	37 (49.3%)	9 (50.0%)	
≥ 3.0 cm	38 (50.7%)	9 (50.0%)	
Ca in situ			0.400 ⁺
No	54 (61.4%)	13 (52.0%)	
Yes	34 (38.6%)	12 (48.0%)	
Lymph node involvement			0.135 ⁺⁺
No	46 (88.5%)	13 (72.2%)	
Yes	6 (11.5%)	5 (27.8%)	
Stage			0.031 ⁺⁺
T0	13 (14.8%)	-	
T1	23 (26.1%)	4 (16.0%)	
T2	24 (27.3%)	5 (20.0%)	
T3	22 (25.0%)	13 (52.0%)	
T4	6 (6.8%)	3 (12.0%)	

⁺ = Pearson's qui-squared test, ⁺⁺ = Fisher's exact test

Conversely, other authors could not demonstrate the independent prognostic significance of squamous differentiation. Mazzucchelli et al. (5), found in a prospective analysis of 70 patients treated according to a program of radical cystectomy alone or followed by adjuvant chemotherapy, that the presence of squamous differentiation along with the depth of invasion and the absence of CIS were the only variables related to a poor survival outcome. However, on multivariate analysis, only the last two variables were independent prognostic factors. Likewise, Frazier et al. (10), in a study of 531 patients

Table 3 – Univariate Cox regression analysis for cancer-specific survival.

	Hazards Ratio	95% CI	p Value
Age	1.42	[0.62 - 3.25]	0.405
≥ 67 years / < 67 years			
Gender	2.41	[0.57 - 10.25]	0.235
Male / Female			
Grade	3.02	[0.40 - 22.77]	0.283
High / Low			
Carcinoma in situ	1.33	[0.59 - 2.99]	0.486
Yes / No			
Tumor size	4.63	[1.50 - 14.30]	0.008
≥ 3 cm / < 3 cm			
Squamous differentiation	3.51	[1.53 - 8.08]	0.003
Yes / No			
Lymph node involvement	3.17	[1.19 - 8.46]	0.022
Yes / No			
Stage			0.030
T1 / T0			
T2 / T0			
T3 / T0			
T4 / T0			

Not possible to calculate

treated with radical cystectomy and followed for a long period at Duke University Medical Center, found that squamous differentiation in the specimen was a predictive factor for poor cancer-specific survival only in univariate analysis. In multivariate analysis only pathological stage, nodal involvement, positive surgical margins, patient age and loss of histologic differentiation achieved independent statistical significance.

In the present series, the finding of squamous differentiation in TCC of the bladder was an independent prognostic factor for disease-specific survival. This finding was associated to a 5.2 times higher risk of dying from disease when compared to patients without squamous differentiation. However, these results must be analyzed carefully. First, the study comprised a retrospective analysis of a relative small number of patients. Second, the lack of information regarding important variables such as lymph node status and tumor grade in 43 and 29 patients respectively may have influenced the

results of final multivariate Cox regression analysis. Third, tumor size, which was an independent prognostic factor along with squamous differentiation, may not be a reliable variable since TUR prior to cystectomy may have precluded an adequate measurement of the tumor. Furthermore, the independent prognostic significance of pathologic stage, which is considered one of the most powerful variables of poor outcome (6), could not be

Table 4 – Multivariate Cox regression analysis for cancer-specific survival.

	Hazards Ratio	95% CI	p Value
Tumor size	5.49	[1.74 - 17.31]	0.004
≥ 3 cm / < 3 cm			
Squamous differentiation	5.21	[1.87 - 14.54]	0.002
Yes / No			

reproduced in the present series. We believe that two factors may have contributed to this. First, the small number of patients included in the analysis, and second the lack of information regarding lymph node status in some patients, since most tumors with advanced stages have also positive lymph nodes.

Finally, the present results suggest that the presence of a squamous component in patients with bladder TCC may be associated with an ominous outcome. Further studies with larger series and multivariate analysis are necessary to confirm these results.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Divergent differentiation is a very peculiar capacity of urothelial tumors (1). Squamous differentiation, defined by the presence of intercellular bridges or keratinization, occurs in up to 20% of urothelial carcinomas (2,3). Glandular differentiation is less common than squamous differentiation (4,5). Several studies have shown that squamous and/or glandular differentiation is an unfavorable feature in patients undergoing radical cystectomy.

In a study from our Institution, we found that 153/165 (92.72%) transurethral resections of the bladder showed conventional urothelial carcinoma and 12 (7.27%) showed squamous and/or glandular differentiation (6). The striking finding was the stage distribution of the tumors with differentiation. All 12 cases were infiltrative (pT1 or pT2) at clinical presentation and none superficial (pTa) ($p < 0.0001$).

Antunes et al., in a very well conducted study, showed that on univariate analysis pathologic stage, squamous differentiation, tumor size and lymph node involvement were significant predictors of bladder cancer-specific survival. However, only squamous differentiation and tumor size were independent prognostic variables on multivariate analysis. The findings emphasize the prognostic importance of squamous differentiation which must be described and detailed in the pathology report.

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The Use of Enoxaparin to Prevent Venous Thromboembolism in Patients Undergoing Radical Retropubic Prostatectomy: Feasibility and Utility

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ABSTRACT

Objective: To assess the utility of enoxaparin in prevention of venous thromboembolism (VTE) in men poorly compliant with pneumatic compression stockings (PCS) in the immediate postoperative period after a radical retropubic prostatectomy (RP).

Materials and Methods: This retrospective study included 47 men who underwent RP at an inner-city tertiary care hospital. All patients were started on enoxaparin 40 mg subcutaneously 6-8 hours postoperatively and daily while hospitalized. Preoperative, operative, and postoperative data were collected and analyzed. Median follow-up was 18 months.

Results: Median patient age was 64 ± 7 years, median prostate-specific antigen level was 4.9 ng/mL and median prostate biopsy-determined Gleason score was 6. Forty-one men (87%) underwent a pelvic lymph node dissection. Median operative time was 181 minutes (range 164-450 minutes). Median estimated blood loss was 700 mL. Approximately 36% of the men wore PCS the recommended > 19 hours/day. On average PCS were worn 10.3 ± 7.5 hours/day. Postoperative complications were not increased in this cohort. Two patients developed pulmonary embolism requiring long-term anticoagulation. There were no mortalities.

Conclusions: In men non-compliant with PCS, initiation of enoxaparin in the immediate postoperative setting was well-tolerated and maintained a low (4%) rate of VTE. Thus, enoxaparin may be useful in adjunct with PCS in these patients.

Key words: enoxaparin; prostatectomy; prostate cancer; venous thrombosis; pneumatic compression stockings
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INTRODUCTION

In the US, radical prostatectomy (RP) is the most common treatment for localized prostate cancer (1) and results in durable, disease-free survival with few complications (2,3). The way we currently perform anatomic RP is due in part to the extensive research and operative experience of a select group of practiced urologists who have refined this

procedure. For example, following adoption of the meticulous dissection technique reported by Walsh et al. (4), physicians reported a decrease in blood loss, lower rates of positive surgical margins, and a decrease in postoperative morbidity (e.g., incontinence and erectile dysfunction). The most common cause for death in the immediate postoperative setting is from a venous thromboembolism (VTE): deep venous

thromboembolism or pulmonary embolism. The incidence of VTE after RP is 1-3% (5,6).

Lower rates of VTE events after RP in men who wear pneumatic compression stockings (PCS) has been demonstrated clearly by previous research (7,8). The efficiency of PCS is directly related to the time they are worn. Westrich & Sculco reported that patients must wear PCS ≥ 19 hours/day after major surgery as an inpatient in order for them to be efficacious (9). But what of the men who are not compliant with wearing PCS? Could we alleviate their potential risk of developing a VTE without causing an increase in complications if we initiated enoxaparin in the immediate postoperative period? Herein, we present the results of 47 men who underwent RP for localized prostate cancer and were at high risk of developing VTE who were treated prophylactically with subcutaneous enoxaparin.

MATERIALS AND METHODS

Study Population

The study included the first 51 consecutive patients with localized prostate cancer who underwent anatomic RP performed at the University of Florida & Shands Jacksonville from October 2003 to December 2005. All data needed for this study was collected and recorded as part of a standard-of-care for these patients. In 2006, Institutional IRB approval was obtained to examine the medical records and gather the pertinent information.

Pretreatment evaluation included medical history, physical examination with digital rectal examination, measurement of initial prostate-specific antigen (PSA) level, and measurement and determination of Gleason score by prostate needle biopsy. Different laboratories were used to measure PSA of different patients. Further evaluations with bone scan or computed tomography were done according to the preference of the treating urologist.

Patients underwent an anatomic RP utilizing a 10 cm infraumbilical midline incision for optimal exposure. Furthermore, the kidney rest on the table was elevated and the table flexed. Median surgical time was 181 minutes (range 164 - 450 minutes).

Tumor Grading and Staging

The 2002 Tumor-Node-Metastasis (TNM) staging system was used for clinical staging (10).

RP specimens were processed as reported previously (11). Although pelvic lymph node dissection can be omitted in patients with a low likelihood of lymph node involvement ($< 2\%$ according to Kattan nomograms) (12), the majority of patients (87%) underwent pelvic lymph node dissection for a concomitant protocol assessing the presence of infectious agents in primary prostatic tumors and regional lymph nodes. Lymph nodes removed during bilateral pelvic lymph node dissection were examined either immediately by frozen section and subsequently by permanent sections, or by permanent section only. RP specimens were graded histologically according to the Gleason grading system (13) and categorized pathologically as organ-confined with negative margins (pT2-), positive margins without evidence of extraprostatic extension (pT2+), extraprostatic extension with negative or positive margins of resection (pT3a- and pT3a+, respectively), or seminal vesicle invasion (pT3b) (14,15).

Outcome Assessment

PCS were placed bilaterally on all patients immediately before surgery and continued until their discharge. Approximately 6-8 hours postoperatively, patients were started on enoxaparin 40 mg administered subcutaneously, which was continued daily during hospitalization. Only four (8%) patients required intraoperative blood transfusion. Because of their propensity to bleed in the operating room, these four patients were not given enoxaparin postoperatively and thus are not included in the final analysis. Hospital records of the 47 patients were reviewed for several key outcomes, estimated blood loss, intraoperative complications, length of hospital stay, and postoperative complications.

Follow-up

Patients returned for evaluation 6 to 8 weeks after surgery and at 4 to 6 month intervals thereafter. Follow-up evaluations included PSA monitoring and digital rectal examinations. Biochemical failure was defined as detectable serum PSA (≥ 0.1 ng/mL). No

patient developed a clinical recurrence without a biochemical recurrence. Follow-up information was obtained from each patient's hospital record or by contacting outside physicians or other hospitals. Median follow-up of the cohort was 18 months.

RESULTS

Characteristics of the study population are presented in Table-1. The patients ranged in age from 45 to 74 years; the median age was 64 ± 7 years. Twenty-eight participants (60%) identified themselves as Caucasian, 17 (36%) identified themselves as African Americans, and 2 (4%) identified themselves as being of another race or ethnicity.

Of the 47 men in the study, 13 (28%) underwent a bilateral nerve-sparing RP, 22 (47%) underwent a unilateral nerve-sparing RP, and 12 (26%)

underwent a non-nerve-sparing procedure. Forty-one men (87%) underwent a pelvic lymph node dissection. The median estimated blood loss was 700 mL (range = 300-1500 mL).

As assessed from nursing staff records, compliance with PCS was approximately 36% (i.e., 36% of men wore the pneumatic compression stockings ≥ 19 hours per day during their hospitalization). The mean length of time PCS were worn was 10.3 ± 7.5 hours/day.

No intraoperative complications were noted. Seventeen postoperative complications were noted. (Table-2). One patient developed a significant drop in his hemoglobin on postoperative day 1 (from 9.6 grams to 7.2 grams). Enoxaparin was discontinued and hemoglobin stabilized by postoperative day 2 with conservative measures. No patients developed clinical signs or symptoms of a lymphocele. The most severe complication was pulmonary embolism, which occurred in 2 (4%) men. Evaluation of PE included arterial blood gas, EKG, chest radiograph, chest computed tomography with contrast, and lower extremity Doppler. The lower extremity Doppler also assessed the pelvic vasculature. No evidence of thrombosis or lymphoceles was evident in the pelvis. One of these two men had a history of cerebrovascular accident and congestive heart failure. More importantly, the two men with pulmonary embolism had reported persistent, excessive sedentary life style upon discharge from the hospital. There were no deep venous thromboses, cardiac events, cerebrovascular accidents, or deaths in the study cohort.

Table 1 – Clinicopathologic characteristics of study cohort.

	N of Patients (n = 47)	%
Age		
Median (years)	64 ± 7	
Range (years)	45 - 74	
Race / Ethnicity		
Caucasian	28	60
African American	17	36
Other	2	4
Clinical tumor classification		
T1c	34	62
T2	11	32
T3	2	4
Preoperative PSA level		
≤ 4.0 ng/mL	12	29
4.1-10 ng/mL	25	48
> 10 ng/mL	10	23
Gleason score		
≤ 6	29	62
7	12	26
> 8	5	11
Microscopic disease*	1	2

* Gleason score not given.

Table 2 – Perioperative complications.

Complication	Number of Events
Postoperative	
Delayed bleed	1
Thromboembolic event	2
Urinary retention	3
Wound infection	1
Bladder neck contracture	10
Death	0
Total	17

Patients may have more than one complication.

Pathologic outcomes are summarized in Table-3. Seventy-seven percent of the patients had organ-confined disease (pT2). Thirty-four percent of the patients had poorly differentiated tumors (Gleason score 8-10). One patient had positive lymph nodes (non-microscopic disease). Surgical margins were positive in 19%. To date, 4 patients (1 with pN+ disease and 3 with pT3a+ disease with extensive margins) have developed biochemical recurrence.

COMMENTS

Enoxaparin is a low molecular weight heparin that has antithrombotic properties. Enoxaparin is indicated for the prophylaxis of deep venous thrombosis, which may lead to pulmonary embolism: in patients undergoing hip replacement, in patients undergoing knee replacement, in medical patients who are at risk of VTE due to severely restricted mobility, and in patients undergoing abdominal surgery who are at risk of VTE (16). Increased age, cancer, pelvic surgery, and extended sedentary periods are associated with a perioperative hypercoagulable state and patients with these characteristics are classified as a medium risk by the Thromboembolic Risk Factor Consensus Panel (16). Thromboembolic events are considered the most important nonsurgical complication following a major urologic procedure (17). One to 3% of contemporary patients undergoing prostatectomy experience a symptomatic VTE (5,6). The most common form of VTE prophylaxis in patients undergoing prostatectomy is PCS (7,8). PCS may only be effective if worn ≥ 19 hours/day (9). For unknown reasons, compliance with wearing PCS was extremely low in our cohort (mean time PCS were worn was 10.3 ± 7.5 hours/day), which is dramatically less than the time needed for greatest effect. Although our patients were non-compliant with PCS, we did not notice an appreciable increase in VTE. This led us to believe subcutaneous enoxaparin may be protective in the postoperative period for patients noncompliant with standard VTE prophylaxis.

The timing of the initiation of VTE prophylaxis may be important as well. Some would argue that in order to prevent VTE, prophylaxis should be started prior to the patient even entering the operating room.

Table 3 – Pathologic characteristics of 47 patients undergoing radical prostatectomy and treated with enoxaparin in the immediate postoperative setting.

	N of Patients	%
Prostatectomy Gleason score		
≤ 7	31	66
8-10	16	34
Pathologic tumor classification		
Organ confined	36	77
Extracapsular	9	19
Seminal vesicle invasion	1	2
Nodal metastasis	1	2
Positive surgical margins	9	19

However, half of the clinically recognized pulmonary embolisms occur after hospital discharge and more than seven days after surgery (18). In addition, a study by Kearon and others evaluating the timing of VTE prophylaxis show little difference in efficacy if started preoperatively versus postoperatively (19). We chose to start the PCS therapy prior to surgical incision and continue their use throughout hospitalization.

Overall, morbidity and mortality in our study are similar to outcomes reported in other larger, recent studies (5,20). The most common postoperative complication in the present series was bladder neck contracture (19%). These patients were treated successfully with transurethral incision of bladder neck contracture without an adverse effect on continence. The most common major complication was VTE (4%). Although our cohort was noncompliant with standard VTE prophylaxis, we demonstrated VTE rates that would have been expected in PCS compliant patients by postoperative treatment with enoxaparin. The two patients who developed pulmonary embolisms were treated successfully with six months of anticoagulation therapy without any subsequent sequela.

With the use of anticoagulation in the immediate postoperative period, there is the potential for increased lymphatic drainage after a pelvic lymph node dissection. Catalona and others reported an increased rate of lymphoceles and/or lymphatic drainage (38%) in patients who received heparin prophylaxis before a RP and lymph node dissection

(21). This finding was not evident in the present study. In fact, there were no symptomatic lymphoceles or prolonged lymphatic drainage in our cohort. We believe this is due to our meticulous surgical technique while performing the pelvic lymph node dissection, which ensured complete ligation of the proximal and distal lymphatic channels.

We recognize that our study has several limitations. First, this is a small retrospective study conducted by a single surgeon in an inner-city, tertiary care facility. These results may not be extrapolated easily to other surgeons or centers. In addition, this study did not assess a control group of men treated with PCS alone. Furthermore, the sample size was not large and the follow-up was short. Because of these limitations, we urge other large facilities to assess VTE rates following RP or other surgeries. If their VTE rates are above those reported here and in the literature, they should consider the initiation of a clinical trial in which enoxaparin is utilized in the immediate postoperative period.

Deep venous thrombosis and pulmonary embolism are serious complications after RP that are largely preventable. Limited prospective data are available describing the optimal form of prophylaxis in these patients. PCS are the most common form of prophylaxis currently used in this group; however, PCS are reported to be effective only if worn for extended periods throughout the day (i.e., ≥ 19 hours/day). In men non-compliant with PCS, the initiation of enoxaparin in the immediate postoperative setting was well tolerated and maintained a low (4%) rate of VTE. Thus, in the postoperative setting in men non-compliant with conventional prophylactic techniques for thromboembolic events, enoxaparin may be helpful.

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Doctors Kogenta Nakamura and Ali Kasraeian contributed equally to the manuscript.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Venous thromboembolism (VTE) is one of the most serious postoperative complications of radical prostatectomy (RP). Although the rate of VTE events has been decreased in men who use pneumatic compression stockings (PCS) after RP, we still face the patients fail to VTE after RP. The authors showed here that the use of enoxaparin to prevent VTE in patients undergoing RP was well tolerated without any major complications. This is an important study for men non-compliant with conventional prophylactic

techniques for thromboembolic events in the postoperative setting. Continued validation to elucidate if the use of enoxaparin in the postoperative period is meaningful for the patients will be critical in the future.

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EDITORIAL COMMENT

Venous thromboembolism (VTE) is a common complication in patients undergoing surgery and pulmonary embolism (PE) is the most preventable death in patients hospitalized for surgical procedures (1). In particular, VTE is considered the most important non-surgical complication following major urologic procedures (2). Among patients undergoing major urologic surgery, 1 to 5% experienced symptomatic VTE. However, postoperative deep vein thrombosis (DVT) is often asymptomatic and fatal PE (estimated to occur in 1:500 patients) (3) may be the first clinical manifestation. Therefore, it is inappropriate to rely on early diagnosis of asymptomatic DVT to prevent serious PE. Actually, it is well known that routine ultrasonographic screening for asymptomatic DVT of lower limbs have a low sensitivity and is quite impractical (4).

Most of the information about VTE prevention in this field is derived from patients undergoing open prostatectomy. Other urologic procedures, including major renal surgery and transplantation, radical cystectomy, and urethral reconstruction, are also associated with an increased risk for thrombosis. Instead, transurethral prostatectomy is associated with a low risk of VTE. Studies published in the last decade have shown that changes in surgical care, more rapid mobilization, and possibly greater use of prophylaxis may have reduced the rate of VTE after major urologic procedures, particularly radical prostatectomy, over time. On the other hand, it should be noted that patients undergoing urologic surgery often carry multiple risk factors for VTE, such as malignancy, advanced age, pelvic surgery with lymph node dissection. A recent prospective study, aimed to evaluate incidence and risk factors for clinically overt VTE occurrence in urologic cancer patients (5), reported an incidence < 1%, but the half of the cases were fatal. In this survey, patients received thromboprophylaxis in about 71% of the cases. The most important risk factors for thromboembolic complications were history of previous VTE (OR 6.0), anesthesia > 2h (OR 4.5), postoperative bed-rest > 4 days (OR 4.4) and age \geq 60 years (OR 2.6).

Data on thromboprophylaxis in urologic surgery are scarce (6); therefore, the optimal approach to

thromboprophylaxis in these patients is not known (1). The use of mechanical methods, both graduated compression stockings and intermittent pneumatic compression (IPC), are likely to be efficacious (7). Heparins, both unfractionated and low-molecular weight, have been demonstrated to be efficacious in patients undergoing urologic surgery (8). However, bleeding complication has been a matter of concern in urologic patients receiving pharmacological thromboprophylaxis (9).

In this issue of the Journal, Nakamura et al. reported a retrospective single Centre experience of combination strategy for thromboprophylaxis with both IPC and enoxaparin 4000 U o.d. Although the study presented several limitations due to the retrospective design, to the low number of patients recruited, and to the absence of a control group, it is interesting to note that bleeding complications was limited to one case, so confirming that pharmacological prophylaxis is safe. Another aspect outlined in the study is the difficulty related to the use of IPC. These devices are poorly tolerated by patients, requires an intense nursing care, and their diffusion is limited to few hospitals. Instead, the subcutaneous administration of heparin is easy to manage and well tolerated by patients. Unfractionated heparin (UH) should be administered 2 to 3 times daily and low-molecular-weight heparins (LMWH) once daily. The once daily administration profile and the lower risk of heparin induced thrombocytopenia with respect to UH, have contributed to the diffusion of the use of LMWH.

Radical cancer operations are being performed more frequently than in the past, consequently, the number of patients at high risk of VTE is growing in urologic departments and specific guidelines for thromboprophylaxis should be used in every hospital (1). It is recommended that (1) in patients undergoing major, open urologic surgery prophylaxis with UH 5000 U 2-3 times daily or LMWH > 3400 U once daily should be used. For patients at high risk of VTE such as cancer patients or patients with history of previous VTE, prophylaxis should be continued for 3-4 weeks after hospital discharge (10). For patients with active bleeding or at high risk for bleeding, mechanical prophylaxis should be used until the bleeding risk de-

creases. The combination of mechanical and pharmacological prophylaxis may be more effective than either alone, and should be limited to patients with multiple risk factors of VTE (1). Instead, there is no specific need for thromboprophylaxis other than early mobilization in patients undergoing transurethral prostatectomy (1,4).

There is good evidence that appropriately used thromboprophylaxis has a desirable risk/benefit ratio and is cost-effective (1), providing an opportunity both to improve patients outcome and to reduce hospital costs.

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Inflammatory Atrophy on Prostate Needle Biopsies: Is There Topographic Relationship to Cancer?

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ABSTRACT

Introduction: Chronic inflammation of longstanding duration has been linked to the development of carcinoma in several organ systems. It is controversial whether there is any relationship of inflammatory atrophy to prostate cancer. It has been suggested that the proliferative epithelium in inflammatory atrophy may progress to high-grade prostatic intraepithelial neoplasia and/or adenocarcinoma. The objective of our study is to compare on needle prostate biopsies of patients showing cancer the topographical relation of inflammatory atrophy and atrophy with no inflammation to adenocarcinoma.

Materials and Methods: The frequency and extent of the lesions were studied on 172 needle biopsies of patients with prostate cancer. In cores showing both lesions, the foci of atrophy were counted. Clinicopathological features were compared according to presence or absence of inflammation.

Results: Considering only cores showing adenocarcinoma, atrophy was seen in 116/172 (67.44%) biopsies; 70/116 (60.34%) biopsies showed atrophy and no inflammation and 46/116 (39.66%) biopsies showed inflammatory atrophy. From a total of 481 cores in 72 biopsies with inflammatory atrophy 184/481 (38.25%) cores showed no atrophy; 166/481 (34.51%) cores showed atrophy and no inflammation; 111/481 (23.08%) cores showed both lesions; and 20/481 (4.16%) showed only inflammatory atrophy. There was no statistically significant difference for the clinicopathological features studied.

Conclusion: The result of our study seems not to favor the model of prostatic carcinogenesis in which there is a topographical relation of inflammatory atrophy to adenocarcinoma.

Key words: prostate; inflammation; atrophy; carcinoma; needle biopsy

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INTRODUCTION

Chronic inflammation of longstanding duration has been linked to the development of carcinoma in several organ systems (1-3). In the prostate, it is controversial whether there is any relationship of atrophy with inflammation (or inflammatory atrophy) to prostate cancer (4-10). De Marzo et al. (5) propose that there is a topographical relation with morphologi-

cal transitions within the same acinar/duct unit, between high-grade prostatic intraepithelial neoplasia (HGPIN) and inflammatory atrophy which occur frequently (7). This finding supports a model whereby the proliferative epithelium in inflammatory atrophy may progress to HGPIN and subsequently to adenocarcinoma. The aim of this study is to compare in cores of needle biopsies of patients showing prostate cancer the topographic relation of inflammatory atro-

phy and atrophy with no inflammation to adenocarcinoma.

MATERIALS AND METHODS

The material of this retrospective study was obtained from 172 consecutive men with cancer on needle prostate biopsies and subsequently submitted to radical retropubic prostatectomy.

Both partial and complete prostatic atrophy were considered. Partial prostatic atrophy was diagnosed according to criteria described by Oppenheimer et al. (11) and complete atrophy by criteria described by Billis (4). Three histological subtypes were identified: simple atrophy, hyperplastic atrophy (or postatrophic hyperplasia) (Figure-1), and sclerotic atrophy. Elastosis of the stroma was a useful microscopic feature for the identification of prostatic atrophy of any subtype (12).

Inflammatory atrophy (prostatic atrophy with inflammation) - Both inactive and active inflammation were considered. Inflammatory infiltrate with lymphocytes, plasmacytes or macrophages was considered inactive. The infiltrate was considered active whenever neutrophils were seen in the stroma. All grades of inflammation were considered according to

a modified consensus development of a histopathological classification system for chronic prostatic inflammation (13): mild (scattered individual inflammatory cells), moderate (clusters of inflammatory cells) and severe (confluent sheets of inflammatory cells) in areas of prostatic atrophy of any kind: simple, hyperplastic (Figure-2) or sclerotic.

According to the pathologic findings, patients were stratified into group A (biopsies with atrophy and no inflammation), and group B (biopsies with inflammatory atrophy).

The frequency of atrophy was evaluated considering all cores of the biopsy as well as only the cores showing adenocarcinoma. Extent of inflammatory atrophy and atrophy with no inflammation was evaluated according to the number of cores showing the lesion. In group B, we counted the cores showing only inflammatory atrophy, cores showing atrophy and no inflammation, and cores showing both lesions. In cores showing both inflammatory atrophy and atrophy with no inflammation, the foci of each lesion were counted using an image analyzer (ImageLab-2000).

The clinicopathological features included age of the patients, preoperative PSA, and biopsy Gleason score.

The data were analyzed using the Mann-Whitney test for comparison of continuous variables

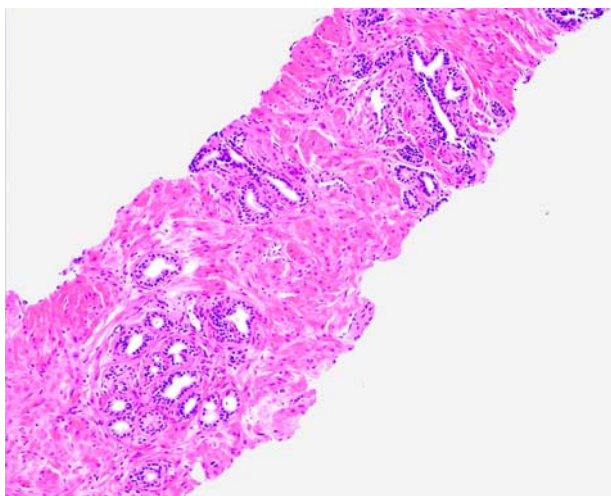


Figure 1 – Atrophy with no inflammation, hyperplastic subtype (HE, X100).

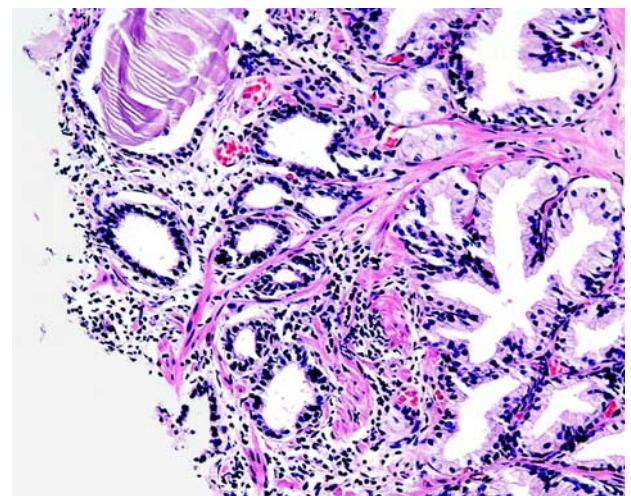


Figure 2 – Inflammatory atrophy, hyperplastic subtype (HE, X200).

with $P < 0.05$ being considered statistically significant. All statistical analyses were performed using Statistica 5.5 (StatSoft, Inc., Tulsa, OK, USA).

RESULTS

A total of 1,088 cores (mean, median and range 6.32, 6 and 1-13, respectively) were obtained from 172 needle biopsies of patients with prostate cancer. Considering all cores of the biopsy, atrophy was seen in 144/172 (83.72%) biopsies; 72/144 (50%) biopsies showed atrophy with no inflammation and 72/144 (50%) biopsies showed inflammatory atrophy. In 57/72 (79.16%) biopsies with inflammatory atrophy inflammation was inactive, and in 15/72 (20.83%) biopsies inflammation was active.

Considering only cores showing adenocarcinoma, atrophy was seen in 116/172 (67.44%) biopsies; 70/116 (60.34%) biopsies showed atrophy with no inflammation and 46/116 (39.66%) biopsies showed inflammatory atrophy (Table-1).

There was a total of 481 cores in the 72 biopsies with inflammatory atrophy; 184/481 (38.25%) cores showed no atrophy; 166/481 (34.51%) cores showed atrophy and no inflammation; 111/481 (23.08%) cores showed both lesions; and, 20/481

(4.16%) cores showed only inflammatory atrophy (Table-2). In the cores showing both lesions, inflammatory atrophy was seen in 193/398 (48.49%) foci, and atrophy with no inflammation was seen in 205/398 (51.51%) foci.

Table-3 shows the clinicopathologic features by groups A and B according to age, preoperative PSA and biopsy Gleason score. There was no statistically significant difference between patients showing atrophy and no inflammation (group A) and patients showing inflammatory atrophy (group B).

COMMENTS

Prostatic atrophy is one of the most frequent mimics of prostatic adenocarcinoma (14). It occurs most frequently in the posterior lobe or peripheral zone (15) and gained importance with the increasing use of needle biopsies for the detection of prostatic carcinoma (16). The frequency of the lesion in autopsies is 85% and increases with age (4). The etiopathogenesis of prostatic atrophy is unknown. Compression due to hyperplastic nodules, inflammation, hormones, nutritional deficiency, systemic or local ischemia, are all factors that may play a role in the pathogenesis of atrophy (4,14,15,17,18). The histologic subtypes of

Table 1 – Frequency of atrophy in 172 biopsies considering only cores showing adenocarcinoma.

Findings	N	%
Biopsies with atrophy (groups A + B)	116/172	67.44
Biopsies with atrophy and no inflammation (group A)	70/116	60.34
Biopsies with inflammatory atrophy (group B)	46/116	39.66

Table 2 – Findings in 481 cores from 72 biopsies showing inflammatory atrophy.

Findings	N	%
Cores without atrophy	184/481	38.25
Cores showing atrophy and no inflammation	166/481	34.51
Cores showing both lesions	111/481	23.08
Cores showing only inflammatory atrophy	20/481	4.16

Table 3 – Clinicopathologic features of 172 patients with prostate cancer in the biopsy by groups A (with atrophy and no inflammation) and B (inflammatory atrophy).

Characteristic	Group A	Group B	p Value
Age (years)			
Mean \pm SD	63.70 \pm 6.30	64.27 \pm 5.60	0.7487 ^(§)
Median	64.50	65.00	
Preoperative PSA (ng/mL)			
Mean \pm SD	10.05 \pm 5.85	10.86 \pm 7.70	0.9076 ^(§)
Median	9.12	8.90	
Gleason score	0		
Mean \pm SD	6.34 \pm 0.73	06.41 \pm 0.66	0.5143 ^(§)
Median	6.00	6.00	

SD = standard deviation, § = Mann-Whitney test.

prostatic atrophy do not represent distinct entities but a morphologic continuum of acinar atrophy. Subtyping atrophy is useful not only for its recognition, and for distinguishing it from prostate cancer (4,16).

Chronic inflammation of longstanding duration has been linked to the development of carcinoma in several organ systems (1-3). In the prostate, it is controversial whether there is any relationship of inflammatory atrophy to prostate cancer (4-10). The term “proliferative inflammatory atrophy” was proposed by De Marzo et al. (5) to designate discrete foci of proliferative glandular epithelium with the morphological appearance of simple atrophy or postatrophic hyperplasia occurring in association with inflammation. According to these authors the morphology of proliferative inflammatory atrophy is consistent with McNeal’s description of postinflammatory atrophy (19), with that of chronic prostatitis described by Bennett et al. (20), and with the lesion referred to previously as “lymphocytic prostatitis” by Blumenfeld et al. (21). De Marzo et al. (5) and Putzi and De Marzo (7) suggest that proliferative atrophy may indeed give rise to carcinoma directly or that proliferative atrophy may lead to carcinoma indirectly via development into HGPIN. This hypothesis by the authors is based on three separate findings providing supportive evidence: 1) A topographical relation with morphologic merging between proliferative inflammatory atrophy and HGPIN in 34% of the inflammatory atrophy lesions; 2) The phenotype of many of the cells in inflamma-

tory atrophy is most consistent with that of an immature secretory-type cell, similar to that for the cells of HGPIN; and 3) proliferative inflammatory atrophy, HGPIN, and carcinoma all occur with high prevalence in the peripheral zone and low prevalence in the central zone of the human prostate.

Favoring a link of inflammation to prostate adenocarcinoma, Cohen et al. (22) found a positive association between *Propionibacterium acnes* and prostatic inflammation, which may be implicated in the development of prostate cancer. However, the authors comment that it is possible that prostatic inflammation may also be caused by other microorganisms which could not be identified by the study, for example obligate anaerobes or species which are difficult to culture under laboratory conditions. They also comment on a second important limitation of the study related to the lack of appropriate negative controls such as prostate tissue from patients without inflammation, atrophy and cancer.

Other studies are at odds with the findings of De Marzo et al. (5) and Putzi and De Marzo (7). In 100 consecutively autopsied men more than 40 years of age, Billis (4) studied the etiopathogenesis of atrophy and its possible potential as a precancerous lesion. There was no statistically significant relation of atrophy to histologic (incidental) carcinoma or HGPIN. The author concluded that prostatic atrophy probably is not a premalignant lesion. In this autopsy study, prevalence of atrophy increased with age and chronic

ischemia caused by local intense arteriosclerosis seemed to be a potential factor for its pathogenesis. In a subsequent study, Billis and Magna (9) stratified the 100 prostates into group A (atrophy without inflammation) and group B (inflammatory atrophy). The groups were correlated to age, race, histologic (incidental) carcinoma, HGPIN, and extent of both these latter lesions. There was no statistically significant difference between groups A and B for all the variables studied. Neither a topographical relation nor a morphologic transition was seen between prostatic atrophy and histologic carcinoma or HGPIN. The authors concluded that inflammatory atrophy does not appear to be associated with cancer or HGPIN.

Anton et al. (6) studying 272 radical prostatectomies and 44 cystoprostatectomies concluded that postatrophic hyperplasia is a relatively common lesion present in about one-third of prostates, either with or without prostate carcinoma. The authors found no association between the presence of postatrophic hyperplasia and the likelihood of cancer and no topographic association between postatrophic hyperplasia and prostate carcinoma foci.

Bakshi et al. (8) studied 79 consecutive prostate biopsies: 54% of initial biopsies were benign, 42% of the cases showed cancer, and 4% HGPIN or atypia. Postatrophic hyperplasia was seen in 17% of benign initial biopsies with available follow-up. Of these, 75% had associated inflammation. There was no significant difference in the subsequent diagnosis of prostate cancer for groups with postatrophic hyperplasia, partial atrophy, atrophy, or no specific abnormality. The authors concluded that the subcategories of atrophy do not appear to be associated with a significant increase in the risk of diagnosis of prostate cancer subsequently.

Postma et al. (10) evaluated whether the incidence of atrophy reported on sextant biopsies is associated with subsequent prostate cancer detection. The authors concluded that atrophy is a very common lesion in prostate biopsy cores (94%). Atrophy in an asymptomatic population undergoing screening was not associated with a greater prostate cancer or HGPIN incidence during subsequent screening rounds.

In the present study, from a total of 172 needle biopsies of men with prostate cancer, 144/172 showed

atrophy; 72/144 (50%) biopsies showed atrophy and no inflammation and 72/144 (50%) biopsies showed inflammatory atrophy. However, considering only cores with cancer, atrophy was seen in 116/172 (67.44%) biopsies; 70/116 (60.34%) biopsies showed atrophy and no inflammation and 46/116 (39.66%) biopsies showed inflammatory atrophy. This finding seems to contradict the topographical model by De Marzo et al. (5) whereby inflammatory atrophy may progress directly to adenocarcinoma or indirectly via development to HGPIN. In cores with adenocarcinoma it would be expected a higher frequency of inflammatory atrophy. Another relevant finding in our study was the evaluation of the extension of inflammatory atrophy in the 481 cores of the 72 biopsies showing this lesion. In only 20/481 (4.16%) cores inflammatory atrophy was the only lesion present. Most frequently cores showed either atrophy with no inflammation (166/481, 34.51%) or both lesions (111/481, 23.08%). A criticism to our findings is that a thin prostate needle biopsy may not represent a real topographic relation between lesions if compared to findings in large specimens such as radical prostatectomy or autopsy prostates. In the study on autopsies with step-sectioning of the prostate, a topographic relation of inflammatory atrophy and HGPIN and/or histologic adenocarcinoma was also not found (9).

There was no statistically significant difference for age ($P = 0.7487$), preoperative PSA ($P = 0.7950$), and Gleason score in the biopsy ($P = 0.5143$) between patients with atrophy and no inflammation and patients with inflammatory atrophy probably indicating no difference in temporal onset and aggressiveness of the tumor in this two groups.

CONCLUSION

The result of our study seems not to favor the model of prostatic carcinogenesis in which there is a topographical relation of inflammatory atrophy to adenocarcinoma. In cores with adenocarcinoma, atrophy with no inflammation was more frequently seen than inflammatory atrophy, and in biopsies with inflammatory atrophy, only 4.16% of the cores showed this lesion as the only finding.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

High-grade prostatic intraepithelial neoplasia (HGPIN) is the most likely precursor of prostatic adenocarcinoma, according to virtually all available evidence. There are other possible findings in the prostate that may be premalignant (Low-grade PIN, inflammatory atrophy, malignancy-associated foci, and atypical adenomatous hyperplasia), but the data for them are much less convincing than that for HGPIN (1).

The paper by Athanase Billis and collaborators entitled “Inflammatory Atrophy on Prostate Needle Biopsies: Is There Topographic Relationship to Cancer?” deals with the interesting topic of preneoplastic lesions and conditions of the prostate, in particular with proliferative inflammatory atrophy (2). The objective of their study was to compare on needle prostate biopsies of patients showing cancer the topographical relation of inflammatory atrophy and atrophy with no inflammation to adenocarcinoma. The result of their study did not favor the model of prostatic carcinogenesis in which there is a topographical relation of inflammatory atrophy to adenocarcinoma. Dr Billis’ study does not exclude that inflammatory atrophy could be an early step in the development of prostate cancer and one of the possible preneoplastic conditions and lesions that precede the appearance of cancer.

Low-grade PIN (LGPIN) - Earlier morphometric and immunohistochemical studies showed that LGPIN has features that are intermediate between normal tissue and HGPIN (1). Little information on LGPIN has been accumulated in recent times. This is probably due to the fact, while HGPIN in needle biopsy tissue is a risk factor for the subsequent detection of carcinoma, LGPIN is not. Currently, LGPIN is not documented in pathology reports due a relatively low risk of cancer following re-biopsy.

In Bostwick’s progression model of PIN to carcinoma, the transition between normal, low-grade PIN, high-grade PIN, and then carcinoma is continuous (3). Few epidemiologic, morphologic, or molecular genetic studies have examined the relation between low and high-grade PIN development. In part, this relates to the difficulty in distinguishing low-grade PIN from normal tissue on the one hand and high-grade

PIN on the other. Nevertheless, Putzi and De Marzo (4) found that lesions that could be considered low-grade PIN often coexisted with high-grade PIN, suggesting either that high-grade PIN is derived from low-grade PIN or that high and low grade PIN arise concomitantly.

Focal Prostate Atrophy as a Morphological Manifestation of a “Field Effect” and a Potential Prostate Cancer Precursor - Pathologists have long recognized focal areas of epithelial atrophy in the prostate that appear more commonly in the peripheral zone of the prostate. These lesions may be associated with chronic inflammation, and less commonly with acute inflammation (5). The term proliferative inflammatory atrophy (PIA) has been proposed (5).

Many of the atrophic cells are not quiescent and possess a phenotype that is intermediate between basal and luminal cells. Intermediate epithelial cells have been postulated to be the targets of neoplastic transformation in the prostate (6). Additionally, PIA cells show elevated levels of GSTP1, glutathione S transferase alpha (GSTA1) and COX-2 in many cells, suggesting that these cells are responding to increased oxidant/nitrosative/electrophilic stress. Many of the molecular and genetic changes seen in HGPIN and cancer have also been documented in PIA (7).

In morphological studies, it has been observed frequent merging of areas of focal atrophy directly with high grade PIN (7). It has been observed these atrophic lesions near early carcinoma lesions, at times with direct merging between atrophic epithelium in PIA and adenocarcinoma (7). Some of such changes could be called atrophic HGPIN.

Malignancy-associated changes (Putative preneoplastic markers with minimal or no morphological changes) - Malignancy-associated changes refer to molecular abnormalities in the epithelial cells that are not usually distinguishable by routine light microscopic examination.

Scant data are available in the prostate. Normal-looking epithelium in prostates with adenocarcinoma may show some molecular abnormalities in GSTP- I and telomerase that are similar to those in cancer (2). These observations are related to the so-

called “enzyme-altered foci” as putative preneoplastic markers (8,9). According to Dr TG Pretlow and co-workers, the most abundant of these lesions with molecular alterations show minimal or no morphological changes (8). Changes occur also in the stroma. Montironi et al (10) have shown that the degree of vascularization in normal-looking prostate tissue from total prostatectomies performed because of a preoperative diagnosis of PCa is close to that of LGPIN.

The transition from normal-looking epithelium to prostate cancer without an intermediate morphological stage identifiable as HGPIN was considered possible (8). This raises the question of the existence of PIN without morphological changes as a precursor of some well-differentiated adenocarcinomas of the transition zone.

Atypical adenomatous hyperplasia – AAH (Adenosis) - Is characterized by a circumscribed proliferation of closely packed small glands that tends to merge with the surrounding, histologically benign glands (11). AAH has been considered a premalignant lesion of the transition zone. A direct transition from AAH to cancer, as it has been observed between HGPIN and cancer, has not been documented. The link between cancer and AAH is probably an epiphenomenon and that the data are insufficient to conclude that AAH is a premalignant lesion.

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EDITORIAL COMMENT

A hypothesis for prostate carcinogenesis proposes that injury to the prostate from a variety of causes leads to chronic inflammation and proliferative inflammatory atrophy (PIA) which may be a risk factor for prostate cancer. Prostatic glandular atrophy can be diffuse or focal with diffuse atrophy resulting from androgen deprivation. PIA is a type of focal atrophy that occurs in the absence of androgen deprivation and occurs in small or large foci, most commonly in the peripheral zone. Recognized morphological types of PIA include simple atrophy and postatrophic hyperplasia in which chronic inflammation as well as increased proliferative activity has been demonstrated. It is unknown whether the other types of focal atrophy, including simple atrophy with cyst formation and partial atrophy have increased cellular proliferation. Therefore, these lesions are currently not considered PIA. A variety of other carcinomas including those in the liver, stomach, large bowel and urinary bladder appear to be related to long-standing chronic inflammation and proliferation. Prostate cancer and its precursor, high-grade prostatic intraepithelial neoplasia (HGPIN) have been linked with PIA lesions through topographical and morphological associations. De Marzo et al. (1) have

shown frequent morphological transitions between HGPIN and PIA suggesting that PIA may be a high-risk lesion for prostate cancer through HGPIN. Although topographical and morphological associations alone are not proofs of a cancer-causing role for PIA lesions, these support a model of prostatic carcinogenesis in proliferative epithelium in chronic inflammation. The authors studied needle core biopsies of patients with prostate cancer and did not show a topographical relationship of inflammatory atrophy to adenocarcinoma. Other studies have shown similar results with inflammatory atrophy found to be a very common lesion. These findings, while not supporting this model of prostate carcinogenesis, do not rule out this association and ultimately experimental animal studies, epidemiological studies and molecular pathological approaches are needed to clarify this hypothesis.

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Evaluation of Acrosomal Status and Sperm Viability in Fresh and Cryopreserved Specimens by the Use of Fluorescent Peanut Agglutinin Lectin in conjunction with Hypo-osmotic Swelling Test

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ABSTRACT

Objective: In this study, we evaluated whether the hypo-osmotic swelling test (HOST) can be used as a vital marker in combination with peanut agglutinin (PNA) - labeling in fresh and cryopreserved spermatozoa.

Materials and Methods: Human sperm populations were exposed to a hypo-osmotic medium for 60 minutes, and then incubated in a 1 µg/mL solution of the fluorescent dye Hoescht 33258 (H33258) for 10 minutes. Excess stain was removed by washing in phosphate-buffered saline (PBS) solution, and the pellet was resuspended in 100 µL of culture medium. Twenty microliters of this solution were subsequently smeared on a microscope slide, and fixed in ice-cold methanol to permeabilize the sperm membranes. The fixed smears were finally incubated in a 40-µg/mL FITC-PNA solution for 20 minutes. Simultaneous assessment of acrosome and viability scores was done in a fluorescent microscope equipped with appropriate filters and phase contrast illumination. The same slide was examined for FITC-PNA labeling, tail swelling, and for Hoechst-33258 staining by interchanging the filters and phase contrast optics.

Results: In fresh specimens, HOST was found to provide viability assessments comparable to those obtained using the H33258 method ($r = 0.95$). However, the results of HOST and H33258 were not correlated in cryopreserved specimens ($r = 0.22$). There was no alteration of PNA-labeling due to the HOST or H33258.

Conclusions: FITC-PNA labeling in conjunction with the visualization of the morphological change induced by exposure to hypo-osmotic solution provides a simple but effective method for establishing the state of acrosomal membrane and viability in fresh human spermatozoa, but this technique is not reliable for cryopreserved ones.

Key words: acrosome; sperm; cryopreservation; Fitc pna

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INTRODUCTION

Specialized sperm function tests are better predictors of fertilizing potential than traditional se-

men parameters assessed by standard semen analysis (1-6). Several functional tests, such as acrosome reaction, hemizona binding assay, sperm morphology, creatine kinase have been proposed to explore sperm

fertilization ability and to predict the rate of in vitro fertilization (IVF) (1,3,5,7). The acrosome reaction test (AR) is a stable parameter of sperm function (8,9) which is useful not only to predict fertilization success, but also as a tool in andrology for research purposes, such as male contraception (10) and gonadotoxic effects of food and drugs (11). The test is based on sperm physiology, and involves capacitation and acrosome reaction. Capacitation prepares the sperm to undergo the acrosome reaction with the accompanying release of lytic enzymes and exposure of membrane receptors, which are required for sperm penetration through the zona pellucida and for fusion with the oolema (12).

Several techniques have been proposed to differentiate acrosome-intact from acrosome-reacted spermatozoa, including cytochemical staining techniques (13,14), indirect immunofluorescence using monoclonal antibodies (15), labeling with fluoresceinated lectins (16,17) and phase-contrast microscopy to examine partial head decondensation (18). There are significant problems associated to the use of the acrosome reaction on endpoint in the evaluation of human sperm function (14,15,17). One of the most important involving the diagnostic technique is the difficulty in differentiating between pathologic acrosomal loss, secondary to a reduction in cell viability, and a true acrosome loss. Although this problem may be overcome by using a DNA-sensitive fluorochromes to monitor viability, such as Hoechst-33258, the technique is labor-intensive and requires dual filter set to allow simultaneous assessment of the acrosome status and viability (16,19). The differentiation between pathological and true acrosomal loss is particularly important when assessing the acrosome status of cryo-thawed spermatozoa, because cryopreservation directly damages sperm membrane, resulting in loss of membrane permeability and subsequent cell death (20), as well as in specimens with absence or limited number of motile sperm forms.

The purpose of this study was to evaluate whether the hypo-osmotic swelling test (HOST) can be used as a marker of viability in combination with fluoresceine isothiocyanate-conjugated peanut agglutinin to monitor the acrosomal status in fresh and cryopreserved spermatozoa.

MATERIALS AND METHODS

Test yolk-buffer freezing medium and sperm washing media (HEPES-modified Biggers-Whitten-Whittingham) were purchased from Irvine Scientific (Santa Ana, CA). Hoechst 33258 (bis-benzimide), fluoresceine isothiocyanate-conjugated peanut agglutinin (FITC-PNA), eosin and nigrosin were obtained from Sigma Chemical Company (St. Louis, MO). Hypo-osmotic swelling solution was prepared by mixing 7.35 g sodium citrate and 13.51 g fructose in 1 liter of distilled water (21). Hoechst 33258 was prepared as a 1000X stock solution by dissolving 1 mg H33258 in 1 mL Dulbeco's phosphate-buffered saline. The stock was frozen at -20°C in 10 µL aliquots in small foil-covered Eppendorf tubes to protect it from light.

Semen samples were obtained from 11 normal healthy volunteer individuals with proven fertility and age ranging from 21 to 35 years old (median 24). Subjects were asked to abstain from ejaculation for at least 48 hours and semen was collected by masturbation into sterile specimen cups. The ejaculate was allowed to liquefy for 30 minutes at 37°C and examined within 1 hour of collection to determine semen characteristics according to World Health Organization criteria (22). A computer semen-analysis of each specimen was performed on a computer-assisted motion analyzer (Motion Analysis; Cell-Trak, model VP 110, Santa Rosa, CA) to assess concentration and motility. Subjects included in this study were selected according to their basic sperm parameters, as follows: volume ≥ 2.0 mL, concentration $\geq 20 \times 10^6/\text{mL}$ and motility $\geq 50\%$.

Cryopreservation procedure - After initial analysis, each specimen was divided into two aliquots of identical volumes. The first aliquot was cryopreserved while the second aliquot underwent acrosomal and viability assessments. TEST yolk-buffer with glycerol was used as a freezing agent for cryopreservation. Briefly, an aliquot of the freezing medium equal to 25% of the original specimen volume was then added to the specimen. The specimen was gently mixed for 5 minutes using Hema-Tek aliquot mixer (Miles, Elkhart, Ind.). This was repeated until an equal volume of freezing medium had been added

to the ejaculate. The specimen was then equally divided into vials for long-term cryopreservation. Cryovials were placed in the freezer at -20°C for 8 minutes and thereafter in liquid nitrogen vapor at -100°C for 2 hours. The vials were then transferred to liquid nitrogen at -196°C for long-term storage. After at least 2 days in liquid nitrogen, the vials were thawed at 37°C for 20 minutes, washed twice to remove the cryomedia and reconstituted in modified-BWW with 5% albumin. After thawing, acrosomal and viability assessments were performed on cryopreserved specimens.

Simultaneous assessment of acrosomal status and viability - The protocol developed for assessing the acrosome status involved the use of a detection reagent targeting the acrosomal region of the sperm head (fluorescein isothiocyanate-conjugated peanut agglutinin - FITC-PNA), in conjunction with both the hypo-osmotic swelling test (HOST) and the supravital staining Hoechst 33258 to monitor sperm viability. For this assay, 100 μL of the sperm specimens were added to 1 mL of hypo-osmotic solution and incubated for 1 hour at 37°C . At the end of this period, the spermatozoa were pelleted by centrifugation at 1000 rpm for 5 minutes and resuspended in 2 $\mu\text{g}/\text{mL}$ Hoechst-33258 solution. The sperm suspensions were incubated for 10 minutes in the dark. Spermatozoa were then washed in phosphate-buffered saline (PBS) solution by centrifugation at 1200 rpm for 5 minutes to remove excess stain, and the pellet was resuspended in 100 μL of BWW. Twenty microliters of this solution were subsequently smeared on a microscope slide and allowed to dry. At least three slides of each sample were prepared, in case of problems with labeling or scoring. The slides were then immersed in ice-cold methanol for 30 seconds to permeabilize the sperm membranes and allowed to air dry. The fixed smears were immersed in a 40- $\mu\text{g}/\text{mL}$ FITC-PNA solution, incubated at room temperature for 20 minutes in foil-covered Coplin jar, and washed gently in PBS to remove the excess label. Scoring was completed within 48 hours of staining.

A Leitz Orthoplan microscope (Leitz, Germany) equipped with phase contrast and fluorescence epi-illumination module was used to examine the slides at 1000X magnification in the

presence of an anti-quenching agent (Cargille immersion oil, type DF, Fisher Scientific, Pittsburgh, PA) to minimize the loss of fluorescence. The same spermatozoon was first examined for tail swelling using phase contrast with halogen illumination (Figure-1). Then, the illumination was changed from halogen to mercury ultraviolet epi-illumination source for assessing FITC-PNA (Figure-2) and Hoechst-33258 labeling (Figure-3). Filter cube I.2 was used for FITC-PNA, which fluoresces "apple-green" and cube A.2 for Hoechst-33258, which fluoresces a bright medium blue. Examination of the same spermatozoon for FITC-PNA labeling and for Hoechst-33258 staining was performed by interchanging the two filters. A total of 200 hundred spermatozoa per sample were scored.

Categorization of sperm tail response to hypo-osmotic solution and staining patterns - Spermatozoa were classified as osmotically competent if tail swelling was observed after exposure to the hypo-osmotic solution (Figure-1). In contrary, spermatozoa were classified as osmotically incompetent if straight tail was observed. Percentage swelling induced by the cryopreservation process was determined in each specimen after thawing and subtracted from the hypo-osmotic swelling test results.

Hoechst-33258 stains the nuclei of damaged cells (dead spermatozoa), which show a bright blue-



Figure 1 – Photomicrography of spermatozoa exhibiting tail swelling after exposure to the hypo-osmotic solution. Spermatozoa were examined under phase-contrast microscopy with halogen illumination at X1,000 magnification.

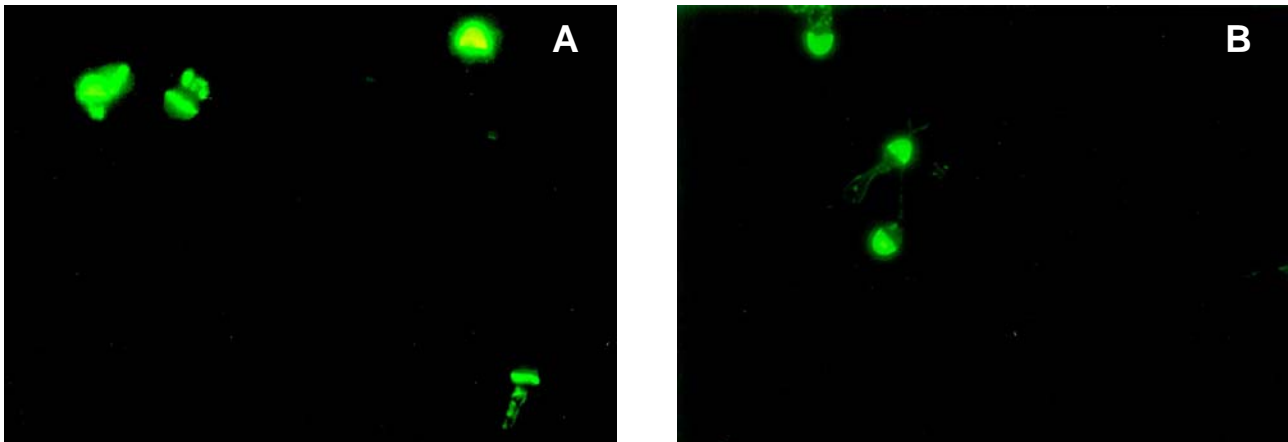


Figure 2 – Photomicrograph of spermatozoa labeled by FITC-PNA. Spermatozoa were examined under fluorescence epi-illumination at X1,000 magnification. Filter cube I.2 was used for FITC-PNA, which fluoresces “apple-green”. A) In an intact acrosome, the acrosomal region of the sperm head exhibited a uniform apple-green fluorescence (left). In a reacted acrosome, only the equatorial segment of the acrosome was stained (right). B) Sperm tail swelling may be also observed if excess background staining is present.

white fluorescence and is excluded from viable cells (live spermatozoa), which show a pale blue fluorescence. Viability staining on Hoechst-33258 was classified as follows. In viable spermatozoa, the sperm head showed a pale-blue fluorescence, and in dead spermatozoa, the sperm head showed a bright blue-white fluorescence (Figure-3) (17).

FITC-PNA binds specifically to the outer acrosomal membrane. Acrosome staining on FITC-PNA labeling was classified as follows. In an intact acrosome, the acrosomal region of the sperm head exhibited a uniform apple-green fluorescence. In a reacted acrosome, only the equatorial segment of the acrosome was stained (Figure-2) (23).

Reproducibility of HOST and acrosomal evaluations - To evaluate the between-observer reproducibility of HOST, one slide from each donor was evaluated blindly by two observers. To determine the within-observer reproducibility of HOST, the same slides were re-evaluated blindly by one observer. The inter- and intra-observer reproducibility of the acrosome scores in fresh and cryopreserved specimen were previously published (24). The average coefficient of variation between observers for acrosomal results was 6.5%. The intraclass correlation coefficient (ICC) between the observers was 0.81 [95% confidence

interval (CI), 0.62-0.91]. The intra-observer coefficient of variation and the ICC for acrosomal evaluations were 1.6% and 0.98 (95% CI, 0.95-0.99), respectively.

Data are expressed as median and interquartile range. The Pearson method with an alpha level of 0.05 was used to correlate the viability results between hypo-osmotic swelling test and Hoechst-33258 staining before

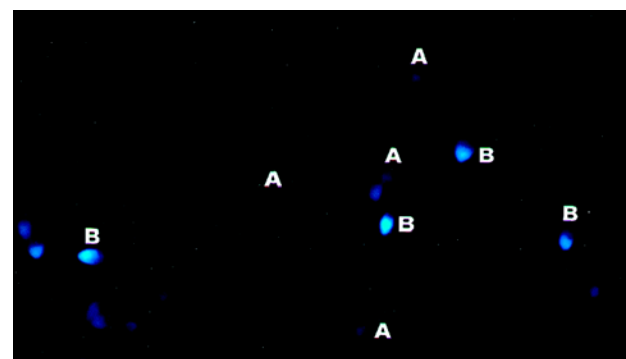


Figure 3 – Photomicrograph of spermatozoa labeled by Hoechst-33258. Spermatozoa were examined under mercury ultraviolet epi-illumination at 1000X magnification. Filter cube A.2 was used for Hoechst-33258, which fluoresces a bright medium blue. Hoechst-33258 stains the nuclei of damaged cells (dead spermatozoa), which show a bright blue-white fluorescence (B) and is excluded from viable cells (live spermatozoa), which show a pale blue fluorescence (A).

freezing and after thawing. Differences in the frequency of the acrosome reaction in viable spermatozoa according to the tail swelling or Hoechst 33258 pattern were evaluated by applying the Wilcoxon signed-rank test. $P < 0.05$ was accepted as statistically different. Statistical analyses were performed using the SAS statistical software package (Cary, NC).

RESULTS

Sperm survival - The nuclear dye Hoechst 33258 was considered as the gold standard to determine viability. The percentage of live spermatozoa in fresh and frozen specimens was 72.0% (64.5%-87.0% interquartile range) and 29.5% (26.0%-36.8% interquartile range), respectively. The percentage of spermatozoa exhibiting tail swelling after exposure to the hypo-osmotic solution was 73.5% (66.0%-85.5% interquartile range) in fresh and 50.0% (43.5%-56.0% interquartile range) in frozen specimens.

In fresh specimens, the majority of viable spermatozoa, which fluoresced pale-blue by

Hoechst-33258 staining, were also swollen by HOST (osmotically competent). The results of the HOST strongly correlated with those obtained by Hoechst-33258 staining ($r = 0.95$, $p = 0.0001$) (Figure-4). After cryopreservation, we observed no correlation between the viability scores measured by HOST and Hoechst-33258 staining ($r = 0.11$, $p = 0.70$) (Figure-5). However, a small percentage of cryo-thawed spermatozoa were swollen before exposure to the hypo-osmotic solution (median = 20.0% [18.0%-23.0% interquartile range]). Even after correcting the HOST results for the swelling expected from cryopreservation, the viability scores measured by HOST and Hoechst 33258 stain showed poor correlation ($r = 0.22$; $P = 0.43$) (Figure-6).

Acrosome reaction - The evaluation of the acrosome reaction was performed by utilizing FITC-PNA. Figure-7 illustrates the importance of differentiating between normally reacted cells and post mortem degeneration of the acrosome. The percentage of cells exhibiting reacted acrosomes in fresh specimens was 28.0% (13.0%-33.5% interquartile range). However, we observed a

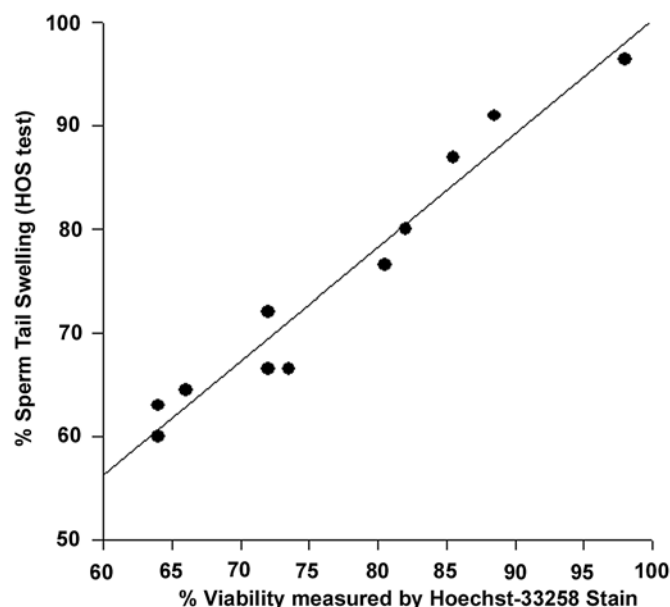


Figure 4 – Correlation of viability results before cryopreservation between sperm tail swelling by HOST and Hoechst 33258. Strong correlation seen between HOST and Hoechst 33258 ($r = 0.95$, $p < 0.001$).

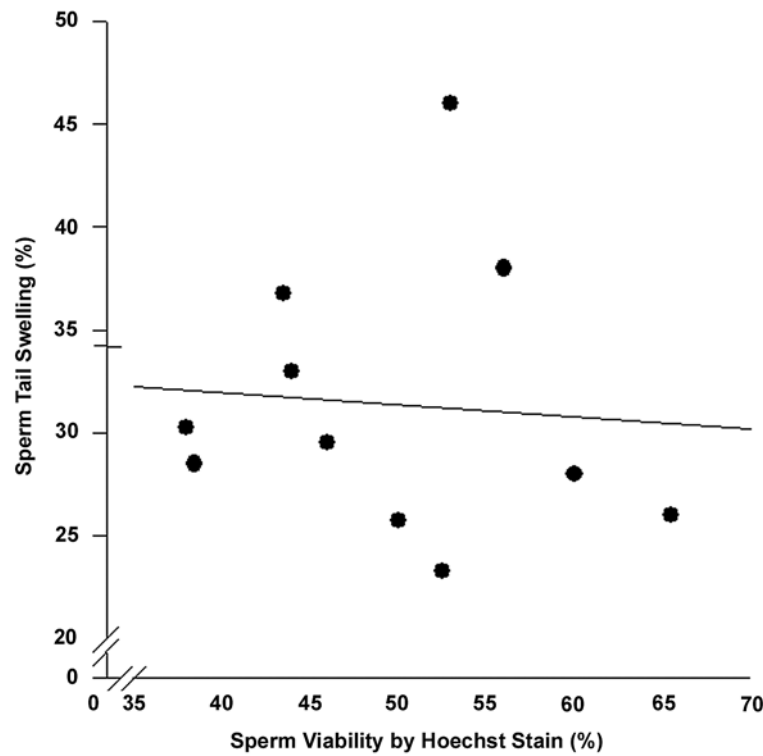


Figure 5 – Correlation of post-thaw viability results between sperm tail swelling by HOST and Hoechst 33258 stain. No correlation was seen between HOST and Hoechst 33258 ($r = 0.11$, $p = 0.70$).

significant reduction in the frequency of reacted acrosomes when only viable spermatozoa, as assessed by Hoechst-33258, were evaluated (median = 7.4% [2.0%-10.9% interquartile range]; $p < 0.001$) (Figure-7).

Utilizing both methods for assessing acrosome reaction in viable human spermatozoa, (1) FITC-PNA and exposure to a hypo-osmotic solution and (2) FITC-PNA combined with Hoechst-33258 stain, similar acrosome reaction rates could be detected in fresh specimens (median = 11.2% [5.9%-15.2% interquartile range] versus 7.4% [2.0%-10.9% interquartile range]; $p = 0.07$). In frozen specimens, the frequencies of acrosome reaction in viable spermatozoa assessed by FITC-Hoechst and FITC-HOST were significantly different (median = 29.6% [23.1%-33.3% interquartile range] versus 19.5% [16.0%-24.5% interquartile range]; $p = 0.01$) (Figure-8).

The average coefficient of variation between observers for HOST was 3.5%. The intraclass correlation coefficient (ICC) between the observers was 0.89 [95% confidence interval (CI), 0.76-0.99]. The coefficient of variation for duplicate evaluation of the same slides was 1.8%. The ICC between the two readings by the same observer was 0.93 (95% CI, 0.89-0.99).

COMMENTS

Standard semen analysis has limited predictive value for assessing the sperm fertilizing potential (25). Functional parameters of oocytes and spermatozoa are crucial for fertilization. Oocytes must be at the proper stage of maturity. Factors in spermatozoa include motility, membrane integrity, ability to bind to the zona pellucida, acrosin activity and membrane

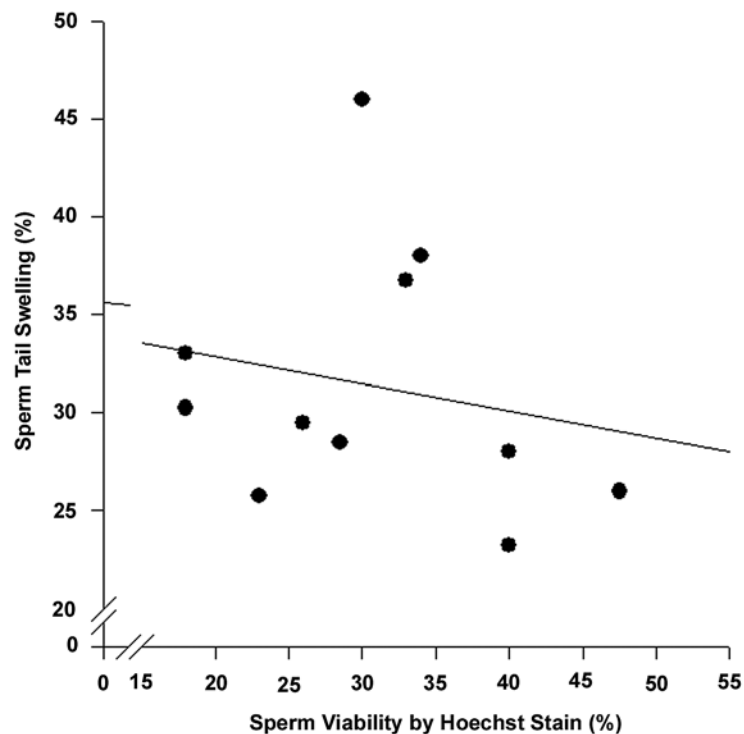


Figure 6 – Correlation of post-thaw viability results between corrected sperm tail swelling (corrected HOST) and Hoechst 33258 stain. No correlation was seen between corrected HOST and Hoechst 33258 ($r = 0.22$, $p = 0.43$).

fusion ability, and also the acrosome reaction, which is of essential importance (12). Failed fertilization related to male factors, which occurs in 5-10% of in-vitro fertilization cycles and 2-3% of intracytoplasmic sperm injection cycles, may be observed in conjunction with apparent normal semen analysis (2,5). For these reasons, several functional tests have been proposed to explore sperm fertilization ability and to predict the success rate of IVF. Sperm morphology evaluated by strict criteria has been shown to be relevant (26). One of the most studied in the past was the zona-free hamster egg sperm penetration assay (SPA). Although good correlation with IVF have been reported, SPA does not represent a clinical suitable test because it cannot be performed routinely, it is expensive and time-consuming, it gives some false-negative responses, and it explores together several functions (capacitation, acrosome reaction and fusion to the oolema) (27). The ideal test system for sperm is IVF of human oocytes,

which is properly governed by ethical constraints and cannot be used for a purely diagnostic purpose. Other tests such as hemizona assay, creatine kinase and the recent assays to examine sperm DNA fragmentation also seem to adequately assess the fertilizing potential of human sperm (7,28,29).

Overall, most sperm function tests are laborious and expensive, and they have yet to be proved clinically relevant for routine use in clinical andrology practice. Alternatively, the acrosome reaction (AR) test, which is a simple, inexpensive laboratory test that can be performed in any andrology laboratory with no restrictions associated with the availability of expertise or the testing material, has been shown to correlate well with fertilization (1-4,8,9). The AR test is based on sperm physiology. Mammalian spermatozoa must undergo a capacitation process before they are able to fertilize oocytes. Capacitation involves major biochemical and biophysical changes in the membrane

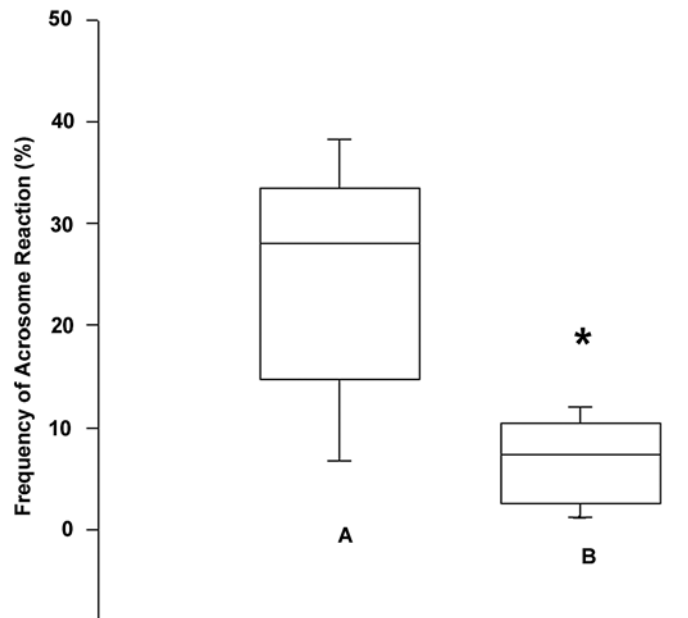


Figure 7 – Evaluation of the frequency of acrosome reaction determined by FITC-PNA and Hoechst 33258 to monitor viability from 11 samples of fertile donors. (A) Total acrosome reaction (normal reacted cells plus post mortem degeneration of the acrosomes) and (B) acrosome reaction in live human spermatozoa (* $p < 0.01$). Box covers the middle 50% of the data values, between the lower and upper quartile. The central line is the median and the whiskers extend out to 80% of the data. Bars represent values between the 5th and 95th percentile.

complex and energy metabolism of the spermatozoa. Moreover, capacitation has been recognized as a time-dependent phenomenon, with the absolute time course being species-specific. Capacitation prepares the sperm to undergo the acrosome reaction with the accompanying release of lytic enzymes and exposure of membrane receptors, which are required for sperm penetration through the zona pellucida and for fusion with the oolema (12). Integrity of acrosomal function seems to be of crucial importance to normal fertilization because acrosomeless round-headed spermatozoa cannot fertilize oocytes, and increased percentages of morphologically abnormal acrosomes were related to IVF failure. Moreover, acrosome evaluation is also a valuable tool in modern andrology for both diagnosis of male infertility and research. Premature acrosome reaction and the inability of the spermatozoa to release the acrosomal contents in response to proper stimuli (acrosome reaction insufficiency)

have been associated with idiopathic male infertility (30). Additionally, the development of contraceptive vaccines involving sperm-specific antibodies that interfere in the acrosome reaction is one of the examples in the research field (10). Toxic potential of dietary substances and drugs can also be evaluated by AR assays. In a recent report, Kumi-Diaka & Townsend investigating the toxic potential of dietary isoflavones on sperm fertility have shown that despite of the fact that light microscopic could not identify detrimental effects of phytochemicals on sperm morphology, suppression of AR in higher doses and induction of AR at lower doses have been demonstrated with AR assays (11).

Therefore, many relevant aspects can be examined by studying the sperm acrosome and determination of the acrosome reaction, such as the true potential of spermatozoa for fertilization, the search for unexplained causes of male infertility and the possibility for male contraceptive development.

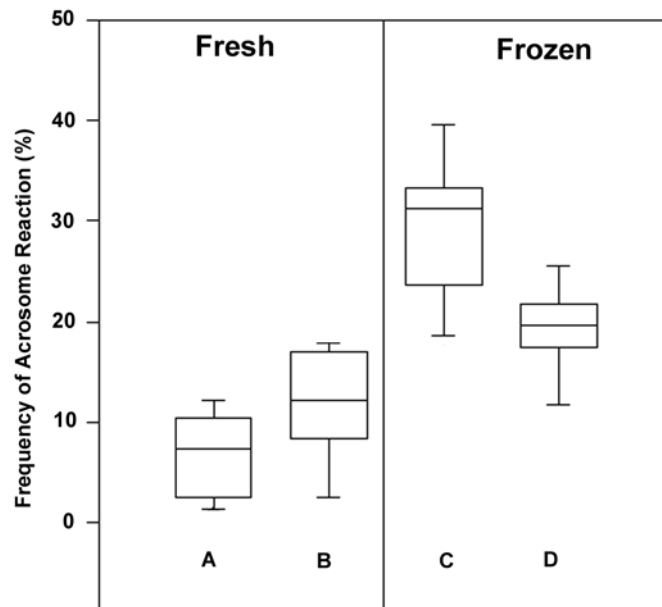


Figure 8 – Evaluation of the frequency of acrosome reaction in live human spermatozoa from 11 samples of fertile donors, determined by (A) FITC-PNA and HOST, and (B) FITC-PNA and Hoechst 33258, in fresh and post-thaw specimens. Similar acrosome reaction rates were detected by both A and B methods in fresh specimens ($P = 0.07$). In frozen specimens, the frequencies of acrosome reaction in viable spermatozoa assessed by A and B methods were significantly different ($p = 0.01$). Box covers the middle 50% of the data values between the lower and upper quartile. The central line is the median and the whiskers extend out to 80% of the data. Bars represent values between the 5th and 95th percentile.

The human acrosome is a membrane-bound organelle, which appears during spermatogenesis as a product of the Golgi complex. It can be visualized by phase contrast light microscopy (18), and with greater accuracy by using electron microscopy, fluorescence (1,3,16,17,19), monoclonal antibodies (15), or simple dyes (13,14). However, electron microscopy and immunofluorescence do not differentiate between normally reacted cells and post mortem degeneration of the acrosome. Cross et al. (1986) employed supravital stain Hoechst 33258 (a fluorescent DNA-binding dye with limited membrane permeability) combined with immunofluorescence technique for evaluation of acrosome reaction in viable spermatozoa (17). They observed a discrepancy between viable spermatozoa (Hoechst 33258 negative), concerning the acrosome reaction, and the total number of acrosome-reacted spermatozoa. Consequently, for exact evaluation of the acrosome reaction as a physiological process leading

to fertilization, the determination of viable spermatozoa that have undergone acrosome reaction is important.

The determination of viability when studying the acrosome status in cryopreserved sperm is of fundamental importance. Cryopreservation directly damages sperm membrane, resulting in loss of membrane permeability and subsequent cell death (20). Cryopreservation can also cause permanent functional damage (sublethal damage), reducing the fertilizing ability of human sperm (19). This reduction in fertility can be explained partially by the reduction in the percentage of normal intact acrosomes and in total acrosin activity. Although damage to the acrosome after cryopreservation may also be secondary to cell death (20), an increase in the proportion of viable acrosome-reacted spermatozoa after cryopreservation has been reported (19). These observations further stress the clinical importance of adequate assessment of the acrosomal status in cryopreserved sperm.

In the present study, we developed a protocol based on Aitken et al. previous work (16) that involved sperm incubation in a hypo-osmotic solution, staining with Hoechst-33258, and staining with FITC-PNA. Hypo-osmotic swelling test (HOST) was originally developed as a clinical test for human spermatozoa (21). The percentage of swollen sperm after incubation under hypo-osmotic conditions reflect the percentage of spermatozoa with intact membranes, as it has been suggested that HOST can also assess sperm viability (31). In the present study, the viability results assessed by Hoescht-33258 and HOST were highly correlated in fresh sperm. The hypo-osmotic swelling test provided a simple, effective and convenient means of evaluating viability of spermatozoa that have been monitored for acrosome status. HOST has potential advantages over dye exclusion techniques (16). It is definitely a valuable alternative to more complex protocols involving the use of fluorochromes in fresh sperm.

On the other hand, our results fail to show correlation between viability by Hoescht-33258 and HOST in freeze-thaw sperm, even after correcting the percentage of spermatozoa swelled due to the cryopreservation process. The poor specificity of HOST in detecting viable sperm in cryopreserved-thawed sperm has been previously demonstrated (31). The reasons for that are unknown, but we speculate that sperm head and tail membranes have different liabilities to the freeze-thawing process. It may be possible that the determining factor for sperm survival after cryopreservation is the membrane integrity of sperm head, which is not assessed by HOST. FITC-PNA labeling in conjunction with the HOST cannot accurately evaluate the acrosome reaction in viable cryopreserved human spermatozoa, and to date protocols involving the use of supra-vital stains have to be used in such cases.

CONCLUSIONS

Simultaneous assessment of acrosomal status using FITC-PNA labeling in conjunction with HOST provides a simple but effective method for establishing the state of acrosomal membrane and to

monitor viability in fresh human spermatozoa. However, FITC-PNA labeling should not be used in conjunction with the HOST to accurately evaluate the acrosome reaction in viable cryopreserved human spermatozoa.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors are to be commended for their efforts to simplify the technique of concurrently assessing acrosome status (reacted vs. nonreacted) and overall sperm viability. The combination of the two methods investigated, the Fluorescein-conjugated peanut agglutinin (FITC-PNA) lectin labeling test and the Hypo-osmotic swelling test (HOST), allows for the simultaneous assessment of acrosome status and overall sperm viability, thus averting the need for dual-filter microscopy. This approach proved to be accurate for fresh sperm, but not so for cryopreserved-thawed sperm, where the HOST assay was found not to correlate with the gold

standard test for sperm viability, Hoeschst 33258 staining. Interestingly, the authors found that even after correcting for sperm swelling expected from cryopreservation, the viability scores measured by HOST and Hoeschst 33258 staining still poorly correlated. As the authors state, this finding suggests that the determining factor for sperm survival after cryopreservation may be the integrity of the sperm head membrane, which is not assessed by HOST. These interesting observations by the authors' make their work exciting, possibly leading to new insights into the mechanisms of sperm viability after cryopreservation and thawing.

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EDITORIAL COMMENT

This paper has investigated whether the hypo-osmotic swelling test and FITC-PNA allow simultaneous assessment of vitality of spermatozoa and their acrosomal status. This appears to be of particular interest since the simultaneous investigation provides evidence if acrosomal loss can be classified as physiological or degenerative. Fresh and cryopreserved samples have been used in this experimental investigation. The authors found that FITC-PNA labeling in conjunction with morphological assessment of spermatozoa after simultaneous HOST facilitates effective evaluation of acrosomal status and viability of spermatozoa in fresh samples.

However, this technique failed to prove reliable in cryopreserved samples.

This experimental study appears to be neat and well executed, methodological flaws cannot be detected. However, the number of investigated subjects and samples has been quite small.

It should be critically mentioned that sperm function tests do not always appear superior versus conventional semen analysis. In fact these tests are usually laborious and expensive in routine analysis and mostly do not result in therapeutic consequences for the clinical andrologist. Results from this and similar studies conclusively are of some theoretical nature.

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REPLY BY THE AUTHORS

We thank Professor Brannigan and Professor Diemer for their comments. We agree with Professor Diemer when he says that sperm function tests are usually laborious and expensive to be included in routine semen analysis. However, some of them are quite simple and inexpensive, and in general, they are better predictors of the male reproductive potential than conventional semen analysis. Additionally, sperm function tests certainly may be very helpful for the clinical andrologist. The assessment of sperm

morphology by strict criteria, direct anti-sperm antibodies measurements and the tests to determine the occurrence of sperm DNA fragmentation, to cite a few, have been incorporated into the clinical practice in the recent years. These tests, which originated from the basic science, were validated as useful tools either to predict the male reproductive potential or to help the clinician define which therapeutic option is best for the infertile couple, i.e., assisted reproduction or conventional andrological treatments.

Laparoscopic Live Donor Nephrectomy in Patients Surgically Treated For Morbid Obesity

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ABSTRACT

In the past, morbid obesity was considered a relative contraindication to renal donation; however, more recent publications have shown that laparoscopic renal surgery is safe and effective for obese donor nephrectomy. We report the performance of a bariatric surgery before the kidney donation in 2 patients in order to improve their medical condition and to reduce their surgical risk to the transplantation procedure. After bariatric surgery, both donors lost more than 30% of their initial corporal weight and their donation procedure was successfully performed, with uneventful postoperative courses.

Key words: *laparoscopy; nephrectomy; living donors; morbid obesity; bariatric surgery*

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INTRODUCTION

Patients who are morbid obese are much more likely to have health problems than persons who maintain a healthy weight. Consequently, these individuals need medical treatment, and bariatric surgery is currently the only effective therapy for this disease. In the past, morbid obesity was considered a relative contraindication to renal donation (1); however, more recent publications have shown that laparoscopic renal surgery is safe and effective for obese donor nephrectomy (1,2). We report on 2 patients in whom we preferred to perform the Roux-en-Y gastric bypass before the laparoscopic kidney donation in order to treat their medical condition, reducing their surgical risk to the live donor nephrectomy procedure.

CASE REPORT

Case 1 - A 23-year-old male donor with body mass index (BMI) 40.9 kg/m² (weight = 121 kg; height

= 1.72 m) and no co-morbidities underwent a laparoscopic Roux-en-Y gastric bypass losing 38 kg, 4 months after the bariatric surgery. Then, he was scheduled for the left hand-assisted laparoscopic live donor nephrectomy, which was uneventful, with an operative time (OT) of 75 minutes, a warm ischemia time (WIT) of 1.8 minutes, and an estimated blood loss (EBL) of 100 cc. He was discharged in the first postoperative day (Figure-1). The serum creatinine of the recipient 5 months after the procedure was 1.1 mg/dl and the donor was weighting 76 kg (BMI 25.7 kg/m²).

Case 2 - A 54-year-old female donor with BMI 48.7 kg/m² (weight = 120 kg; height = 1.57 m) and mild hypertension had undergone a laparoscopic bariatric surgery in another institution, losing only 20 kg in 4 months. She came to our service and was submitted to a laparoscopic revisional bariatric surgery, reducing the size of the gastric pouch and increasing the length of the Roux limb. Three months after surgery her BMI was 32.4 kg/m² (Weight = 80 kg) and she underwent a pure left laparoscopic donor

nephrectomy (Figure-2) with an OT of 90 minutes, a WIT of 2.2 minutes, and an EBL of 80 cc. She was discharged in the postoperative day 1. Two months after the kidney donation, the serum creatinine of the recipient was 1.1 mg/dL and the BMI of donor was 32 kg/m², with no need for antihypertensive medication.

COMMENTS

Morbid obesity is an important public health problem. It is associated with serious co-morbidities (hypertension, diabetes, peripheral resistance to insulin, dyslipidemia, etc.), it shows a high prevalence globally, and it is associated with a high mortality rate (3). Moreover, when morbid obese patients need any surgical procedure, they present a significant challenge for the laparoscopic surgeon. In addition to the technical challenges of positioning and instrumentation, these patients are reported to have a propensity for postoperative and anesthetic complications (2).

Population studies have shown that obesity is associated with increased risk for proteinuria, and the development of proteinuria signals a marked increased risk to develop renal failure. Acceptance of obese individuals as living kidney donors is controversial related to possible increased risk for surgical complications and concern that obesity may contribute to long-term renal disease (4).

Chow et al. (1) analyzed non-obese (BMI < 30) and morbidly obese patients (BMI ≥ 30) referred for hand-assisted donor nephrectomy finding similar shortened hospital stays and surgical times for both groups. They concluded hand-assisted donor nephrectomy is safe and effective, not increasing morbidity in morbid obese donors.

Jacobs et al. (2) compared markedly obese (BMI > 35) and ideal-size control (BMI < 30) donors scheduled for laparoscopic nephrectomy and they observed the donor operations in the markedly obese were significantly longer by an average of 40 minutes, obese donors were more likely to require conversion to open nephrectomy than ideal-size donors (7.3% vs. 0%) and postoperative complications were equal in the two groups, although the obese donors'



Figure 1 – Patient on the day of discharge.



Figure 2 – Patient on the surgical table and final aspect of the surgery. The infra-umbilical incision was used to remove the kidney because she already had this surgical scar due to a previous hysterectomy.

complications tended to be cardiopulmonary problems. They concluded that despite the longer operative time, the increased port size requirement and the higher conversion rate in the markedly obese group, these differences are fairly small, and the procedure of laparoscopic donor nephrectomy itself appears appropriate to consider for the markedly obese renal donor.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Long term follow-up of renal obese donors is limited, as obesity has been considered relative exclusion criteria until recently. While obese donors showed a trend to higher mean arterial pressure and a higher glomerular filtration rate, there were no significant differences from normal donors (1). Another aspect is the possibility that they may be at greater risk for developing type II diabetes mellitus later in life and the unknown impact of nephrectomy on the obese patients who subsequently develops diabetes or hypertension (2).

The idea of performing a bariatric surgery in such group of donors may be very helpful for not only reducing the morbidity of the donation itself but also offering some effective therapy for morbid obesity.

This special group of donors should be submitted to a very strict selection criterion and who are highly motivated to donate could be accepted. The selected criteria should be based upon blood pressure, family history of diabetes and cardiovascular disease

and reinforcing the importance of a careful and long term follow-up.

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Laparoscopic Treatment of Traumatic Intraperitoneal Bladder Rupture

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ABSTRACT

Traumatic intraperitoneal bladder rupture requires surgical suture and bladder drainage. In stable patients the laparoscopic approach is the best short recovery and less traumatic treatment allowing visualization of the entire peritoneal cavity to exclude others lesions. We present one case of successful laparoscopic treatment of this entity.

Key words: *bladder; wounds and injuries; laparoscopy*

Int Braz J Urol. 2007; 33: 380-2

INTRODUCTION

Traumatic intraperitoneal bladder rupture requires surgical suture and bladder drainage. In stable patients the laparoscopic approach is the best short recovery and less traumatic treatment allowing visualization of the entire peritoneal cavity to exclude others lesions.

CASE REPORT

A 20-year-old female presented to hospital with complains of abdominal pain and hematuria after alcohol ingestion and a two floors fall with ventral collision. She was hemodynamically stable and the radiological evaluation showed a right pubic ramus fracture and free peritoneal liquid, discontinuity of bladder wall and normal kidneys through sonography (Figures-1 and 2). The cystography made evident an intraperitoneal bladder rupture (Figure-3).

The patient was submitted to laparoscopic exploration with three trocars, a 10 mm umbilical trocar and two 5 mm trocars, one in each iliac fossa. The surgeon's position was on the patient's left side to allow inspection of pelvic structures. The laparoscopic findings were blood and urine in the peritoneal cavity, a 5 cm bladder rupture in the dome and no other lesions. The cavity was cleaned and the bladder sutured with a continuous one layer 3-0 polyglactin suture.

The patient was discharged from hospital in the 5th postoperative day due to the need of bed rest for pelvic fracture consolidation. Fourteen days after surgery the bladder catheter was removed with favorable evolution.

COMMENTS

Treatment recommendations for bladder rupture are well established as bladder catheter for ret-

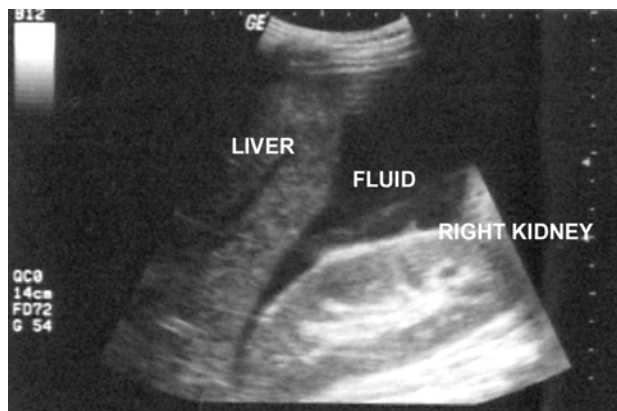


Figure 1 – Sonography showing free intraperitoneal fluid.

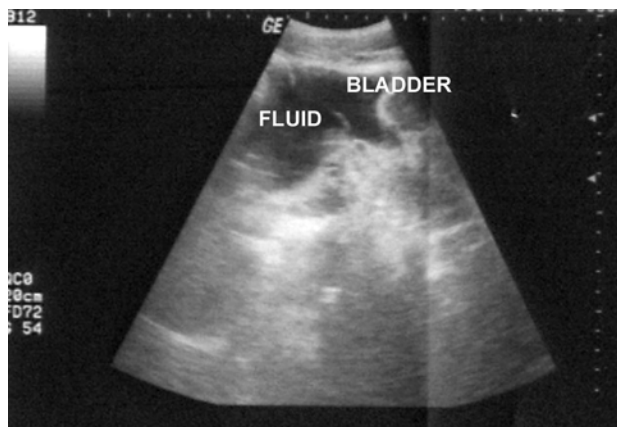


Figure 2 – Sonography showing discontinuity of peritoneal bladder wall.

roperitoneal perforations and cystorrhaphy for the intraperitoneal ones (1).

Laparoscopy is a minimally invasive technique to diagnose and eventually treat abdominal trauma. It can avoid laparotomy in 63% of the cases, decreasing its associated morbidity (2). In hemodynamically stable patients without diffuse peritonitis, the diagnostic laparoscopy can be used in stab wounds, gunshot wounds with questionable peritoneal penetration and in blunt trauma with free peritoneal fluid or equivocal physical examination. In the presence of simple and accessible injuries the therapeutic laparoscopy is performed. Bladder intraperitoneal rupture is of easy



Figure 3 – Cystography showing intraperitoneal bladder rupture.

correction through laparoscopic approach (2) and in the eventually presence of concomitant extraperitoneal rupture, the bladder drainage after surgery can treat it, if the rupture is not complex, avoiding an open surgery.

Laparoscopic repair of intraperitoneal bladder perforation was first described in 1994 and since then, a few cases of such approach have been reported to treat traumatic, spontaneous and iatrogenic bladder rupture, avoiding laparotomy (3).

The aim of this report was to stimulate the practice of laparoscopic exploration in stable trauma and remember the urologists the laparoscopic approach to any form of peritoneal bladder rupture.

CONFLICT OF INTEREST

None declared.

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Lower Urinary Tract Dysfunction in Children. What Do Pre-School Teachers Know About It?

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ABSTRACT

Objective: To evaluate the basic knowledge of pre-school teachers who deal with children between the ages of 4 and 7 years, who present signs of lower urinary tract dysfunction (LUTD).

Materials and Methods: We performed a survey with 50 teachers from 9 private schools working with pre-school children. The criteria for selection were if teachers were certified or non-certified elementary school teachers - NCEST and the amount of professional experience.

Results: Thirty-three teachers considered that the normal daily urinary frequency should be from 4 to 7 times. Two of the 50 teachers considered it normal to urinate less than 4 times per day and 15 teachers considered more than 7 times per day as normal. There was no difference between the 2 categories of certified or NCEST nor between those with more or less than five years of professional experience. Thirty-three percent believed that to urinate more than 4 times during a class period (4-5 hours) could indicate a urinary problem. There was a statistically significant difference among the certified and NCEST but not in terms of time of professional experience. If during this period the child would not ask to urinate, only 18% considered that as an indication of urinary problem. When asked about the symptoms that would indicate urinary urgency and urge incontinence, only 24% of the teachers connected it with urinary problem. There was no difference in terms of professional background or professional experience in these 2 last analyses.

Conclusion: Our data shows evidences that private pre-schools teachers are not well informed of the clinical manifestation of LUTD.

Key words: children; urinary incontinence; etiology; enuresis; schools

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INTRODUCTION

Currently children spend most of their day at school giving teachers increasing responsibility as educators and health promoters. For that reason, educators should have a comprehensive understanding about the physical, mental and social characteristics of chil-

dren regarding growth and development processes and health problems that might occur in different ages.

The Brazilian Ministry of Health acknowledges the importance of good pediatric health practices during school years by developing actions to prevent diseases and to empower factors of protection (1). During that period, children are facing experiences

where habits and attitudes are being modeled. Health promotion should also occur at pre-school age. The definition of “pre-school age” varies among authors as being from 2 to 6 years old or between the ages of 3 and 7 (2). The teacher is responsible for the educational development at school, which includes actively monitoring health deviations, which are sometimes undetected by the children and their family.

Lower urinary tract dysfunction (LUTD) occupies an important place among the causes of urinary losses and urinary tract infections in children from the age of 4 years old. LUTD is clearly associated to urinary infection, vesicoureteral reflux, renal scar and psychological changes (3-6). Clinically it is characterized by symptoms of urinary urgency, urge incontinence without neurological evidence or urinary tract infection. The clinical evidences (conditions or manifestations), such as urinary incontinence, urinary urgency, urinary contention habits, and interrupted voiding are frequently misdiagnosed and may impact the psychological, emotional and social well fare of the child. It is relevant for the teachers to know how to identify the clinical symptoms above because the children spend most of their time at school under their teacher’s care. The objective of this study is to evaluate the basic knowledge of teachers working with children between the ages of 4 and 7 years in relation to the major manifestations (we believe it to be better than evidences) of LUTD.

MATERIALS AND METHODS

A questionnaire (Figure-1) was prepared by the researchers and taken by 50 pre-elementary level teachers (pre-elementary level includes children from 4 to 7 years of age) from 9 private schools chosen by convenience. The interviewer delivered the questionnaire to the teacher’s work place and explained that it was to be self-administered and anonymous. The responses were compared taking into account the type of professional background: if they are pedagogues or non-pedagogues (certified or non-certified elementary school teachers) and if they have more or less than 5 years professional experience working in the area.

The statistic analysis was performed comparing the proportions using the Qui-square or Fisher test. For continuous variables purposes the “T” test was applied. For statistic significance, P value less than or equal to 0.05 was considered.

RESULTS

Thirty-three professionals were graduated as certified teachers and 17 of them were not. The average time of teaching was 10 years, varying from 0.1 to 24. Thirty-one of the 50 teachers had 5 years of experience or more while 19 teachers had less than 5 years experience.

Regarding urinary frequency; 33 answered that the urinary daily frequency would be around 4 and 7 times, 2 thought that the normal frequency would be less than 4 times per day and 15 considered it normal to urinate (they chose the questionnaire’s option four) more than 7 times per day. There was no difference between certified and non-certified teachers nor among the professionals with 5 years or less experience ($P = 0.37$ and 0.17 , respectively).

Teachers were asked about the following questions (Table-1) and the results are shown below.

Question: A child frequently asks to urinate 4(four) or more times during a school period (from 4 to 5 hours) - From all the teachers interviewed, 30% considered this normal and 33% believed that this behavior could represent a urinary problem. Fifty-five percent of the certified teachers believed that this could represent a urinary problem as opposed to 17.64% of the non-certified teachers ($p = 0.03$). This rate was 36.8% and 35.4% for the group of professionals with more or less than 5 years of experience, respectively ($p = 0.9$).

Question: A child rarely asks to urinate during a school period (from 4 to 5 hours) - From the all the groups, 20% considered this as a normal event and 18% as a urinary problem. From the groups of pedagogues and non pedagogues and the professionals with more or less than 5 years of experience, 30.3% and 11.8% ($p = 0.18$) and 26.3% and 9.8% ($p = 0.26$), respectively answered that these changes could happen due to urinary problems.

Questions:

- 1) Are you a certified elementary school teacher (are you a pedagogue)?
Yes () No ()
- 2) Do you have more or less than 5 years professional experience working as an elementary school teacher?
More than 5 years () Less than 5 years ()
- 3) In your opinion how many times is normal for a child to ask to urinate during the course of a day (24-hour period)?
() 3 times or less
() 4 to 5 times
() 6 to 7 times
() more than 7 times
- 4) A child frequently asks to urinate 4 (four) or more times during a school period (from 4 to 5 hours). In your opinion this is:
() Normal
() The child wants to play
() This behavior represents a urinary problem
() None of the above
- 5) A child rarely asks to urinate during a school period (from 4 to 5 hours). In your opinion this is:
() Normal
() A behavioral / emotional problem
() A urinary problem
() None of the above
- 6) A child has acquired urinary control (potty training), but needs to run to the bathroom to avoid wetting his (her) pants. Sometimes he (she) has already wet his (her) pants. In your opinion this is:
() Normal
() Laziness
() A urinary problem
() None of the above
- 7) Up to what age do you consider it normal for a child to urinate in his or her pants?
_____ years
- 8) Up to what age do you consider it normal for a child to urinate in bed (night enuresis)? _____ years

Figure 1 – Questionnaire applied.

Table 1 – Distribution of teachers' answers for each question.

Questions	N	%
A child frequently asks to urinate 4 (four) or more times during a school period (from 4 to 5 hours). In your opinion this is:	15	30
Normal	7	14
The child wants to play	19	38
This behavior represents a urinary problem	9	18
None of the above		
A child rarely asks to urinate during a school period (from 4 to 5 hours). In your opinion this is:	10	20
Normal	15	30
A behavioral / emotional problem	9	18
A urinary problem	16	32
None of the above		
A child has acquired urinary control (potty training), but needs to run to the bathroom to avoid wetting his (her) pants. Sometimes he (she) has already wet his (her) pants. In your opinion this is:		
Normal	6	12
Laziness	22	44
A urinary problem	12	24
None of the above	10	20

Question: A child has acquired urinary control (potty training), but needs to run to the bathroom to avoid wetting his (her) pants. Sometimes he (she) has already wet his (her) pants - From the group of teachers, 12% considered it normal and 24% considered a urinary problem. It was found that 30.3% and 11.7% ($p = 0.18$) of the group of pedagogues and non pedagogues and 26.3% and 22.5% ($p = 0.38$) of the group of professionals with more or less than 5 years of experience, respectively, considered that this would be an alteration in the urinary tract.

The results for the other questions asked are shown below.

Question: Up to what age do you consider it normal for a child to urinate in his or her pants? - The age varied from 2 to 15, with 3.9 years old as an average. Ninety per cent believed that children stop losing urine up to 5 years old. There was no statistical dif-

ference between the group of pedagogue and non-pedagogue and also regarding the group of professionals with more or less than 5 years of experience, believed that children stop losing urine up to 5 years old. There was no statistic difference among the pedagogues and non-pedagogues nor in terms of amount the time working as a professional ($p = 0.17$ and 0.43 , respectively).

Question: Up to what age do you consider it normal for a child to urinate in bed (night enuresis)? - In this question, 88% considered that the child could have nocturnal enuresis up to 7 years old. The average age was 4.3 years old varying from 2 to 10 years old. There was a statistical difference between the average age suggested by the pedagogues and non-pedagogues, but not when compared with the time of professional experience ($p = 0.02$ and 0.38 , respectively).

COMMENTS

Our data shows that the teachers have a significant lack of knowledge about the subject of LUTD, despite its relevance and frequency. Hellstrom et al. emphasized that around 6% of the girls and 3.8% of the boys had daily urinary incontinence at 7 years old (7). Simple urinary instruction measures could revert those symptoms and that despite the high rate of spontaneous remission, some children have urinary infection and high post-urinary residue, vesicoureteral reflux and even detrusor hypocontractility where it is necessary to use clean intermittent catheterization (3-5).

There was no difference between time of professional experience and the quality of the responses. There was a statistically significant difference in two questions regarding the answers of the pedagogues and non-pedagogues, demonstrating that the type of professional background can have some impact in the problem recognition. For example, when asked about the children who urinate four times or more during the class period, there was a statistically significant difference among pedagogues and non-pedagogues. Even so, the rate of pedagogues that considered it as a urinary problem was only 56%. Frequency in children deserves some clinical urological evaluation since not only does this represent the possibility of disturbances of an emotional order, but it also could be the clinical manifestation of a urological disease (8). Even so, only 24% of the teachers believed that clinical signs of urge incontinence represent urological abnormalities while 44% pointed out that the child loses urine simply because she or he does not feel like going to the toilet. Urinary incontinence and manifestation of bladder over activity makes the child feel extremely embarrassed. The interpretation of these facts as a laziness or untidiness often leads to punishing or singling out the children for their lack of willpower.

Another remarkable consideration is that 10% of the teachers considered it normal for a child to urinate in his or her underwear after the age of 5, an age on which a child is already expected to have fully developed urinary control. Also when asked what they thought of a child who does not frequently ask to go to the toilet in order to urinate in a period of 4-5 hours,

33% of the teachers considered it normal. Prudent urinary health prescribes that children must be stimulated to avoid spending such a long period of time without urinating. Bladder over distention may cause bladder over activity, urinary infection and histological alterations such as collagen deposition (9,10).

In Cooper's studies it has been observed that only 18% of public elementary school teachers in the USA have received some form of information about abnormalities on the functioning of the urinary bladder or bowel (11). This demonstrates that even in developed countries, there is too little information about this theme. These authors also suggest a training program to the teachers about elimination disturbances.

CONCLUSION

Our data shows that teachers working with children at ages between 4-7 years, in the private educational system, have too little information about clinical occurrences of the LUTD. An educational process lead by professional educators needs to be implemented in order that children receive proper orientation about LUTD, while at school.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors are to be congratulated on exploring an important, but frequently ignored area. As noted in their manuscript, children spend a significant amount of their waking hours in school. With an increase in the number of children attending pre-school it is important to evaluate the level of knowledge pre-school teachers hold regarding a child's basic biological functions. In this study, the authors demonstrate inconsistent answers among a group of 50 pre-school teachers. For the most part this did not seem to relate to the teachers' previous training, which likely reflects a deficit of training regarding this topic in the curriculum for future teachers.

We previously reported similar findings in public elementary school teachers in the United States. Since many toileting habits are established during pre-school, the findings in the present study are potentially even more relevant. The authors of the present study

also propose a training program regarding pediatric toileting for professional educators. Since a significant number of children with urinary incontinence or recurrent urinary tract infections benefit from practicing improved bladder habits, teaching these habits during pre-school could have significant public health benefits. Therefore, further studies to evaluate the efficacy of teaching future educators what constitutes normal and abnormal pediatric bowel and bladder habits seem warranted.

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Steerable Antegrade Stenting: A New Trick of the Trade

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ABSTRACT

Introduction: Whereas a retrograde attempt to insert an indwelling stent is performed in lithotomy position, usually renal access is gained in a prone position. To overcome the time loss of patient repositioning, a renal puncture can be performed in a modified lithotomy position with torqued truncus and slightly elevated flank. There is a two-fold advantage of this position: transurethral and transrenal access can be obtained using a combined approach. In the present study, this simple technique is used to position a floppy guide wire through a modified needle directly through the renal pelvis into the ureter.

Materials and Methods: The kidney is punctured in the modified lithotomy position under sonographic control using an initial three-part puncture needle. A floppy tip guide-wire is inserted into the collecting system via the needle after retrieving the stylet. The retracted needle is bent at the tip while the guide-wire is secured in the needle and the collecting system. The use of the floppy tip guide-wire helps to insert the curved needle back into the kidney pelvis, which becomes the precise guidance for the now steerable wire. The desired steerable stent is positioned under radiographic control in a retrograde fashion over the endoscopically harbored tip of the guide-wire. Two patient cohorts (newly described method and conventional method) were compared.

Results: The presented steering procedure saves 16.5 mean minutes compared to the conventional antegrade stenting and 79.5 Euros compared to the control group.

Conclusion: The described combined antegrade-retrograde stent placement through a bent three-part puncture needle results in both clinical superiority (OR time, success rate) and financial benefits.

Key words: ureter; stent; nephrostomy; kidney

Int Braz J Urol. 2007; 33: 389-394

INTRODUCTION

Retrograde ureteral stenting is a daily routine in endourologic procedures. Large prostatic glands, transitional cell carcinoma of the bladder, impacted ureteral stones, kidney transplants and orthotopic as well as incontinent diversions belong to those challenging cases, where a successful retrograde stenting is not always possible; especially if the ureteral ori-

fice is involved in a pathological process, antegrade access is sometimes preferable.

The technique of antegrade stent placement has been in the armamentarium of endourologists for decades. Three critical steps are necessary to be successful: 1) access of the collecting system, 2) introduction of a guide-wire into the ureter and 3) passage of the ureteral segment that could not be passed in a retrograde fashion.

Whereas a retrograde attempt to insert an indwelling stent is normally done in the lithotomy position, usually renal access is gained in the prone position. To overcome the time loss of patient repositioning, the renal puncture can be performed in a modified lithotomy position with a slightly elevated flank. A major advantage of this position is the combined approach transurethral and transrenal access (1).

This position, in particular, is the easiest way to gain a safe access below the 12th rib, in the lower or middle calyx, resulting in an unfavorable angle to the pyeloureteral junction. Many different techniques are reported to solve this issue, such as j-shaped ureteral catheters, “cobra” or “hook”-angiographic catheters, bent wires, peel-away sheaths, assistance of rigid or flexible nephroscopes and dozens of other more or less useful and expensive tools (2).

This study demonstrates a simple technique by using only the puncture needle and a floppy guide-wire to pass the guide-wire into the pyeloureteral junction.

MATERIALS AND METHODS

Patients Recruitment

A retrospective chart review was performed on 14 consecutive patients receiving an indwelling ureteral stent using the presented technique, which were compared to the following 15 consecutive patients, who received the stent in the conventional technique with the additional nephrostomy tube. Mean age in this group was 65.5 years (control group 67.5 years). Four patients had acute urinary retention (control = 6) and 10 had chronic hydronephrosis (control = 9), caused by malignancy in 6 patients (control = 6) vs. benign disease in 4 cases (control = 3).

OR time (puncture to successful introduction of the guide-wire in the ureter), success rate of the intubation of the proximal ureter, blood transfusions as well as complications in both groups were recorded and analyzed. Costs for each procedure were recorded and comparatively evaluated.

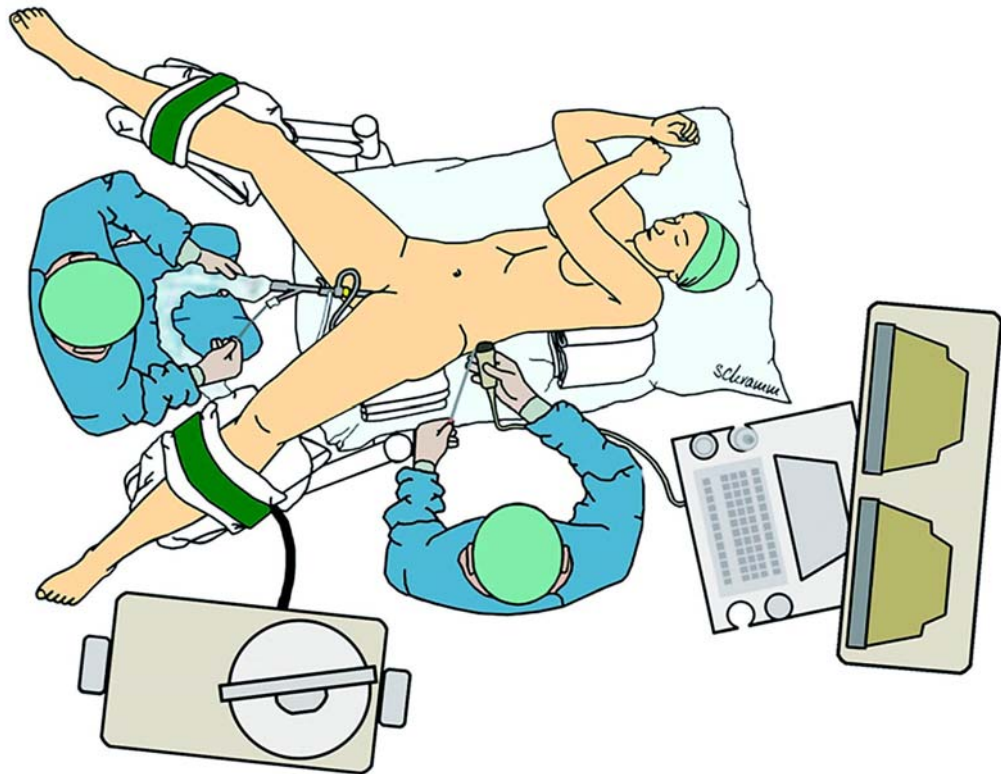


Figure 1 – Patient position on the table with both transurethral and percutaneous access.



Figure 2 – Original (left) and bent (right) puncture needle both with stylet.

Surgical Technique

The patient is paced in a lithotomy position and the patient is slightly elevated at the site of the potential kidney puncture (Figure-1). A retrograde evaluation of the ureter is done. After deciding to use an antegrade or combined approach to place a ureteral stent, the kidney is punctured under sonographic control with a three-part puncture needle (Bard GMBH, Karlsruhe, Germany) 1.3 mm in diameter with MS-cut, thus facilitating visibility in the ultrasound. Urine is collected for culture before radiopaque contrast medium is injected into the renal cavity. The renal pelvis, pyeloureteral junction and calyces are identified; a sensor guide-wire (Boston Scientific, Nanterre Cedex, France) with a hydrophilic floppy tip is inserted into the collecting system via the needle after retrieving the stylet.

The retracted needle is bent at the tip at about 3-4 cm length in a smooth curvature (Figure-2) while the guide-wire is secured in the needle as well as in the collecting system. The use of the floppy wire results in the possibility of inserting the curved needle once again into the kidney as the needle acts as a precise guidance for the now steerable floppy guide-wire (Figure-3).

The wire is guided through the ureter into the bladder and preferably harbored with an extracting forceps. The end of the guide-wire is secured with a clamp at the skin level and the desired steerable stent is positioned under radiographic control in a retrograde fashion over the harbored tip of the guide-wire. Finally, the wire is extracted through the puncture and the stent is released in its correct position.

In the standard technique, a peel-away sheath is inserted after placing the guide-wire in the calyceal system and either a “billiard-like” procedure with the floppy wire or an attempt with angiographic catheters is used to intubate the ureter. After harboring the guide-wire through the meatus, the stent is placed in the same way as mentioned above and a 9 Fr. Pigtail nephrostomy is placed in the renal pelvis for at least one day.

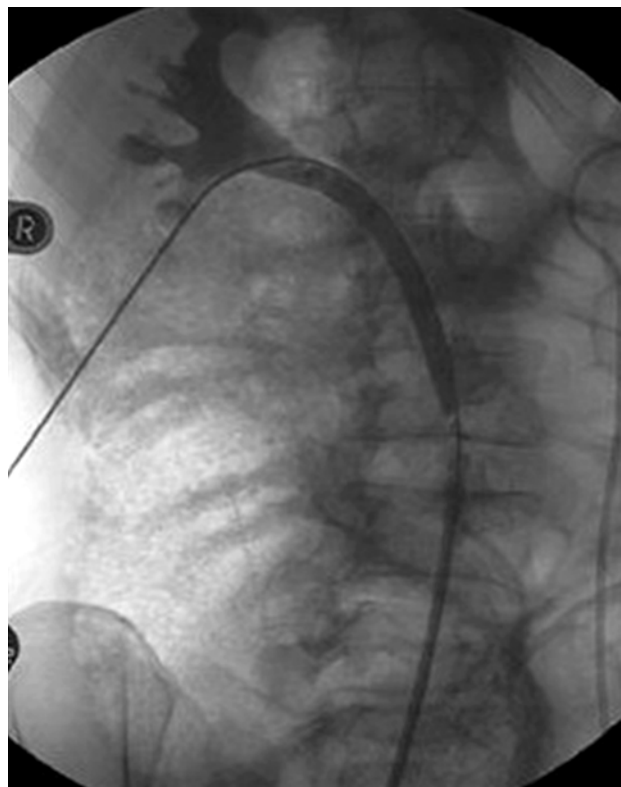


Figure 3 – Placing the floppy guide-wire into the ureter with bent needle through the lower calyx in modified lithotomy position.

A Foley catheter is placed in the bladder and a perioperative prophylaxis is administered with a twice-daily oral application of 250 mg ciprofloxacin.

RESULTS

With the new procedure, a puncture of the lower calyx was achieved in 7 cases and the middle calyx or renal pelvis in 7 patients. Direct access into the ureter was gained in 1 case. In one case, primary access was not possible due to an infundibulo-ureteral angle of less than 20° (on antegrade pyelography). After dilatation of the access tract, a metal 15 F nephroscope sheath was inserted and intubation was facilitated by flexible nephroscopy. In 10 of the 14 cases, the placement of the wire into the bladder and therefore combined stenting was possible. After successful stenting, no nephrostomy tube was required after removal of the guide-wire. OR time (puncture to intubation of the proximal ureter) was 9.5 minutes.

In the control group, the lower calyx was punctured in 7 cases and the middle calyx or renal pelvis in 8 cases. Accidental direct access was gained one time, whereas dilatation of the nephrostomy tract, insertion of a peel-away sheath and guidance with angiographic catheters was successful in 9 and aided by flexible ureteroscope (Flex-x, Storz, Tuttlingen, Germany) in 3 cases. OR time (puncture to intubation of the proximal ureter) was performed in an average in 26 minutes.

The nephrostomy tube was extracted the first postoperative day in all cases in the control group.

Mean additive costs in the control cohort were 79.5 euros. The higher costs were caused by the use of nephrostomy tube, peel-away sheath, and angiographic catheter.

Mechanical problems of the needles were not observed after bending (e.g. broken needles, cut wires, etc).

Fever did not occur in either the study nor in the control group; no major complications were reported and no blood transfusions were necessary.

COMMENTS

Using the new torqued lithotomy position facilitates fast access in all patients including the control

group. This technique requires an ultrasound guided puncture because of the inability to sufficiently contrast the collecting system in a retrograde fashion. Another positioning with prone split leg and flank roll position is reported by Grasso et al. (3). The advantages of the technique described here, compared to the approach of Grasso, are easier positioning of the patient and facilitated access with semi-rigid instruments, whereas only radiographic controlled puncture is more difficult.

The use of floppy tip guide-wires avoided accidental puncture of the contra-lateral wall of the renal pelvis, which resulted in extravasation and therefore bad vision after application of radiopaque contrast medium.

Surprisingly, about 7% (n = 1) of initial guide-wire placements resulted in direct intubation of the ureter in both patient groups; in all other patients the presented steering procedure resulted in major time saving (16.5 minutes).

In comparison with another published approach by a radiologist with a success rate of 88% using pre selected patients, 57% were excluded and a two stage approach was performed later (4). The presented approach, which has been performed many times, provides the urologist in even more sophisticated cases (e.g. tumor, stricture etc.) the potential to perform a one-stage procedure with the possibility of frequent immediate transurethral intervention.

The use of a combined approach is initially presented by Wirth et al. (5). The dilatation of the access tract using the bent needle as a steering guide was less traumatic. This results in a safe approach to retract the guide-wire without the need of a nephrostomy or sealing of the tract by gelatine matrix haemostatic sealant (6). The average cost saving of the steerable approach is 79.5 Euro.

Additional placement of an indwelling stent in the same session, in case of failed retrograde attempt and without time loss caused by patient repositioning, further reduces hospital and especially OR time related costs (2).

CONCLUSION

The described combined antegrade-retrograde stent placement by using a bent initial three-

part puncture needle instead of the common equipment and technique of antegrade stenting results a better clinical outcome (OR time, success rate) and financial benefit.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

This paper introduces a technique of antegrade double-J ureteral stent placement in a single session, for cases in which retrograde access is not possible. The proposed simultaneous cystoscopic and percutaneous renal access method affords greater safety compared to antegrade fluoroscopic guidance alone.

The real benefit of positioning the patient in this manner is that percutaneous access can be obtained if an initial attempt at retrograde ureteral stenting fails. Traditionally, the patient would have to be repositioned prone, or awakened for referral to the interventional radiologists for percutaneous nephrostomy tube placement.

One limitation of this technique is that some urologists do not routinely perform sonographically guided renal puncture. Another point of caution is that in the patient with urosepsis from obstructive

uropathy, initial percutaneous nephrostomy drainage is warranted, rather than trying to place a ureteral stent across the obstructed segment in a single setting.

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EDITORIAL COMMENT

The combination of retrograde and antegrade procedures for ureteral stenting, especially in difficult cases, such as patients with ureteral strictures and urologic lesions, where conventional stenting has failed, has been previously described in the literature (1,2). The “rendezvous technique”, as so elegantly described, is a well-established technique in order to increase the success rates, even in antegrade stenting procedures (3). The loss of time in repositioning the patient from prone to lithotomy position is sometimes an issue, particularly in countries where the concept of reducing operative time is of great importance. The present study, which is evaluating the potential of a renal access in a slightly modified lithotomy position, combining transurethral and transrenal approach at the same time, is worthy of noticing.

The authors are presenting a punctured technique in a one-stage procedure that seems feasible and convenient to perform, reducing the time of the process, with the possible accumulation of a financial benefit. Nevertheless, the exclusive requirement of ultrasound guidance and the small number of cases, whereas patient selection criteria were not unequivocally clarified, necessitate the further evaluation of this method in the field of ureteral stenting.

Antegrade stent placement is a well-established procedure, which can manage ureteral strictures and obstruction with great success (4,5). This newly described technique, that facilitates the transurethral and transrenal approach at the same time,

can only offer another valuable implement to the arsenal of the endourologists and we believe that in time will prove its merit in selected cases.

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Mini-Invasive Collagen Sling in the Treatment of Urinary Incontinence Due To Sphincteric Incompetence

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ABSTRACT

Objective: To assess the technical feasibility of mini-invasive sling procedure and present preliminary results in the treatment of urinary incontinence due to sphincteric insufficiency.

Materials and Methods: Thirteen patients (6 males, 7 females, 8 with myelomeningocele, 1 with tethered spinal cord, 3 with bladder exstrophy, 1 with epispadias) underwent sling procedure with porcine dermis acellular collagen matrix (Pelvilace™, Bard medical, UK). The median age was 15.5 (range 8.9-27.5) years. A suprapubic catheter was inserted for the measurement of leak point pressure during the operation. In females vaginal and in males perineal incision was used for sling insertion. The sling was introduced under cystoscopic control. The sling was not fixed with sutures. The outcomes were reviewed at 1, 6 and 12 month after the operation.

Results: The median leak point pressure increased from 21.5 (range 5-25) cm H₂O to 85 (range 70-100) cm H₂O. At 1 month 8 and at 6 months 3 out of 13 patients were dry. At 12 months, none out of 11 patients was completely dry. However, at 12 months some improvement in incontinence was detected in 9 out of 11 patients. Two patients had primary failures. One patient got sling erosion to urethra after a tightening attempt. In one patient detrusor overactivity increased after the sling procedure.

Conclusions: Pelvilace™ sling is safe and easy to introduce in both males and females if pelvic floor anatomy is normal. Although immediate results were promising in neuropathic incontinence, the results seem to deteriorate to unacceptable low level already during the first year. In exstrophy patients the results are generally poor.

Key words: urinary incontinence; children; neuropathic bladder; suburethral sling

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INTRODUCTION

Mini-invasive tension-free vaginal tapes (TVT) have become popular in the treatment of female stress urinary incontinence (1). Unlike healthy females, the children with stress incontinence usually do not have functional sphincter mechanism and, therefore, the treatment is very challenging. The typi-

cal cases of sphincteric insufficiency in children are neuropathic problems such as myelomeningocele (MMC) and congenital anomalies such as bladder exstrophy (2). Fascial slings with tension have been used in these conditions with success rates of around 70% (2,3). Mini-invasive TVT techniques have not gained popularity in pediatric urology. In children with non-functioning sphincter mechanism, some tension

is needed in the sling. With synthetic materials the risk of erosion probably increases with tension. In the present study we examined the feasibility of mini-invasive technique with biological material to manage sphincteric incompetence in children and young adults. Short term outcomes as well as the technique of the sling procedure are described in patients who had neuropathic or congenital causes of incontinence.

MATERIALS AND METHODS

Thirteen patients with refractory incontinence due to sphincteric incompetence underwent porcine dermis acellular collagen matrix sling (Pelvilace™, Bard medical, UK) insertion from August 2004 to June 2006. The patients were considered to have a low-pressure bladder although anticholinergic medication was started in 8 of them preoperatively. The study was prospective and observational. The median age of the patients was 15.5 (range 8.9-27.5) years. There were 6 males (3 with MMC and 3 with bladder exstrophy) and 7 females (5 with MMC, 1 with tethered spinal cord, and 1 with epispadias). Ten had previously had unsuccessful periurethral injections with dextranomer/hyaluronic acid copolymer (Deflux R). All the patients used clean intermittent catheterizations (CIC). Five patients had undergone bladder augmentation because of urinary incontinence; one of those had augmentation concomitantly with the sling procedure.

Suprapubic bladder catheter was inserted for the measurement of leak point pressures. Pressure was generated to full bladder during general anesthesia with manual compression on the lower abdomen. There was no muscle relaxation at the time of leak point measurements. In females a vaginal and in males a perineal incision was used. The proper location of the sling was determined with the aid of cystoscopy. Urethral wall was approached in the area of mid urethra in females and distal to the colliculus seminalis in males. Insertion needles were introduced on both sides of urethra and brought out above pubic symphysis. After cystoscopic examination the sling was pulled in its place with insertion needles. The sling was tightened so that the leak point pressure increased to a minimum of 70 cm H₂O. One male

with bladder exstrophy required two slings before the leak point pressure increased. The sling was cut at the skin level above the symphysis without suture fixation. In males the perineal incision was closed in two layers and in girls the vaginal incision was closed in one layer using absorbable sutures. CIC was started two days after operation and the suprapubic catheter was removed if no postoperative problems were noted.

The functional outcome in terms of incidence of wet pads was analyzed at 1 and 6 month in all 13 and at 12 months postoperatively in 11 patients. The patients were asked to change dry pads after every catheterization during the last two weeks. Because all patients made catheterization five times a day, 70 pads were used during two weeks. In addition to the number of wet pads the patients were asked to register if the pads were really wet (major leaks) or damp (minor leaks).

Before the operation all of the patients, except one with total incontinence, had undergone a urodynamic study. Six months after the operation a control study was available in nine patients. Abdominal and bladder pressures were measured with 4 Ch feeding tubes. Subtracted detrusor pressure was measured simultaneously using computerized equipment (Dantec Menuet, Denmark). Bladder filling was performed with a separate 6 Ch feeding tube with the rate of 10 mL/min. Bladder capacity and maximal pressures during the filling were recorded. Urethral pressure profile was also measured with an empty bladder and maximal closing pressure was recorded. Pre- and postoperative urodynamic results were compared with a paired t-test.

RESULTS

During the insertion of the sling the median leak point pressure increased from 21.5 (range 5-25) cm H₂O to 85 (range 70-100) cm H₂O. Two males had primary failures. Sling erosion to urethra was detected one month postoperatively in one patient with bladder exstrophy following an attempt to tighten and fix the sling. Cystoscopic forceps ablation of the sling material was attempted unsuccessfully. However, in

control cystoscopy three months later, no sling material could be detected. In one patient the insertion needle perforated the bladder. The needle position was corrected before the insertion of the sling and there were no adverse late effects. Transurethral catheterization was started after two days in all except three patients. One had a continent stoma and another had undergone concomitant bladder augmentation. One male with exstrophy was not able to do CIC during the first week. One boy with MMC experienced some difficulties in CIC during the first months. During the first month another patient had slight discharge from abdominal incision that ceased with antibiotic treatment. The male patient with simultaneous augmentation and sling procedure had no immediate postoperative problems.

Eight out of 13 patients had achieved total continence one month postoperatively and one had minor leaks (Table-1). One male with bladder exstrophy was totally incontinent as well as another patient with MMC. Another male with bladder exstrophy had polyuria due to diabetes mellitus and he was leaking between most catheterizations. However, he was no more totally incontinent, and remained dry 1-2 hour after CIC. At six months 3 out of 13 evaluated patients were completely dry and six had minor leaks when bladder overfilled. Four had significant amounts of wetting. At 12 months all 11 patients that could be evaluated had incontinence episodes. 5 of them were wet between every CIC. However, 7 out of 11 had mainly minor leaks when the bladder was overfilled. The degree of incontinence in 9 out of the 11 patients was lesser compared to the preoperative situation after one year follow-up.

In urodynamic studies the median pre- and postoperative bladder capacities were 339 (range 237-663) mL and 507 (range 330-824) mL respectively ($p = 0.0186$). The patient who had the simultaneous augmentation with the sling procedure had 81 cm H₂O maximal detrusor pressure preoperatively. In the other patients maximal preoperative detrusor pressures were low 14 (range 3-38) cm H₂O. There was a non significant increase in detrusor pressures postoperatively to 21 (range 2-97) cm H₂O ($p = 0.3249$). However, in one patient the increase in maximal detrusor pressure was significant (from 18

cm H₂O preoperatively to 97 cm H₂O after the sling procedure). The maximal closing pressures in urethral pressure profile increased significantly from the median preoperative values 22 (range 5-42) cm H₂O to 38 (range 25-63) cm H₂O ($p = 0.0037$). In 8 patients anticholinergic medication was started before the sling procedure because of slight detrusor overactivity at the end of filling. In the two patients Botulinum toxin type A (Botox®) injection therapy has been attempted postoperatively. The primary results were promising in both of them. However, the effect subsided after two months in one but the other has had a good effect more than one year.

COMMENTS

In women sling procedures for urinary incontinence have been introduced about 100 years ago (1). Originally autogenic fascia was used with good success rates and good durability (1). Synthetic materials have been used later to avoid major abdominal incision, but the erosion rates have been quite high ranging from 2 to 23% (4). Mini-invasive tension free sling techniques have been used in healthy females with good primary success rates. Continence rate after TVT has been 85% with synthetic material and 89% with biological material (5). The long-term success with synthetic sling materials has also turned out to be good (6). The complication rates following TVT are low in healthy females (7). Sling suspension with commercially available products has also been successfully used in males after radical prostatectomy (8).

In children insertion of allogenic fascial slings have resulted in urinary continence in 25-78% patients with a small risk of urethral erosion (2,3,9,10).

Commercial products have been also used in pediatric patients. In a series of 20 children insertion of acellular small intestine submucosal collagen sling in an open operation has been reported to yield complete dryness in 70% of patients after a mean of 13 months follow-up (11). However, there are no reports of mini-invasive sling techniques in pediatric patients. The reason may be that there is a well-documented erosion risk of foreign material to the urethra especially when tension is applied to the sling. In addition,

Table 1 – Patients with Pelviline™ sling procedure and the number of wet pads during last 2 weeks at preoperative period as well as at 1, 6 and 12 months postoperatively. All the patients have clean intermittent catheterizations 5 times a day and used 70 pads during 2 weeks.

Number of Wet Pads / 70 Pads						
	Age (y)	Preop	1 month	6 months	12 months	Bladder Treatment
<hr/>						
Male						
MMC	8.9	70	0	0	70*	simultaneous augmentation
MMC	9.3	70	0	70*	26*	tolterodine, Botox®
MMC	15.1**	70	70	70		oxybutynin
Exstrophy	10.1**	70	70	70	70	
Exstrophy	13.4	19*	0	3*		previous augmentation, oxybutynin
Exstrophy	15.5	70	42*	42*	70	previous augmentation
Female						
MMC	12	70	0	28*	70*	oxybutynin
MMC	15.8	70	2	2*	70*	oxybutynin
MMC	26.2	70	0	0	42*	previous augmentation
MMC	27.5	28	0	7	3	oxybutynin, Botox®
MMC	28.9	70	0	40*	35*	previous augmentation
Tethered cord	18.5	30	14	16	16	oxybutynin
Epispadias	15.5	70	0	0	35*	oxybutynin

MMC = myelomeningocele; * = minor leaking, especially at full bladder; ** = total failure.

the instrumentation of mini-invasive techniques is designed for adult females. In the present series we started to apply mini-invasive technique in adult females, but gradually have lowered the patient age and also began to use the technique in male patients. In the present study the sling was originally applied with a slight tension without fixation sutures. In these patients no erosion was detected. In one patient with primary failure the sling was tightened and fixed to fascia after one week. This, however, resulted in sling erosion to urethra. Tension was required because of scar tissue from previous operations.

The primary early result was good in 9 out of 13 patients (69%). Eight patients were completely dry and one had minor incontinence episodes only if the bladder got overfilled. During follow-up more patients started to leak especially if the bladder got overfilled. At 6 months 5 out of 13 patients (38%) were still considered to have a good result. After 12 months follow-up all evaluated 11 patients had some degree of incontinence. However, 9 out of 11 pa-

tients reported that their incontinence was of lesser degree than before the operation. In urodynamic studies there was a significant increase in bladder volumes and maximal urethral closing pressures postoperatively.

In one patient with increasing postoperative leaks a significant increase in detrusor overactivity could be seen in urodynamic studies. Botulinum toxin-A treatment in addition to anticholinergic medication has been attempted in this patient as well as in other patient with lesser degree of overactivity. The first patient has had benefit over a year, but the second patient got a continence for only two months. The increase in bladder pressures is a well-recorded phenomenon that is often detected after bladder outlet surgery (12). It has also been reported previously that the sling procedure results are better in augmented patients (10). Urinary leaking may protect upper urinary tract if detrusor overactivity increases postoperatively. In the present patients none developed upper tract dilatation. Another possible reason for in-

crease in leaking patients during the follow-up is that the sling material may not be durable. In the patient with sling erosion to urethra, the remnants of the sling inside the urethra had disappeared completely 3 months postoperatively. The increase of incontinence rate after 6 months follow-up also suggests that the durability of the sling material is poor. The durability of the cross-linked porcine dermis grafts has also been questioned previously (13). The non-fixation technique of the sling used in this study may also have an adverse effect on the results. On the other hand it is very unlikely that the sling might loosen after first few weeks.

The operation itself was easily performed in both boys and girls. The only operative difficulties occurred in the two boys who had been operated previously for bladder exstrophy. Both had wide pubic symphysis and scar tissue in the operative area. One of these two patients required excess tension in the sling to achieve sufficient increase in the outflow resistance. However, this resulted in sling erosion. The other required two slings simultaneously to achieve high enough leak point pressure. In one female the insertion needle perforated the bladder. After correction of the position of the insertion needle the operation was completed with no adverse postoperative effects. In our series only one patient had a continent stoma. The others were performing CIC transurethrally. However, all the patients were warned preoperatively that a continent stoma might be required afterwards. None of the patients required continent urinary diversion later on, although one male had temporary problems with CIC during the first months postoperatively.

CONCLUSIONS

Pelvilace™ sling is easy to insert in both boys and girls with stress urinary incontinence and with normal pelvic anatomy. Although the primary results were encouraging in the neuropathic patients the outcome appears to worsen already between 1 and 6 months postoperatively. This may be attributed to poor durability of the sling material. At one-year follow-up the results appear to be unacceptably poor despite some degree of subjective improvement.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Currently, there is no consensus regarding which treatment is best adapted for urinary incontinence of neurogenic bladders. Therefore, it remains challenging to treat this pathology both medically and surgically. The risk of rapid degradation of the upper urinary tract requires close monitoring of these patients in order to offer possible treatment options. Degradation of renal function and incontinence can be greatly improved by clean intermittent self catheterization and pharmacological therapy. Nevertheless, many patients experience persistent leakage. The mechanism of incontinence can result either from a low bladder capacity or low compliance, non inhibited detrusor activity or from sphincteric deficiency. Numerous procedures have been proposed to increase bladder outlet resistance particularly in children with neurogenic bladder dysfunction. The therapeutic choices aim to achieve an equilibrium between urethral and bladder strength and protection of the upper urinary tract as well as urethral resistance and bladder compliance.

In cases of urinary incontinence due to neurogenic bladders, the therapeutic choices are based on the analysis of several parameters. The first is the clinical picture, including the severity of incontinence, dysuria and urgency. The second parameter is urodynamics for patient assessment, with data on bladder compliance, detrusor hyperactivity, dyssynergia, and urethral pressure. Moreover, in Europe the leak point pressure is often used to evaluate female urge incontinence, however, it is not a standard procedure in children for urodynamic evaluation. Another parameter is the patient's functional independence, including the aptitude for voiding and catheterization. The final parameter is the degree of understanding and acceptance of patient re-education and monitoring, as well as the daily routine environment of the patient.

Several techniques are currently available to increase urethral resistance in children with neurogenic bladder. Injections of bulking agents are one technique; however, this approach is not recommended for

treating sphincteric insufficiency in the myelodysplastic pediatric population (1-3). Urethral lengthening, i.e. Kropp's procedure provides good but inconstant results in terms of continence, however catheterization can be difficult particularly in male patients (4,5). Moreover, modifications described by Pippi Salle in order to improve catheterization problems have resulted in reduced continence (6). Artificial sphincters can be complicated by an urethral erosion when associated catheterization is required for voiding as in the case of many patients with spinal dysraphism (7,8). The outcome complication of erosion and problems with catheterization suggest that this approach is not recommended when the urethra is catheterized.

Furthermore, rectus fascial slings have been reported to provide continence in 50% to 93% of cases (9-12). In contrast, it is known that myelodysplastic children frequently have a poor nutritional status or have undergone prior abdominal procedures responsible for deficient and unusable fascia.

Taskinen et al. performed TVT minimally invasive procedure with porcine dermis acellular collagen matrix (Pelvilace™, Bard Medical). Several authors have reported slings using collagen-based biomaterials, which have shown efficacy for urinary stress incontinence. However, there is a wide variability in terms of collagen content consistency and subsequently therefore in clinical results (13-15). At our institution, in treating female urinary incontinence, the transobturator tape (TOT) procedure is preferred as it provides less postoperative retention rate and fewer per and postoperative complications (16). The absence of need to retropubic space puncture significantly limits the risk of severe complications such as those reported with TVT, bowel and iliac vessel, injuries. Therefore, the large veins of the Santorini's plexus are avoided. Minimally invasive TVT procedure is in fact no longer used in our department.

Moreover, the above mentioned authors used the leak point pressure (LLP) possibly as a predictor of good results, as it has been shown that LLP is helpful in the diagnosis of urinary incontinence. Nevertheless, it appears to be of minimal benefit in predicting the outcome of the mini-invasive TVT procedure (17).

In cases of urinary incontinence due to neurogenic bladder, we recently reported our results on the bladder wall wraparound procedure in association with a bladder augmentation. This procedure provides good results for continence in association with a bladder augmentation particularly in women (18).

In conclusion, the main problem in comparing studies reported in the literature remains the definition of continence and the definition of success rates. In fact, many authors have included "improved" cases as successes. Urinary incontinence due to neurogenic bladder remains challenging to treat patients medically and surgically. However, this must be performed in specialized centers.

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EDITORIAL COMMENT

The study by Taskinen et al. analyzes the technical feasibility and outcome of the tension free sling (porcine dermis acellular collagen) for the treatment of urinary incontinence in 13 patients with neuropathic bladder or bladder exstrophy. The authors concluded that the procedure is safe and easy to perform. However, the results in terms of continence improvement after one year of follow-up were poor, despite being promising in the first months. According to the authors, these poor continence rate results may be attributed to poor durability of the sling material. However, even at 6 months of follow-up only 38% of the patients were dry. Different studies have

demonstrated the efficacy of TVT or TOT in female stress incontinence with a long term success rate ranging between 70-80%. These results are significantly better when stress rather than mixed incontinence was the preoperative situation and when the incontinence grade was mild or moderate. Therefore, in my opinion, some of the reasons for the unsatisfactory continence rate results in this study were that urinary incontinence in neuropathic bladders or exstrophy patients is more complex than simple stress incontinence because, most of the time, incontinence has mixed causes. Moreover, the cause of incontinence in these patients is more functional than

anatomical and the incontinence is severe in many cases. We could speculate that these poor long-term continence results could be improved by selecting these patients in a more appropriate way. Most exstrophy patients have had prior bladder neck surgery with scar tissue around it and this increases the risk of sling erosion and worsens the continence results after a sling procedure. Therefore, in these patients the sling is not a good option to improve continence. One could improve the continence results with this procedure in neuropathic patients only in those with a mild or moderate incontinence who have a bladder with good com-

pliance and low pressure. However, unfortunately this kind of neuropathic patient is not frequent. In these patients that are amenable to a sling procedure, it might be better to use more durable or even synthetic materials and to tighten the sling.

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EDITORIAL COMMENT

The treatment of urinary incontinence in children due to insufficient urethral resistance is challenging. There are two groups in the pediatric population in whom an incompetent sphincter could cause urinary incontinence. In children with myelodysplasia urinary incontinence is related to an incompetent sphincter alone in only a few patients. Most cases are associated with an overactive detrusor. In the group of patients with bladder exstrophy, continence can be achieved by a bladder neck procedure, which creates an outlet obstruction. Patients with incontinence after a bladder neck procedure represent one of the most challenging groups in pediatric urology. These patients need an operation with a high success rate, because incontinence in older children and adolescence is associated with severe social and psychological problems for the patient and their relatives.

This is an honest report on results using an artificial sling (Pelvilace™ from Bard medical). It includes 13 patients; most were older children and/or young adults (median age 15.5 years, range 8.9 – 27.5). The sling was implanted due to sphincteric incompetence in 8 patients with myelodysplasia, one had a tethered chord and 4 patients belong to the group with bladder-exstrophy-epispadias complex. Shortly after the procedure 8 of the 13 patients were dry. However, after 12 months none of the 11 patients with follow-up were dry. In one patient the sling eroded the urethra.

In patients with a neurogenic bladder and sphincteric incompetence, a low pressure bladder or reservoir is mandatory before an outlet procedure can be performed. Even if there is no hyperactive bladder previous to the procedure, after increasing the outlet

resistance hyperactivity can occur. It is important to understand the natural history of myelodysplasia. The neurology changes over time (deterioration of the hydrocephalus, hydromyelia, the Arnold-Chiari malformation, tethering of the spinal cord and/or the nerve roots and so on). It is a dynamic process needing close monitoring, because these children have a risk for future upper tract deterioration.

After conservative management, the surgical options depend on the neurological and mental status of the patient. It is absolute mandatory that these patients are able to perform a clean intermittent catheterization (CIC) before any procedure is performed to achieve continence. Compliance is another point. These patients have to do CIC on a regular basis. If the patient is not able to perform a CIC or is non-compliant, an incontinent diversion may be the better solution. If the patient depends on other people to perform the CIC, she or he has no benefit from a continence procedure. A colonic or ileal conduit seems to be the better solution for these patients instead of living with diapers. The colonic conduit has especially proven to be a safe procedure in the long run (1).

Those who are compliant and are able to perform a CIC have a couple of surgical options. If these patients are able to perform a CIC via the urethra, a facial sling plasty or a bladder neck procedure can be performed. However, this is not possible in obese patients and sometimes after orthopedic surgery at the spine, because they can not reach the meatus. For the fascial sling the continence rate is between 40-100% with a revision rate of 15% (2). Bladder neck reconstruction using the Salle or Kropp technique is much more complicated and continence can be expected in 50-81% of the patients (2). If the patient really wants to become dry and has good compliance, bladder neck closure together with a continent cutaneous stoma would be the next step. In cases with a small non-compliant bladder continent cutaneous diversion should be considered. Particularly in those patients in whom reimplantation of the ureters is required, performing a continent diversion may be even easier rather than performing a complicated bladder augmentation, reimplantation of the ureters, bladder neck closure and creation of a cutaneous stoma (3,4), where

the complications risks may be even higher. In the older group of patients, an artificial urinary sphincter is a good option if the patient is ambulatory and able to handle the mechanism. The continence rates are between 76-100% (2), the revision rate could reach 100% in the long run.

In patients with bladder exstrophy and a suitable bladder plate, primary bladder closure together with genital reconstruction should be the first choice. In patients with an incontinent epispadias with an open bladder neck, reconstruction is recommended. However after failure of primary reconstruction, urinary diversion using the recto-sigmoid pouch or a continent cutaneous diversion should be considered. In this group of patients, who have a low success rate, if the primary procedure fails, a procedure with an acceptable complication rate and a high continence rate is needed (5). The concept of preserving the bladder with multiple operations and ending up with bladder neck closure, bladder augmentation, continent cutaneous stoma, the risk for metabolic complications and secondary tumors is not different to a secondary urinary diversion. However, the number of operations may be less.

Looking at the honest results of the presented series using an artificial sling, this operation should not be used in children. The success rate is not acceptable, even if this is a minimally invasive procedure.

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EDITORIAL COMMENT

Pediatric sphincteric incompetence remains a challenge for urologic surgeons. Management options include periurethral injection, bladder neck reconstruction, artificial sphincter placement, or slings. In general injection therapy has been least successful, while the artificial urinary sphincter most successful, but concern the artificial sphincter will need periodic revision throughout life has spurred interest to develop alternatives. Currently in the US patients with exstrophy/epispadias complex typically undergo bladder neck revision by either the Young-Dees or Leadbetter-Mitchell approach, whereas children with neuropathic sphincteric incompetence receive slings.

The authors managed patients with exstrophy/epispadias and neuropathic sphincteric incompetence with slings, testing a minimally invasive approach currently popular in adults with stress urinary incontinence. They used intraoperative leak point pressure measurements to determine when the sling was sufficiently tight. At one month follow-up 9 (69%) of 13 patients were dramatically improved, but by 1 year most were again requiring multiple pads daily even if the amount of leakage was less than preoperatively. Postoperative urodynamics were obtained at 6 months, but it would have been useful to report subsequent changes in the 5 patients whose pad use increased over the next 6 months to determine if sling support was lost.

Slings for neuropathic incontinence have been placed both loosely or tightly, in a "U" or "X" shape from pubis under the bladder neck and back to pubis, or wrapped 360° around the bladder neck for compression and support. Several published series show all these techniques effective and durable with follow-up greater than 1 year. Therefore it appears a more invasive surgical procedure may be rewarded with a longer period of improved continence. Another potential advantage to surgery through an abdominal incision is simultaneous creation of an appendicovesicostomy, which may greatly facilitate intermittent catheterization and promote self-care. In my institution we routinely perform a 360° sling with appendicovesicostomy.

A comment regarding augmentation in children with sphincteric incompetence is also warranted. The authors report 1 patient with simultaneous enterocystoplasty for detrusor pressures of 80 cm water. However, they did not provide information regarding bladder capacity or response to anticholinergics in this child, nor did they explain why a bladder outlet procedure was needed when such high intravesical pressures could be achieved. Two other patients with exstrophy had prior augmentation before their bladder neck procedure, as did 2 with myelomeningocele. Since it cannot be determined which exstrophy bladders will enlarge when the outlet is enhanced, we perform bladder neck surgery first

and reserve augmentation for those who do not achieve increased bladder volume over time. Augmentation for neurogenic bladders with low outlet resistance usually will not resolve incontinence, and I personally believe most children undergoing slings do not, and will not, require augmentation if managed with anticholinergic medications in sufficient dosages (1).

The authors are commended for considering a minimally invasive technique and for clearly reporting pad usage both preoperatively and at intervals postoperatively. Loss of initial improvement in most

patients and erosion of the sling in another suggest open surgical placement of autologous slings provides more durable results in patients with neuropathic sphincteric incompetence.

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REPLY BY THE AUTHORS

In our study, sphincteric incompetence was considered the main reason for urinary incontinence in all patients except the one who had unusually high-level bladder overactivity in spite poor sphincter. The diagnosis of the sphincteric incompetence was based on patient history, leak point pressures and urethral pressure profile measurements. The extrophy patients had had previously Young-Dees operation to the bladder neck without adequate success. Previously we have had some success with injectable debulking agents in neurogenic patients and sometimes in nonneurogenic patients. Because according to our experience even a slight increase in outlet resistance may lead to continence in some

of these difficult patients, we decided to attempt mini-invasive collagen sling in a hope that it would be slightly more efficient and stabile than a debulking agent. The primary results were satisfactory, but unfortunately, the result was not long lasting. Undoubtedly synthetic sling materials would produce better long lasting results. However, in a growing child the use of synthetic material would lead to erosion and also in full grown patients the erosion rate would probably be higher than in a traditional tension free technique, because in these patients some tension is needed. It seems, that autologous fascia is best material at this moment, if a sling operation is attempted in these patients.

Insulin 3-Like Hormone and its Role in Epididymo-Testicular Descent

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ABSTRACT

Purpose: The role of insulin 3-like (Insl3) hormone signaling in the testicular descent process has been demonstrated. The purpose of the present study was to evaluate epididymal development in Insl3-deficient mice.

Materials and Methods: Heterozygous and homozygous Insl3 mutants of a mixed CD1 X 129/Sv genetic background were generated by breeding Insl3^{-/-} females with Insl3^{+/-} males, and their genotypes were determined by polymerase chain reaction. On the first postnatal day, newborn males were sacrificed, embedded in paraffin, and cut in 4 µm sections. Sections were stained with hematoxylin/eosin and immunoreacted with anti-α actin antibody.

Results: An analysis of stained sections indicated an arrest in the development of the epididymis in all homozygous mice. The cauda and corpus of the epididymis were undersized. Compared to the heterozygous epididymis, the homozygous epididymis had fewer peritubular layers and dwarfish musculature. We confirmed this with immunostaining with monoclonal antibodies against α-smooth muscle actin.

Conclusion: Defective development of the smooth musculature in the epididymis of Insl3 homozygous mutant mice, combined with its high intraabdominal undescended position, supports previous observations regarding the importance of intact epididymis morphology and function for descent of the epididymo-testicular unit.

Key words: cryptorchidism; epididymis; Insl3; mice, mutant strains

Int Braz J Urol. 2007; 33: 407-13

INTRODUCTION

During early embryonic development of the urogenital tract, mesentery connects the gonads and the Wolffian and Müllerian ducts to the abdominal wall. During male and female development, two parts of the genital mesentery, the cranial suspensory ligament and the caudal genital ligament gubernaculum, are believed to be responsible for sexual dimorphism in the position of testis and ovary (1). It was reported that defects in this developmental process could cause cryptorchidism. Cryptorchidism is the most common

disorder of sexual differentiation in humans, with a 3.5% incidence in term newborns (2).

The mechanism controlling testicular descent in mice was determined by analyzing mouse lines that lack insulin-like 3 (Insl3) hormone and its receptor, Lgr8/Great (3). Bilateral cryptorchidism in Insl3- and Lgr8- deficient mice is due to impaired development of the gubernaculum (4,5). These findings clearly demonstrate the role of Insl3 signaling in the process of testicular descent.

Restricted expression of Insl3 in pre- and postnatal Leydig cells is mediated by steroidogenic

factor 1 (SF1). Ins13 secretion is dependent on the differentiating effect of leutinizing hormone (LH) on Leydig cells and is independent of steroidogenic LH-mediating action (6-8). In Ins13- deficient mice, the development of epididymis that descends with the testis was considered to be normal and had no influence on descent of the epididymo-testicular unit (5). The goal of the present study was to evaluate epididymal development in Ins13- deficient mice and determine whether epididymal development is involved in the process of testicular descent.

MATERIALS AND METHODS

Heterozygous and homozygous Ins13 mutants of mixed CD1 X 129/Sv genetic background were generated by breeding Ins13^{-/-} females with Ins13^{+/-} males, and their genotypes were determined by polymerase chain reaction (4). On the first postnatal day, newborn males were euthanized with carbon dioxide gas, fixed with Bouin's fixative, and embedded in paraplast. To evaluate epididymal development in Ins13- deficient mice, 5 Ins13 homozygous and 3 Ins13 heterozygous mice were sectioned at 4 μ m. One homozygous mouse was cut in the frontal plane, and the remaining four homozygous and three heterozygous mice were cut in the sag-

ittal plane. Serial sections were stained with hematoxylin and eosin and examined under a light microscope.

For immunohistologic analysis, selected sections were mounted on slides. After deparaffinization, sections were treated with a 3% hydrogen peroxide/methanol solution to block endogenous peroxidase. Sections were preincubated for 1 h with 5% normal goat serum in 0.05% Triton X-100- phosphate buffered saline (PBS) and incubated overnight at 4°C in 1:200 diluted monoclonal anti- α actin antibody (Dako). Sections were washed with PBS and incubated with peroxidase-conjugated goat anti-mouse antibody at a 1:500 dilution (Dako) for 1 h at room temperature. After washing with PBS, immunoreactivity was detected by incubating the sections in a solution containing 3,3'-diaminobenzidine tetrahydrochloride.

RESULTS

The testes of all homozygous mice were localized either in a high intraabdominal position in proximity to the kidney (7/10) or in a transversal ectopic position, adjacent to the contralateral partner. In contrast, all 6 testes from heterozygous mice were located at the bladder neck (Figure-1). The gubernacular bulb (scrotal attachment) was less developed in homozygous mice compared to heterozy-

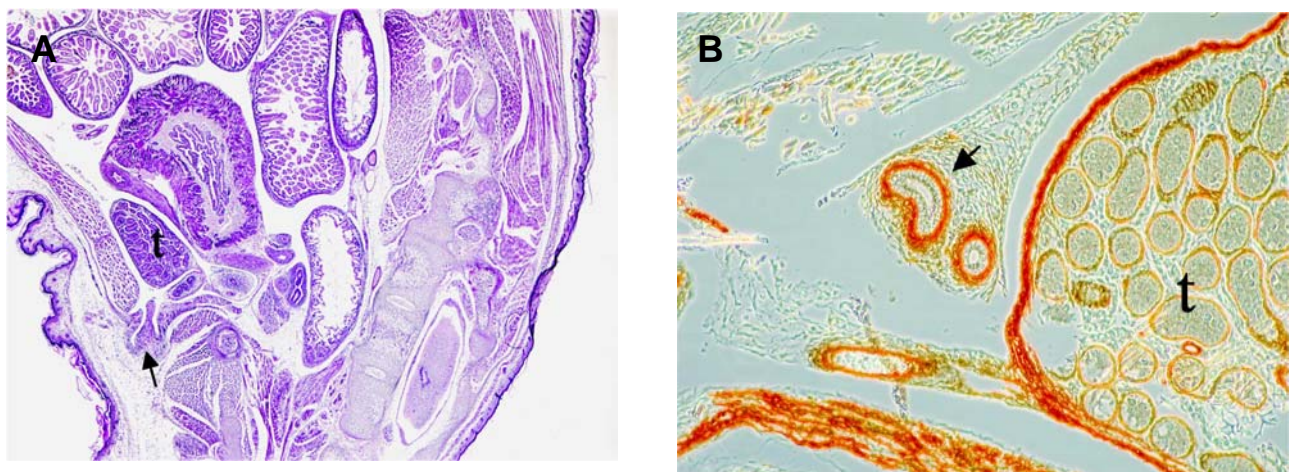


Figure 1 – A) Sagittal section of a heterozygous Ins13 mouse. The testis (t) is located at the bladder neck with developed cauda epididymis. The arrow points towards the gubernacular bulb, where the tip of the gubernaculum inserts. B) Immunostaining of the cauda epididymis showing strongly stained smooth muscle arranged in a circular fashion around the epididymal duct (arrow). The tunica albuginea and testicular peritubular connective tissue are also stained.

gous mice (Figure-2). In all homozygous mice, epididymis development was arrested. Both the cauda and corpus of the epididymis were severely under-sized (Figure-2). Compared to heterozygous mice, the epididymis of the homozygous mice had fewer peritubular layers and displayed a dwarfish musculature. Immunohistological staining for α -smooth muscle actin confirmed this (Figure-2). Immunostaining was absent in the testis and epididymal peritubular muscle layers of $Ins13^{-/-}$ mice, while it was strongly expressed in $Ins13^{+/-}$ mice (Figure-1). Interestingly, blood vessels stained intensely for α -smooth muscle actin in $Ins13^{+/-}$ and $Ins13^{-/-}$ mice, indicating a specific role of $Ins13$ in myogenesis of peritubular epididymal muscle layers (Figure-2). This

novel observation indicates that $Ins13$ signaling is involved in regulating the development of smooth muscle of the epididymis and testis.

COMMENTS

The role of the epididymis for descent of the epididymo-testicular unit has been postulated previously in experimental animals and human (9-11). August-Copenhagen-Irish rats have a congenital defect that frequently causes arrested development of a single ipsilateral Wolffian duct (9). If the Wolffian duct fails to form in the early developmental stage, the testis does not descend (9-11).

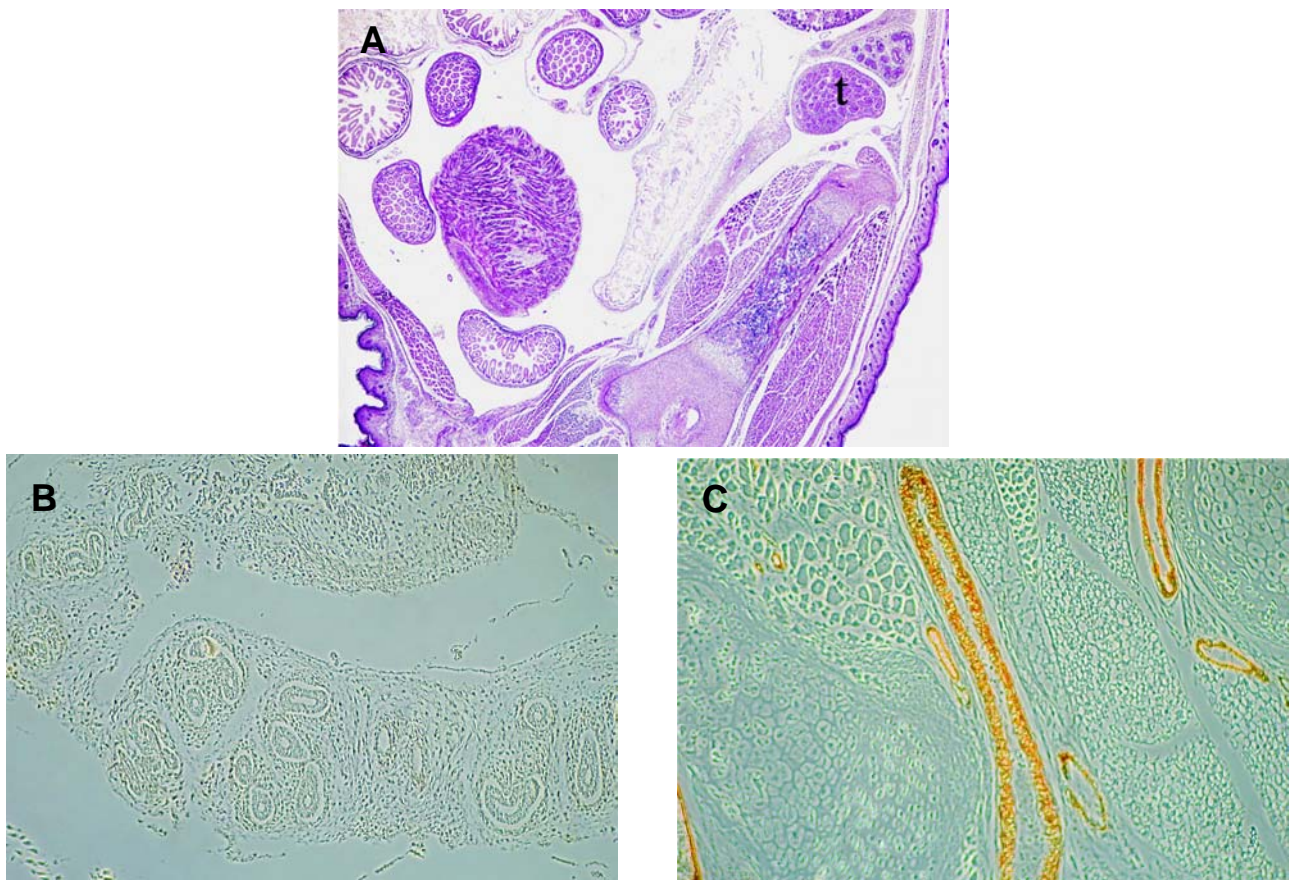


Figure 2 – A) Sagittal section of a homozygous $Ins13$ male mutant mouse with epididymis and testis (t) located in proximity to the lower kidney pole. The cauda and corpus of the epididymis are underdeveloped as is the gubernacular bulb region. B) Smooth musculature is absent around the epididymal duct in $Ins13$ homozygous male mutant mice. C) Vessels stained for monoclonal antibodies to smooth muscle actin in homozygous mice.

Treatment with LH-releasing hormone induces epididymo-testicular descent in 60% of naturally cryptorchid mice; and in these mice, increased testosterone secretion normalized the underdeveloped cryptorchid epididymis (10).

In 1984, Frey & Rajfer (12) reported that the distal gubernaculum is an absolute prerequisite for testicular descent, and they attempted to prove this by dissecting the distal part of the gubernaculum, repeating the experiment of Bergh et al. (13). However, shortly before birth, the rodent scrotum is partially inverted in the abdomen, giving an impression of being a part of the distal gubernaculum. It is self-evident that if the scrotum is stunted in its development, as Bergh et al. (13) showed, then the descent cannot take place. In contrast, scrotal development is normal in the vast majority of common cryptorchidism cases.

Since the gubernaculum in cryptorchid boys regresses after birth, the crucial question is why hormone treatment induces testicular descent, even though there is no gubernaculum in cryptorchid boys. In a placebo-controlled study (14) complete epididymo-testicular descent was achieved in cryptorchid boys who received hormone treatment. Hormone treatment induced a significant increase in serum testosterone (14). Boys with successful descent of the epididymis and testis had a normal-sized epididymis, while the majority of non-responders and surgically treated cryptorchid boys had small, irregular epididymes (15). Appropriate hormone treatment was capable of inducing increased testosterone secretion to stimulate further development of the epididymis and induce its descent into the scrotum (14,15). Our observation of defective development of the smooth musculature in the epididymis in *Ins13* homozygous mutant mice, combined with its high intraabdominal undescended position, supports previous observations regarding the importance of intact epididymis morphology and function for descent of the epididymo-testicular unit. Finally, the fact that there are animals with descended epididymes (chinchilla) but undescended testes, but no mammals with descended testes and undescended epididymes, underscores the necessity of epididymal, rather than testicular, descent (16).

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Although the authors have written to be focused on clarifying the controversy about the role of Ins13 on the development of epididymis, they go further and stress the importance of epididymis for the descent of a testis. However, the epididymis is not mandatory for the descent (1,2). Contrary to the stated in the paper, the ACI rats have descended testes (3,4).

Their observations revealed a defective myogenesis in testis, epididymis and gubernaculum and supported the role of Ins13 for myogenesis in special structures (5,6).

Their observation of defective myogenesis, together with the controversial role of epididymis, does not support their final conclusion about the importance of ins13 for the descent of epididymo-testicular unit, and how does the defective myogenesis affect the descent remain obscure in their conclusion.

Since Ins13 has a role in the myogenesis, and one of the current explanations of descent involves propulsion by the smooth muscle that depends on

myogenesis in the gubernaculum (7), their observation of defective myogenesis in the gubernaculum does not support the epididymal descent as they conclude, but seems to support the place of failed propulsion resulting from defective myogenesis.

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EDITORIAL COMMENT

According to the current view, normal testicular descent occurs in two phases. The first trans-abdominal phase (until week 15) is mainly depended on insulin-like peptide 3 (INSL3). The second inguinoscrotal phase is completed by week 35 and it is mainly depended on androgen action (1). In addition, androgens are of crucial importance for the development of the Wolffian duct derived organs, p.ex. epididymis. Testicular descent is conducted by gubernaculum, which is attached to the epididymis, which in turn is attached to the testis. Usually cryptorchidism is associated to the defective growth of the gubernaculum. However, epididymis is also important for testicular descent. This becomes evident also in some clinical situations. Sometimes the tip of the epididymis has grown to the scrotum together with the gubernaculum, while the other end of the elongated epididymis is lying in the abdominal cavity with the

testis. About one third of the cryptorchid testes are associated with some degree of epididymal abnormalities. In the present study, it is suggested that defective INSL3 action in addition to defective androgen action may cause abnormalities at least to the epididymal smooth musculature. It is unclear if epididymal abnormalities in general or the smooth muscle abnormalities detected in this study have some adverse effect for the fertility. Certainly, the surgeon has to be careful not to divide abnormal epididymis instead of gubernaculum during the operation.

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REPLY BY THE AUTHORS

The two stages of testicular descent are an old story presented by Gier & Marion in 1969 and 1970 (1,2) a long time before John Hutson even began his research. Furthermore, he published that the first phase of testicular descent is under the control of Mullerian Inhibiting Substance (MIS); this assertion is not true. Regarding INSL3 role in epididymo-testicular descent he should not be given credit for INSL3 only because he wrote about it in a review article. It is not his original discovery.

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Disposition of the Striated Urethral Sphincter and its Relation to the Prostate in Human Fetuses

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ABSTRACT

Objective: To describe the arrangement of the muscle fibers of the striated urethral sphincter and its relationship with the prostate during the fetal period in humans.

Materials and Methods: We analyzed 17 prostates from well preserved fresh human fetuses ranging in age from 10 to 31 weeks postconception (WPC). Transversal sections were obtained and stained with Gomori's trichrome and immunolabeled with anti alpha-actin antibody.

Results: We found that the urethral striated sphincter (rhabdosphincter) is located on the periphery of the smooth muscle and there was no merge between striated and smooth muscle fibers in any fetal period. In the prostate apex, the striated sphincter shows a circular arrangement and covers completely the urethra externally, whereas adjacent to verumontanum, it looks like a "horseshoe" and covers only the anterior and lateral surfaces of the urethra. Near the bladder neck, in fetuses younger than 20 WPC, we have found striated muscle fibers only at the anterior surface of the prostate, while in fetuses older than 20 WPC, the striated muscle covers the anterior and lateral surfaces of the prostate.

Conclusions: The urethral sphincter muscle covers the anterior and lateral surfaces of the urethra in all fetuses older than 20 WPC, close to the bladder neck and at the distal prostate. In the region of the prostate apex, the urethral sphincter covers completely the urethra circularly. The knowledge of the normal anatomy of the urethral sphincter in fetuses could be important to understand its alterations in congenital anomalies involving the base of the bladder, the bladder neck and the proximal urethra.

Key words: prostate; urethral sphincter; growth and development; fetuses; anatomy

Int Braz J Urol. 2007; 33: 414-20

INTRODUCTION

Many anatomic structures are involved in the micturition mechanism such as the bladder base, the prostatic urethra, the membranous urethra and the musculature present in those regions. The disposition of the muscular fibers is important to understand the functional role of those structures that are part of the

so-called sphincteric mechanism, acting both in the increase of the urethral pressure and during bladder voiding (1-3).

The main areas involved in the process of urinary continence are located next to the bladder neck and in the distal portion of the prostatic urethra. The latter is formed by three muscular layers; two internal layers (longitudinal and circular) of smooth muscle and

another external one (circular) formed by striated muscle, being the latter the external striated urethral sphincter itself (1,4).

The anatomic relationship between the external striated urethral sphincter and the prostate apex is decisive in the maintenance of the urinary continence after radical prostatectomy and in many reconstructive surgeries, as for example, surgeries for vesical exstrophy (5,6).

The detailed description of the musculature involved in the urinary continence mechanism is necessary due to the frequency of surgical manipulations on that region, which can harm the sphincter (5). The striated sphincter was well described recently through techniques of computerized reconstruction and magnetic resonance (7-9). The structure of the striated sphincter, disposed like a collar, and its alterations during embryo and fetal development could explain the higher incidence of vesicoureteral reflux in boys when compared to girls (10,11).

The studies that assess the disposition of the external striated urethral sphincter or the distribution of the smooth and striated muscle in the initial phases of the human development are scarce (11,12). The objectives of this work are to describe the localization and direction of the striated fibers of the external striated urethral sphincter during the human fetal period and to analyze the relationships between the smooth and striated muscle layers with the prostatic urethra.

MATERIALS AND METHODS

We studied 17 blocks containing the prostate, the urethra and the periprostatic musculature, obtained from well preserved fresh human fetuses, ranging in age from 10 to 31 weeks postconception (WPC). The fetuses died of causes unrelated to the urogenital tract and no external evidence of congenital malformations was detected. The gestational age of the fetuses was estimated according to the foot length principle (13-16), which is nowadays this is the most acceptable method to estimate the fetal age. The relationships between the fetal age, the weight and the vertex-coccyx length (VC) is shown on Table-1.

The fetal pelvis was carefully dissected with the aid of a X2.5 magnifying glass. After dissection, the prostate was removed and immersed in a Bouin solution for 48 to 72 hours. Afterwards the material was immersed in paraffin and sections of 5 µm thick were made. The sections were stained with Gomori's trichrome to verify the integrity of the specimens and to demonstrate the striated musculature.

The immunostaining procedures were performed with Zymed® primary monoclonal anti-alpha smooth muscle actin with appropriate positive and negative controls. Briefly, sections from formalin fixed, paraffin embedded samples were de-waxed, hydrated in a graded series of ethanol solutions of decreasing concentrations until the solution was all water and then washed in phosphate buffered saline (PBS) for 5 minutes. The sections were treated for 10 minutes with 3% hydrogen peroxide solution in methanol to block endogenous peroxidase activity. The sections were washed in three drops PBS, incubated in a humid chamber for 10 minutes with 1% goat serum, and then incubated a humid chamber with primary antibody predilute 30 a 60 minuts.

Table 1 – The table presents fetuses' ages in weeks post conception, the weights in grams and the vertex-coccyx length (VC) in millimeters.

Fetus	Age	Weight	VC Length (mm)
1	10	88	64
2	14	140	125
3	14	103	130
4	16	230	160
5	18	311	175
6	18	340	180
7	19	390	185
8	20	350	180
9	20	71	190
10	20	381	180
11	21	531	220
12	25	698	230
13	25	805	240
14	25	751	240
15	29	1190	270
16	30	1800	290
17	31	1790	280

Subsequently, the sections washed in three drops PBS and incubated at room temperature in a humid chamber with the biotinylated secondary antibody (Histostain-plus Kits Zymed) for 20 minutes, washed in three drops PBS and incubated at room temperature in a chamber with streptavidin- peroxidase-conjugate for 10 minutes. The sections were washed in three drops PBS and revealed by treating with a 3'-diaminobenzidine tetrahydrochloride solution containing 0.1% volume in volume hydrogen peroxide, and washed in distilled water, dehydrated in an increasing concentration series of ethanol solutions and mounted with rapid mounting media for microscopy.

The present study was approved by the Research Ethics Committee of our institution.

RESULTS

The striated musculature is the most external layer of the prostate, being clear the separation of this layer from the extraprostatic adjacent tissue (Figure-1). Internally, the striated muscle is in contact with the prostate stroma, mainly formed by collagen and smooth muscle. Also here the transition is evident even though not in a linear way as it is seen in relation to the extraprostatic tissue but through extensions both of connective tissue rich in collagen and the smooth

muscle, in direction of the striated muscle. Various regions present these extensions, however, it was never observed a mixture between striated and smooth muscle fibers.

In all fetal ages studied we have detected muscle fibers extending from the prostate apex to the base. These fibers did not totally involve the prostate and were more evident anteriorly, presenting a horse-shoe disposition. The muscle fibers were disposed in an external layer formed by striated muscle and an internal layer formed by smooth muscle fibers (Figure-2).

We have found striated fibers in the prostate lateral surfaces only in fetuses with more than 20 WPC. We did not find any striated muscle in the mid and proximal posterior surface of the prostate in none of the cases. At the prostate apex the striated muscle surrounds all the urethra and its fibers are circularly disposed (Figure-3).

In a fetus with 10 WPC we have observed an important concentration of muscular fibers restricted to the ventral region of the prostate (Figure-4). As the fetuses growth we observed an extension of the muscle fibers for the lateral surfaces of the prostate with a progressive increase from 18 to 25 WPC (Figure-5). The prostates of the fetuses with more advanced age presented more smooth muscle in their lateral surfaces (Figure-6).

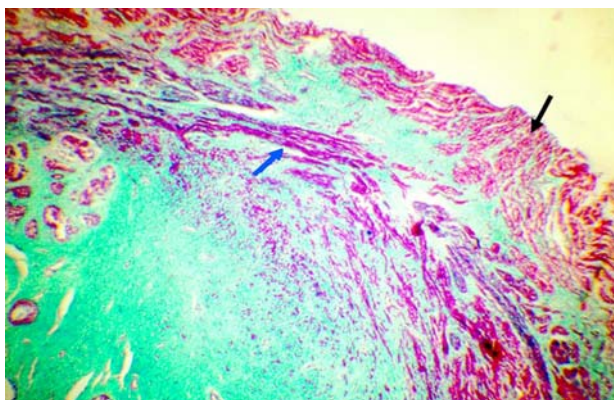


Figure 1 – Fetus with 20 WPC. Section through the prostate base. Striated muscle is located externally (black arrow) and smooth muscle is located internally (blue arrow). Gomori's trichrome, X100.

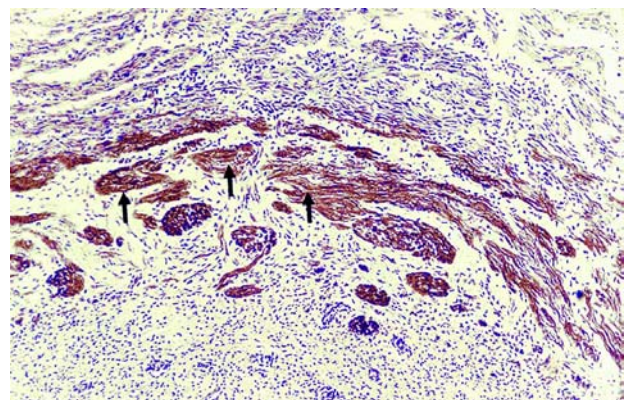


Figure 2 – Fetus with 20 WPC. Section through the prostate base. The smooth muscle fibers can be observed restricted to the anterior and lateral surfaces (arrows). Immunolabelling with anti alpha-actin, X100.

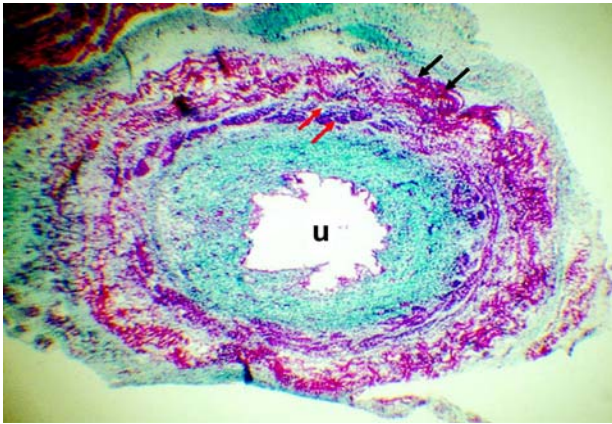


Figure 3 – Fetus with 10 WPC. Section at the level of the prostate apex where we can observe that striated muscle layer (black arrows) as well as smooth muscle layer (red arrows) involve the urethra (u) circumferentially. Gomori's trichrome, X40.

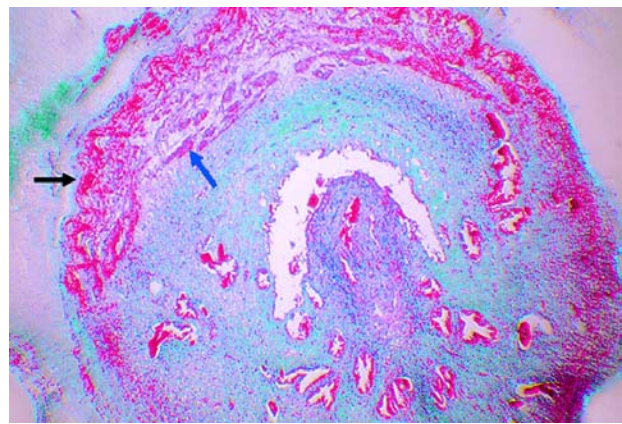


Figure 4 – Fetus with 10 WPC. Section at the level of the verumontanum depicts the external striated urethral sphincter (black arrow) and the smooth muscle fibers (blue arrow). Notice that the muscle does not involve all the circumference of the prostate, being restricted mainly to the anterior region. Gomori's trichrome, X40.

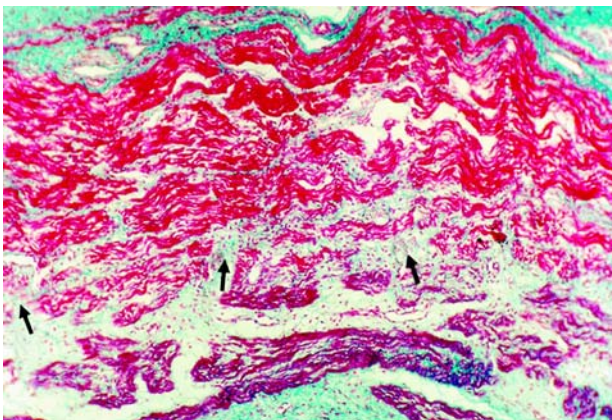


Figure 5 – Fetus with 25 WPC. Section at the level of the prostate base where the lateral region of the gland can be observed. The transition line between the layers of striated muscle and smooth muscle, formed by digitations of collagen (arrows) can be clearly evidenced. Gomori's trichrome, X100.

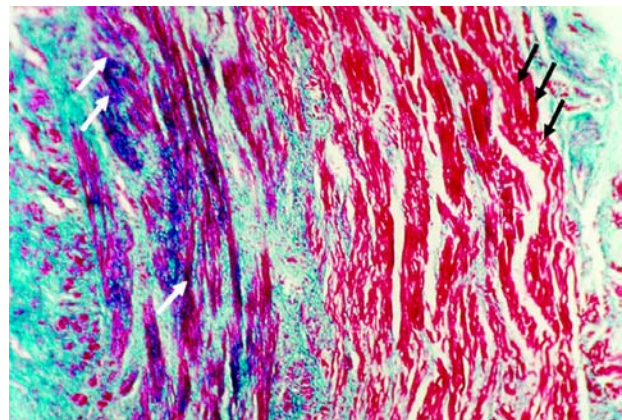


Figure 6 – Fetus with 30 WPC. Section at the level of the verumontanum, where in this older fetus we can now observe the extension of the striated muscle (black arrows) and the smooth one (white arrows) for the lateral region of the prostate. Gomori's trichrome, X100.

In the specimens where an immunohistochemistry with anti-alpha actin antibody was performed, that evidence the smooth musculature, we confirm that the muscular fibers that were not labelled (striated muscle) were localized more externally. The stained labelled fibers (smooth muscle), on the other hand were localized more internally and in close contact with the prostatic capsule (Figure-2).

COMMENTS

The components of the bladder neck, distal third of the prostatic urethra, and of the prostate apex actively participate in the process of urinary continence. The circular smooth muscle of the bladder neck is a direct extension of the longitudinal layer of the detrusor muscle.

During the bladder distention there is a stretch of the longitudinal muscular fibers and this increase in tension is transmitted to bladder neck circular fibers, determining the closure of the urethra. On the other hand, with the descent of the bladder neck during micturition, those circular fibers assume an oblique direction (2). The circular layer of smooth muscle is prominent in the regions of the prostate base and middle prostate, while the longitudinal layer is more evident in the distal portion (18). In our study we have observed a circular smooth muscle layer localized mainly at the prostate base, while the longitudinal muscle layer was more evident at the prostate apex.

Previous studies have evidenced that the circular striated fibers of the distal sphincter assume a longitudinal direction when reaching the lateral surface of the prostate, ascending to the bladder neck (4,12). Other works show the presence of striated muscle near the bladder neck, however in the lateral and anterior positions (2,4,12). In our study we observe near the bladder neck, striated fibers localized in the prostate anterior and lateral regions. In none of the sections performed at the base of the prostate we observed striated muscle on its posterior surface.

The striated musculature of the urethral sphincter surrounds the urethra in the region of the prostate apex, but does not surround the prostate in the verumontanum level as well as in the prostate base, presenting a horseshoe aspect, confirming the findings of previous studies performed in fetuses (11,19). Our findings agree with those of Yucel & Baskin (11), that evidenced a change in the development pattern of striated sphincter during the fetal period and the horseshoe aspect of the musculature in the superior portions of the prostate. Ludwikowski et al. (10) reported that they did not find changes in the development pattern of the striated sphincter during the fetal period studied and did not find at any age the sphincter surrounding the prostatic apex, that are against our findings.

During the performance of the endoscopic surgeries of the prostate a resection of the supramontanial portion of the prostatic urethra is performed, that is the region where generally occurs the growth of the adenoma (20). The quantity of striated muscle in this region is inferior to that observed in the

inferior portions of the prostate. The region above the verumontanum is mainly constituted by smooth muscle, however this musculature is little damaged, since the smooth muscle is compressed in the direction of the surgical capsule by the adenoma. In this way, the incidence of incontinence after the transurethral resection is minimal.

The longitudinal and circular portions of the striated sphincter form an arch when analyzed together. The urethra penetrates in the anterior region of the bladder base and descends obliquely through the prostate crossing this arch of striated muscle. The striated muscle circular portion is separated from the urethra by mucosal glands and smooth muscle. The sphincter fibers are transversal in comparison with the longitudinal fibers of pubovesical ligaments that are placed anterior to the sphincter, separated from those only by a narrow band of conjunctive tissue of the retropubic space (5,12,21).

In adults, the anterior and posterior surfaces of the sphincter are close related to an extensive prostatic vascular plexus. The integrity of the muscle as a distinctive structure is lost due to the advancement of the vascular plexus, making it difficult to describe this structure (12). In fetuses, we found a clear separation between the striated muscle and the prostate peripheral tissue, similar to a capsule.

Oerlich (12) describes that the muscle fibers of the mesenchyme start to present striations in fetuses with 115 mm VC length, and a complete distinction of striated and smooth fibers is observed in fetuses with 245mm VC length. We have found striations in all prostates studied from the age of 10 WPC (64 mm VC length), and those fibers are different from the smooth muscle fibers in a very evident way. The presence of sphincteric muscle in the prostatic region in fetuses of the third trimester was also noticed by Ludwikowski et al. (10) and by Sebe et al. (19).

Striated muscle fibers are continuous and inseparable from the smooth fibers of the urethra and interdigitations occur in the contact plane between the two types of fibers. There is no kind of fascia between the two areas (12, 22-24). In our sample we have found the same interdigitations between the two muscular types, even though no fascial structure has been found.

At the verumontanum level and in the prostate base we have found an overlay in the lateral surfaces by the striated urethral sphincter. In the prostate apex, the fibers are disposed with a circular orientation, while in the middle prostate did not present a defined direction. The relationship between the prostate and the external urethral striated sphincter changes with the prostate development, mainly concerning their lateral surfaces. With the lateral growth of the lobes, that depends upon individual characteristics, the striated fibers localized over the lateral surfaces become more separate. The extension in which the lateral surfaces will be overlaid by such fibers is variable and will depend on the development of the lateral lobes(12).

We conclude that the external striated sphincter surrounds all the urethra at the prostate apex and involves the anterior and lateral surfaces. Near the bladder neck the musculature is found only at the anterior face of the prostate in fetuses until 20 WPC, while in fetuses with more than 20 WPC we can observe an extension of the striated fibers to the lateral surfaces. The direction of the striated fibers is predominantly transversal at the prostate apex, at the anterior surface of the prostate base and at the middle of the prostate. However, at the prostate lateral region of the middle prostate its disposition is aleatory.

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CONFLICT OF INTEREST

None declared.

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Re: Penetrating Ureteral Trauma

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Int Braz J Urol, 33: 142-150, 2007

To the Editor:

Penetrating ureteral injuries from external violence is rare, as evidenced by this report of 20 reported injuries over an 8 year period from Sao Paulo by Fraga et al. This article is another in a long line of papers, emphasizing that a high index of suspicion is needed to reliably diagnose ureteral injuries. Again, the majority of penetrating ureteral injuries are diagnosed intra-operatively, with direct exploration the most accurate method. Ureteral peristalsis is not a reliable indication of viability or of adequate vascularity. The most reliable way to determine ureteral viability is by incision and monitoring for a bleeding edge. Intravenous indigo carmine is also helpful in identifying ureteral injury by extravasation of blue dye from the injury site. Another method to test ureteral integrity is by cystotomy and retrograde injection of blue dye by pediatric feeding tube.

Although none of the patients studied here underwent imaging prior to surgical exploration, intravenous urography is often the primary imaging study employed to evaluate ureteral integrity, yet results can be very variable. IVU findings suggestive of ureteral injury are incomplete visualization of the entire ureter, ureteral deviation or dilatation, urinary extravasation, hydronephrosis, and delayed or non-visualization of the injured renal unit. One-shot IVU, however, has little value for assessing ureteral integrity. (1)

For the unstable patient, the method of “damage control” was not employed or mentioned in this article on ureteral injuries. Typically, when the patient is too unstable to undergo lengthy ureteral reconstruction, a “damage control” approach of temporary cutaneous ureterostomy over a single “J” ureteral stent or pediatric feeding tube should be performed (2). An alternative method of last resort is ureteral ligation, proximal to the injury, followed by a percutaneous nephrostomy tube when stable. Intraoperative placement of a nephrostomy tube is time consuming and more difficult than one appreciates – it should be avoided. Definitive reconstruction is delayed until the patient has stabilized from his other injuries.

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Re: Perineural Invasion by Transitional Cell Carcinoma of the Bladder in Patients submitted to Radical Cystectomy: What is the Prognostic Value?

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Int Braz J Urol, 33: 161-166, 2007

To the Editor:

The paper by Antunes et al. is an excellent contribution to a controversial issue: the importance of perineural invasion as a prognostic factor for bladder cancer after radical cystectomy. The relationship between perineural invasion and prognosis has been demonstrated to be poor in a number of malignancies. Particularly in the prostate, perineural invasion may have importance as a predictor of extraprostatic extension. In the bladder, controversy exists on whether the pathologic features of vascular (blood and/or lymphatic), and perineural invasion have any role as prognostic indicators. In a study cited by Antunes et al., on univariate analysis lymphatic, blood vessel and perineural tumor invasion showed strong prognostic significance. However, on multivariate analysis only blood vessel invasion, invasion depth and regional lymph node status were independent prognostic factors (1). In another paper also cited by Antunes et al., univariate analysis revealed that vas-

cular invasion, lymphatic invasion, and perineural invasion were significant prognostic predictors of overall survival. However, only the tumor stage and vascular invasion proved to be independent prognostic predictors of disease-specific survival on multivariate analysis (2). Independent of the controversy, in my opinion vascular and perineural invasion in vesical cancer should be commented on the pathology report.

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Re: Dorsal Onlay Buccal Mucosal Graft Urethroplasty in Long Anterior Urethral Stricture

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Int Braz J Urol, 33: 181-187, 2007

To the Editor:

In this review of 43 patients with long anterior urethral stricture, the authors evaluated urethral reconstruction using dorsal onlay buccal mucosa graft with very high success rate.

I agree that ventral graft revascularization seems less reliable than dorsally securing a graft with quilting stitches to the corpora cavernosa. From a personal experience, dorsal onlay provides better visualization and less bleeding, especially for bulbar urethral part.

However, there are some issues that should be pointed out. It is unusual that idiopathic stenosis was the most frequent cause of stricture in their series; I suppose that most of these are uncovered lichen sclerosis and infectious etiology. I think that "simple technique" could be applied before for ventral grafting; dorsal onlay grafting, especially in very long strictures is a very sophisticated method, which requires great experience and dexterity to ensure successful outcome without serious complications. Despite great experience, the authors mentioned the need for blood transfusion in two patients, which proves that in the hands of less experienced surgeons this can be a very dangerous procedure. The authors mentioned 16 cases of panurethral strictures and the stricture length ranged from 3-9 cm; I wonder are these cases of very short penises or the stricture did not involve whole anterior urethra. In panurethral stenoses, the graft should be as long as the penis in erect state, otherwise, postoperative ventral penile

curvature as well as penile shrinkage could occur. Thus, inlaying should be in stretched or even better in erect penis.

Normal urethral stricture limits, which are determined during surgical reconstruction based on macroscopic aspect only, are not always sufficient to determine normal urethral part. Microscopic studies on presumed healthy urethral ends showed structural changes, fibrosis, which is probably the cause of residual anastomotic stenoses.

Also, we use postoperative suprapubic urinary drainage in all of our patients. Repaired urethral part is stenting by 10F fenestrated stent for 7 days for two reasons: postoperative graft wetting as well as to enable evacuation of sperm in young patients due to nocturnal ejaculations. Since the sperm is the main reason for infection, we advise to all of our patients to void once after ejaculation in order to clean urethra.

Despite these few criticism and comments, I nevertheless congratulate the authors for their experience with dorsal onlay buccal mucosa graft urethroplasty in long anterior urethral strictures.

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Re: Results of Novel Strategies for Treatment of Wilms' Tumor

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Int Braz J Urol, 33: 195-203, 2007

To the Editor:

Multimodality treatment, including chemotherapy, has resulted in a significant improvement in the survival of children with Wilms' tumor (WT), from approximately 30% in the 1930s to more than 85% in the modern era (1). This excellent work by Tucci and associates shows the results of treatment of 53 children with WT, that were treated according to protocols of the Brazilian Wilms' Tumor Study Group, exception made to 16 cases with stage I tumor, who received a short duration postoperative treatment with vincristine. This group of patients showed a disease-free survival rate of 100% in a median time of 101 months. On the other hand, the overall and disease-free survival of 10 patients with recurrent WT at 5 years was only 42.8%.

The results of this report are comparable to others in the literature, that support the use of less-aggressive adjuvant chemotherapy for patients with low stage disease (1,2). As most children in this group had favorable histology, no conclusion can be obtained regarding the influence of this important aspect, since favorable histology seems to be another factor that enables stratification of patients for a reduced chemotherapy in all stages of the disease, including stage-I (2).

The authors also describe unsuccessful results of re-treatment of children who relapse after initial treatment. More recent works, however, show a significant improvement of long term survival (up to 60%) in such patients who are treated with inten-

sive-dose salvage chemotherapy regimes including ifosfamide, carboplatin and etoposide, as well as autologous hematopoietic stem-cell rescue (3).

Further improvement in adjuvant therapy regimes can also be obtained by neoadjuvant chemotherapy, that concomitantly enables a technically easier and safer surgical removal of the tumor, without the risks and hazards of tumor spillage (4,5).

The aim of clinical trials nowadays is to reduce chemotherapy for children with low-risk tumors, therefore reducing its side effects, and to improve it in patients with high-risk Wilms' tumor, including those with anaplastic, bilateral and recurrent tumors (1,6).

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Re: Prevalence and Associated Factors of Enuresis in Turkish Children

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Int Braz J Urol, 33: 216-222, 2007

To the Editor:

In this article, the authors aimed to determine the prevalence and associated factors of enuresis in Turkish children and tried to identify common methods of enuresis management. The sample was drawn using a short but detailed and clear questionnaire distributed to the parents of 1,500 school children aged 6-12 years, covering five schools selected randomly, with a high response rate (89%).

Although their overall prevalence of nocturnal enuresis is apparently comparable with previously published epidemiological surveys, the importance of the study is that it demonstrates that enuresis is a frequent disorder in childhood, also in Turkey, although many medical doctors and parents still under-

estimate this issue. The traditional concept is that most cases of enuresis are caused by a developmental immaturity of voiding control, and most enuretic children will ultimately acquire normal control with increasing age.

The authors stated that the prevalence of enuresis decreased with age; of the 6-year-old children, 30.8% still wetted their beds, while none of those aged 12 years did so. These results might suggest a very high spontaneous resolution rate but the figures have to be interpreted with caution since only a small number of children in the age group 6 and 12 (n = 13 and 34 respectively) are a major limitation of this study.

The authors refer to the classical study of Forsythe et al. which dates from 1974 showing a spontaneous cure rate of 14% annually between the ages of 5 and 9, and 16% between 10 and 19 years (1). Recently however, Yeung et al. reported no significant drop in prevalence after the age of 10 (2). As age increases there are an increasing proportion of enuretic patients with more severe bedwetting. Enuretic children aged more than 10 years and adolescents, have significantly more daytime urinary symptoms and incontinence compared to younger children (3). Patients with severe symptoms are much more likely to have persistent problems into adulthood. Consequently, it seems that spontaneous cure only applies to patients with rather mild enuretic symptoms. This argues against an expectant and conservative approach towards enuresis. Therefore we are convinced that these recent findings have major clinical implications for both primary and secondary care centers. First of all, enuresis in children aged

more than 10 years and adolescents is complex in nature and also in treatment, and therefore these patients should be referred instantly. Second, children with severe or not monosymptomatic nocturnal enuresis have a much lower spontaneous cure rate than generally accepted, making a policy of waiting with appropriate treatment not longer defensible.

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REPLY BY THE AUTHORS

Previous studies demonstrated that the prevalence of enuresis tends to decrease with increasing age, and it was more common in boys than in girls. Similarly, in the present study, 30.8% of the children were wetting their beds at 6-years-old whereas none of them was wetting their beds at 12-years-old. However, as outlined in the discussion section, a small number of children in the groups of 6-years-old (n = 13) and 12-years-old (n = 34) was the limitation of our study.

Dr JL Dehoorne states that enuresis prevalence did not decrease after 10-years-old and with the increasing age the prevalence of severe enuresis increases, referring to the study of Yeung et al. On the other hand, in our study, severe enuresis (bedwetting everyday) rate was 33%, nevertheless, enuresis prevalence decreased with increasing age. Similarly, Serel et al. (1) reported severe enuresis prevalence as 26% and enuresis prevalence at age 7 and 12, as 15.1% and 4% respectively. Kanaheswari

et al. (2) demonstrated that the prevalence of bedwetting 2 or more times a week was 54.4%. In their study, they concluded that the rate of enuretic children decreased significantly with increasing age.

We believe that enuresis prevalence decreases as the child grows, however, severe enuresis is a different situation that could be managed separately.

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Re: Prevalence and Associated Factors of Enuresis in Turkish Children

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Int Braz J Urol, 33: 216-222, 2007

To the Editor:

Authors investigated the prevalence of nocturnal enuresis and associated factors of enuresis in Turkish children. The response rate was 89% and overall prevalence of nocturnal enuresis and diurnal enuresis were 17.5% and 1.9%, respectively. Some factors were associated with enuresis. They concluded that the prevalence of nocturnal enuresis in Turkish children was not different from others and that families do not have sufficient attention about enuresis.

First of all, it is hopeful to follow the standardization of terminology of lower urinary tract function in children and adolescents 1, to make it easier to compare studies and decrease confusion among researchers. The report 1 recommended that the ambiguous term diurnal enuresis should be avoided. Second, when conducting a questionnaire survey, it must be important to use a validated and reliable questionnaire. The major problem, here, is

whether the questionnaire was a validated and reliable one or not, to evaluate lower urinary tract symptoms in children. Most of the questionnaire surveys have the same drawbacks as this one: the use of unvalidated questionnaires and no comparative data. Sureshkumar et al. reported the validity and reliability of a questionnaire 2.

Third, there is no consensus about a simple question that should complete the questionnaire; parents, children or both? In general, it is not so straightforward to evaluate nocturnal enuresis and overactive bladder symptoms accurately in children. For children, it is too difficult to assess the presence of urgency and to count the episodes of nocturnal enuresis and the frequency of daytime voiding. On the other hand, as authors concluded, parents may be unable to report their child's frequency of daytime voiding, presence of urgency and incontinence, and even episodes of nighttime urinary incontinence until

they have a chance to observe the child at home and complete a bladder diary. A bladder diary could be an important adjunctive measure to objectively assess these and other parameters.

In conclusion, terminology and a bladder diary could be a useful tool when a questionnaire survey about lower urinary tract symptoms in children was conducted.

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Re: Surgical Technique Using AdVance™ Sling Placement in the Treatment of Post-Prostatectomy Urinary Incontinence

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Int Braz J Urol, 33: 231-237, 2007

To the Editor:

The publication of this article follows the recent increase in interest for new minimally invasive solutions in the treatment of post-prostatectomy incontinence (PPI). The authors present a new technique to treat PPI using a polypropylene monofilament mesh via a transobturator approach. The surgical technique is described in detail and so far, 4 patients have been treated. There is no information about postoperative outcomes.

Patient selection was restricted to mild to moderate PPI, using 3 pads/day on average. Although

the artificial urinary sphincter (AUS) is considered the gold standard in the treatment of PPI, there is a need for more minimally invasive treatment options for two reasons. First, many patients do not want to undergo a surgical intervention associated with a reoperation rate up to 37% within 10 years (1). Second, many patients suffer from a mild to moderate incontinence due to an intrinsic sphincter deficiency (ISD) which can be well treated with a less invasive treatment and lower morbidity. Furthermore, if treatment fails an AUS can be implanted in a second stage.

Minimally invasive procedures for PPI consist of bulking agents, readjustable periurethrally implanted balloons (ProAct®), perineal bone-anchored male slings (Invance®), readjustable retropubic slings (Argus®) and the newly presented transobturator sling (Advance®). Except the AUS all minimally invasive procedures have the limitation that compression can only be exerted in one direction which has to be similarly appropriate for continence and micturition (2-5). This limitation applies also to the transobturator sling.

After radical retropubic prostatectomy the Retzius' space is scarred due to dissection of the prostate. One major advantage of the transobturator approach is that bladder perforation can be avoided which is more likely using the retropubic approach.

The most important issue in male slings seems to be finding the force of compression on the urethra to develop continence and to enable micturition. In this context the transobturator sling shifts the bulbar urethra cranially and serves more as a suspension rather than a compression. The idea behind this sling is to mimic the rectourethralis muscle. Interestingly, after placing the sling a minimal gap remains between the sling and the bulbar urethra giving the impression that the urethra is less or not compressed. A sophisticated tensioning of the sling is not necessary during the procedure.

It should be considered that the transobturator sling is not readjustable. Further studies are needed to determine whether there is a need for a readjustable sling to maintain continence in the course of several months.

Despite these limitations, the transobturator sling poses a promising option in the field of minimal invasive treatment of post-prostatectomy incontinence.

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UROLOGICAL SURVEY

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STONE DISEASE

Preventing Migration of Stones during Fragmentation with Thermosensitive Polymer

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J Endourol. 2007; 21: 504-7

Purpose: To define a method of stabilizing stones during extracorporeal (SWL) and intracorporeal lithotripsy with a thermosensitive polymer.

Materials and Methods: Using a thermosensitive polymer that is either a liquid or a gel, depending on the temperature, both calcium oxalate and plaster of Paris phantom stones were placed in the polymer gel or saline, and SWL was performed. Comparisons were made between the effectiveness of the fragmentation in the two media. Also, in-vivo studies using the polymer to prevent migration of ureteral stones were performed in swine. Electrohydraulic lithotripsy was used on a small stone implanted in the distal ureter with the polymer instilled proximally. Once in the ureter, the polymer converted to a gel. After completion of the procedure, the polymer was restored to a liquid form by infusion of cold saline and expelled from the ureter. Three of the pigs underwent treatment of the stone, convalesced for 7 days, and then had urine collections from both ureters to compare the glomerular filtration rates, fractional sodium excretion, urine/plasma creatinine ratio, and urine/plasma urea ratio on the treated and the contralateral (control) sides.

Results: The polymer did not enhance fragmentation when used with SWL but prevented stone migration in the in-vivo studies. The physiologic parameters were not significantly different on the treated and the control sides. The polymer was easily removed from the ureter by infusing cold water.

Conclusion: The use of this thermosensitive polymer proximal to ureteral stones prevents migration and is not traumatic to the ureter.

Editorial Comment

The authors describe the use of a novel thermosensitive polymer to stabilize calculi during endourological procedures. The technique was not successful in an in vitro model of ESWL. Previous studies have demonstrated inhibition of stone fragmentation by ESWL when a mineral oil medium surrounds the stone. It is thought to occur by interference with the cavitation effects of ESWL, and a similar effect may occur with the new polymer evaluated in this study.

The authors did not evaluate the upper collecting system acutely after intracorporeal lithotripsy in the porcine model. This is an important step to be able to conclude that the polymer did not migrate into the renal pelvis or calyces. Was this to occur, the patient may experience transient obstruction until the polymer dissolved 2 hours later.

Clinical applications of this polymer would require the use of warmed endoscopic irrigation fluid to prevent dissolution of the polymer. It would be important to evaluate the toxicity of combustion by-products of the polymer to determine what might be anticipated if it were inadvertently targeted with the holmium laser. It would also be important to evaluate interactions of the polymer with a ureteral stent left post-operatively – could this impact polymer dissolution?

As such, the polymer holds promise as a method to prevent stone migration during ureteroscopy. One would need to quantify the volume of polymer required, which may vary based on the degree of ureteral dilation above the calculus. One might propose that the polymer could facilitate stone fragment retrieval during PCNL.

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Instillation of Skin, Nephrostomy Tract, and Renal Puncture Site with Ropivacaine Decreases Pain and Improves Ventilatory Function After Percutaneous Nephrolithotomy

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J Endourol. 2007; 21: 499-503

Background and Purpose: Pain after percutaneous nephrolithotomy (PCNL) is well investigated, but no optimal management strategy has yet been defined. Ventilatory changes after uncomplicated PCNL remain obscure. We investigated whether pain can be managed with a combination of a parenteral non-narcotic drug and instillation of a local anesthetic into the operative field. We also measured ventilatory changes early after PCNL to determine whether this analgesic modality improves ventilatory status.

Patients and Methods: In a randomized blinded study, 34 well-matched patients underwent PCNL with single subcostal access. At the end of the operation, 30 mL of either 0.02% ropivacaine or saline was instilled into the renal puncture site, nephrostomy tract, and skin. Postoperatively, patients received parenteral metamizol (dipyrone) (500 mg/dose) on demand. Pain visual analog score (VAS), peak expiratory flow rate (PEF), and blood-gas analysis were performed at 2, 6, and 24 hours postoperatively. The number of analgesic doses required was recorded.

Results: The VAS at 6 hours, time to first analgesic demand, and total analgesic need were significantly lower ($P = 0.001$, 0.008 , and 0.001 , respectively) in the ropivacaine group, whereas the PEF at 2 and 6 hours was significantly higher ($P = 0.001$ for each). Analgesic use in the first 12 and 24 hours was lower in this group. Blood-gas analysis was within the normal range in both groups. Time of surgery and hemoglobin decrease were not significantly different.

Conclusions: A decrease in PEF indicating restricted ventilation appears early after PCNL. Because these patients were chosen carefully to have normal function preoperatively, this decrease was attributed to nociception. A combination of ropivacaine instillation with metamizol decreases pain and analgesic use and improves PEF more than use of metamizol alone. Such a multimodal pain-management strategy is effective in minimizing postoperative opioid use with proper pain management, resulting in better ventilation.

Editorial Comment

This well-designed study sets a new standard for the evaluation of perioperative pain and respiratory function after PCNL. Visual analog pain scores and analgesic requirements were markedly less in the patients receiving instillation of local anesthesia at the conclusion of the study, and this correlated well with improvements in peak expiratory flow. However, the impact on pain scores and respiratory function wore off by 24-hours postoperative, the impact on analgesic requirements were maintained for up to 24 hours.

The authors were meticulous in their technique. First, Ropivacaine was selected for its long half-life (8 hours) and high liposolubility (for the perirenal fat) and its low cardiac toxicity. Secondly, the authors instilled 10 cc in the renal parenchyma as the nephroscope was withdrawn, 15 cc in the nephrostomy tract alongside the nephrostomy tube and 5 cc at the skin incision.

Previous studies have demonstrated that less opioid utilization translates into earlier control of pain, early mobilization, improved respiratory function, shorter hospital stay and lower costs. As such, instillation of local anesthesia at the completion of PCNL should be strongly considered.

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ENDOUROLOGY & LAPAROSCOPY

Decreased Complications of Contemporary Laparoscopic Partial Nephrectomy: Use of a Standardized Reporting System

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J Urol. 2007; 177: 2067-73

Purpose: We report complications of laparoscopic partial nephrectomy in a contemporary cohort of 200 patients using a standardized complication reporting system.

Materials and Methods: The records of 200 consecutive patients undergoing laparoscopic partial nephrectomy between September 2003 and November 2005 were reviewed. Mean tumor size was 3 cm and mean parenchymal invasion depth was 1.8 cm. There were 97 central tumors (48.5%) and 9 tumors (4.5%) in a solitary kidney. Complication severity for each patient was graded using a 5-tiered scale based on National Cancer Institute Common Toxicity Criteria. Statistical analysis was done to assess risk factors associated with complication events.

Results: A total of 35 patients (17.5%) had complications. The overall complication rate was 19%. Of the complications 29%, 42%, 26% and 2.6% were grades I to IV, respectively. There were no grade V complications. Median blood loss was 150 ml. Hemorrhagic and urine leak complications occurred in 9 (4.5%) and 4 patients (2%), respectively. Conversion to open partial and laparoscopic radical nephrectomy was done electively in 2 (1%) and 1 patients (0.5%), respectively. Compared to previously reported data on the initial 200 patients in our laparoscopic partial nephrectomy cohort this contemporary group of 200 had statistically significant decreases in overall, urological and hemorrhagic complication rates despite an increase in tumor complexity ($p = 0.02$, 0.04 and 0.04 , respectively).

Conclusions: Increased experience with advanced laparoscopic techniques has allowed a significantly decreased complication rate following contemporary laparoscopic partial nephrectomy, which now appears comparable to that of open partial nephrectomy. A standardized complication reporting system is advocated.

Editorial Comment

Laparoscopy partial nephrectomy has been challenged and questioned as treatment of renal tumors < 4 cm. The authors demonstrated an improvement in their complications rates due to the vast number of procedures and their learning curve. The authors used the NCI-CTC reporting system for surgical complications, which apparently standardizes definitions of complication events and enables clear comparison of the frequency and severity of events among various series. In conclusion, although the learning curve may be steep for certain laparoscopic procedures, this minimally invasive approach seems to mimic and is comparable to the open counterpart.

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Early Results of Robot Assisted Laparoscopic Lithotomy in Adolescents

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J Urol. 2007; 177: 2306-2310

Purpose: The treatment of large stone burdens in children is difficult and often requires multiple procedures using a combination of therapies. Recently, laparoscopy has been shown to be effective in the management of larger stone burdens. We report our experience with robot assisted laparoscopic lithotomy in adolescents, and describe our technique.

Materials and Methods: We retrospectively reviewed our experience with robot assisted laparoscopic pyelolithotomy in 5 patients operated on between 2002 and 2005. Mean patient age at surgery was 16.6 years, and mean followup was 15.4 months.

Results: Cystine was the etiology in 4 patients with staghorn stones. The remaining patient had calcium oxalate stones and concurrent ureteropelvic junction obstruction. After pyelotomy stones were removed by a robotic grasper or by a flexible cystoscope introduced through a robotic port. One of the patients had an indwelling ureteral stent placed preoperatively, while 4 had stents placed robotically intraoperatively. Mean operative time was 315.4 minutes (range 165.0 to 462.0), and mean estimated blood loss was 19.0 ml (0.0 to 50.0). Mean hospital stay was 3.8 days (range 2.3 to 5.7), and mean narcotic usage was 2.1 mg/kg morphine (1.5 to 3.5). One patient with a cystine staghorn calculus required conversion to an open procedure because of inability to remove the stone. Of the 4 cases completed robotically 3 were rendered stone-free and 1 had a residual 6 mm lower pole stone.

Conclusions: The early results of robot assisted laparoscopic lithotomy reveal that the procedure is safe and efficacious. Further prospective studies comparing other minimally invasive procedures used for similar stone burdens are needed to determine the benefits of this procedure and its role in stone management.

Editorial Comment

Laparoscopic assisted lithotomy procedures have been successfully described in the literature. With the advent of robotic surgery, the learning curve may be facilitated, especially in the reconstructive steps. The authors demonstrated their pioneering work emphasizing the technical feasibility and efficacy of robotic assisted lithotomy in adolescents with large stone burden. The investigators recognize that PCNL, ESWL and ureteroscopy are first line therapies in the management of pediatric renal stones. Nonetheless, this minimally invasive approach is another viable treatment option, particularly if the child has failed other minimally invasive techniques.

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IMAGING

Detection of Bladder Tumors with Dynamic Contrast-Enhanced MDCT

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AJR Am J Roentgenol. 2007; 188: 913-8

Objective: In a small pilot study, we assessed whether early-phase dynamic contrast-enhanced MDCT can be used to detect bladder tumors and whether thin reconstruction improves the detection rate.

Subjects and Methods: Thirty-six patients (30 with 59 cystoscopy-proven bladder cancers and six with normal bladders) underwent dynamic contrast-enhanced MDCT of the pelvis and abdomen. Images were obtained from the symphysis pubis to the diaphragm 70 seconds after injection of 100 mL of contrast medium. McNemar test was used to compare sensitivity per patient, segment, and tumor and specificity per patient and segment for each of three reconstruction methods: 5-mm sections with no overlap (i.e., 5-mm axial images), 2.5-mm sections with 1.25-mm overlap (i.e., thin-section axial images), and 2.5-mm sections with 1.25-mm overlap and multiplanar reformation (MPR) (i.e., thin-section axial images with MPR).

Results: MDCT with a combination of thin, overlapped sections and MPR depicted all but one of 47 bladder tumors larger than 5 mm but only five of 12 tumors 5 mm or smaller. There were no false-positive findings. Per-tumor sensitivity was significantly better with thin-section images with MPR (90%) and thin-section images alone (86%) than with 5-mm axial images (80%) ($p < 0.05$). Per-segment sensitivity was significantly better with thin-section images with MPR (95%) and thin-section axial images alone (87%) than with 5-mm axial images (79%) ($p < 0.05$). Per-patient sensitivity and per-patient and per-segment specificity did not differ with the three methods.

Conclusion: Dynamic contrast-enhanced MDCT of the pelvis shows promise for the detection of bladder tumors. Use of thin-section images with MPR and thin-section axial images alone had a significantly better rate of detection of bladder tumors than use of 5-mm axial images.

Editorial Comment

The authors show the ability of thin (2.5 mm) and overlapped sections and multiplanar reconstruction (MPR) to depict small bladder tumors. Thin-section images (2.5 mm) with MPR were used to detect all but one of 47 bladder tumors larger than 5 mm but only five of 12 tumors 5 mm or smaller. There were no false-positive findings. The sensitivity for detecting bladder tumors 5 mm or smaller was significantly better for thin-section images with MPR and thin-section axial images (both, 58%) than for 5-mm axial images (25%) ($p < 0.05$). Use of thin-section axial images improved the detection rate only for tumors smaller than 5 mm. MPR improved the detection of tumor in the bladder dome and tumors adjacent to normal anatomic structures.

Multidetector CT-urography has been shown to be an effective single comprehensive examination in the evaluation of patients with hematuria or with risk for the development of urothelial malignancies. Since protocols for MDCT urography varies from each institution, most MDCT urography images are obtained in the unenhanced phase (detection of calculi), nephrographic-phase (detection of renal masses) and excretory-phase (detection of urothelial lesions). Some authors recommend that MDCT urography should be performed only after adequate cystoscopy since these protocols do not allow adequate evaluation of the bladder.

Since January 2006, we have been using in our institution similar technique described by the authors as part of MDCT urography (1). This additional phase of MDCT-urography is used only in patients with macroscopic hematuria and with no previous cystoscopy. We agree with the authors that this “the bladder-wall phase” (scans at 60 or 70 seconds after intravenous injection of contrast), allows the detection of small bladder tumors. However, we need to keep in mind that this additional phase cause significant increase in the effective radiation

dose to the patients (18 to 25 mGy). For this reason, this protocol should be used with caution and primarily in older patients with macroscopic hematuria and absence of previous cystoscopy.

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Can High-Attenuation Renal Cysts be Differentiated from Renal Cell Carcinoma at Unenhanced CT?

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Radiology. 2007; 243: 445-50

Purpose: To retrospectively determine if renal cell carcinoma can be differentiated from high-attenuation renal cysts at unenhanced computed tomography (CT) based on Hounsfield unit measurements and heterogeneity. **Materials and Methods:** The Human Investigation Committee at our institution approved this study with waiver of informed consent. This study was compliant with the HIPAA. Fifty-four pathologically proved renal cell carcinomas in 54 patients (36 men and 18 women; average age, 53 years; range, 23-90 years) and 56 high-attenuation renal cysts in 51 patients (30 men and 21 women; average age, 63 years; range, 28-86 years) were retrospectively evaluated at unenhanced CT. Two independent readers reviewed randomized unenhanced CT images and obtained Hounsfield unit readings of each mass. A subjective determination of lesion heterogeneity was also performed by using a four-point scale (1: homogeneous, 2: mildly heterogeneous, 3: moderately heterogeneous, 4: markedly heterogeneous). Statistical analysis was performed by using Bland-Altman regression tree, classification and regression tree, and Shapiro-Wilk normality test.

Results: The average attenuation of cysts for reader 1 was 53.4 HU (range, 23-113 HU) and for reader 2 was 53.8 HU (range, 21-108 HU). The average attenuation of neoplasms for reader 1 was 34.7 HU (range, 21-60 HU) and for reader 2 was 38.4 HU (range, 22-60 HU). For cyst heterogeneity, a score of 1 was given in 55 of 56 (98%) cysts for reader 1 and in 53 of 56 (95%) cysts for reader 2. For neoplasm heterogeneity, a score of 1 was given in 35 of 54 (65%) neoplasms for reader 1 and in 36 of 54 (67%) for reader 2. Given the distribution of cyst and tumor attenuation values and lesion heterogeneity, a homogeneous mass measuring 70 HU or greater at unenhanced CT has a greater than 99.9% chance of representing a high-attenuation renal cyst.

Conclusion: The findings from this study may help differentiate high-attenuation renal cysts from renal cell carcinomas at unenhanced CT and may suggest the next appropriate imaging study for definitive characterization.

Editorial Comment

A hyperdense cyst refers to a cyst that demonstrates high attenuation on nonenhanced CT scans. Hemorrhage or proteinaceous debris is the most common cause, but renal cell carcinoma may eventually demonstrate similar

findings. A hyperdense renal cyst can be considered benign if it is sharply margined or homogeneous or demonstrates a hematocrit effect on nonenhanced and contrast-enhanced scan and demonstrates no significant enhancement on post-contrast scans. Because internal structures within a hyperdense renal cyst cannot be well evaluated by nonenhanced CT, US or MR imaging can be used for the differentiation. When sonography is performed, the mass is usually cystic but occasionally do not present all the sonographic criteria for a simple cyst. Actually internal septations and absence of posterior wall through-transmission are frequently found.

The authors present an interesting observation, which should be useful for adequate characterization of hyperdense renal lesion found on nonenhanced CT scans particularly in those patients submitted to a non-contrast CT scans for the detection of urolithiasis. They found that the attenuation of a renal mass and its degree of heterogeneity are useful findings in distinguishing a high-attenuation renal cyst from renal cell carcinoma on unenhanced CT images. If the density of the mass is greater than 70 HU and the mass is homogeneous, there is a chance of almost 100% (99.9%) that the mass is benign hyperdense renal cyst. They concluded that in this situation there is no need for contrast enhanced CT scan and high-resolution US studies or MR imaging can be used as complimentary test.

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UROGENITAL TRAUMA

Management of High Grade Renal Trauma: 20-Year Experience at a Pediatric Level-I Trauma Center

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J Urol. 178, 246-250, 2007

Purpose: In the last 20 years the management of high grade, blunt renal trauma at our institution has evolved from primarily an operative approach to an expectant nonoperative approach. To evaluate our experience with the expectant nonoperative management of high grade, blunt renal trauma in children, we reviewed our 20-year experience regarding evaluation, management and outcomes in patients treated at our institution.

Materials and Methods: We retrospectively studied all patients sustaining renal trauma between 1983 and 2003. Medical records were reviewed for mechanism of injury, assigned grade of renal injury, patient treatment, indications for and timing of surgery, and outcome. Injuries were categorized as either low grade (I to III) or high grade (IV to V).

Results: We reviewed the medical records of 164 consecutive children who sustained blunt renal trauma between 1983 and 2003. A total of 38 patients were excluded for inadequate information. Of the remaining 126 children 60% had low grade and 40% had high grade renal injuries. A total of 11 patients (8.7%) required surgical or endoscopic intervention for renal causes, including 2 for congenital renal abnormalities and 1 for clot retention. Eight patients (6.3%) required surgical intervention for isolated renal trauma, of whom 2 (1.6%) required

immediate surgical intervention for hemodynamic instability and 6 (4.8%) were treated with a delayed retroperitoneal approach. Only 4 patients (3.2%) required nephrectomy. All patients receiving operative intervention had high grade renal injury.

Conclusions: Initial nonsurgical management of high grade blunt renal trauma in children is effective and is recommended for the hemodynamically stable child. When a child has persistent symptomatic urinary extravasation delayed retroperitoneal drainage may become necessary to reduce morbidity. Minimally invasive techniques should be considered before open operative intervention. Early operative management is rarely indicated for an isolated renal injury, except in the child who is hemodynamically unstable.

Editorial Comment

Henderson et al. is another paper supporting that contemporary management of blunt renal injury in the child is expectant management (1). They had a surprisingly high percentage of Grade IV and Grade V (shattered kidney) injuries that were managed successfully. As in other solid organs like the spleen and liver, where blunt trauma is managed almost exclusively conservatively, the same is true for the kidney. Clearly, the management pendulum for even high grade blunt injuries has shifted to a nonsurgical algorithm. Only in the exsanguinating and unstable patient, is surgical exploration of blunt renal injury an absolute indication. All other kidney injuries are just relative indications. One proviso when dealing with trauma in children, however, is that they do not manifest changes in their vital signs until severe degrees of blood loss. Due to increased physiologic reserve, vital signs in the child can stay in the normal range even in the presence of shock. Tachycardia and poor skin perfusion are often the only signs of hypovolemia. Only blood volume losses greater than 30% in children manifest drops in blood pressure, narrowed pulse pressure, and absent peripheral pulses.

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Management and Hospital Outcomes of Blunt Renal Artery Injuries: Analysis of 517 Patients from the National Trauma Data Bank

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J Am Coll Surg. 2006; 203: 612-7

Background: Blunt renal artery injuries are rare and no single trauma center can accumulate substantial experience for meaningful conclusions about optimal therapeutic strategies. The purpose of this study was to assess the incidence of renal artery injuries after different types of blunt trauma, and evaluate the current therapeutic

approaches practiced by American trauma surgeons and the effect of various therapeutic modalities on hospital outcomes.

Study Design: This was a National Trauma Data Bank study including all blunt trauma admissions with renal artery injuries. Demographics, mechanism of injury, Injury Severity Score, Abbreviated Injury Score for each body area (head, chest, abdomen, extremities) injuries, type of management (nephrectomy, arterial reconstruction, or observation), time from admission to definitive treatment, and hospital outcomes (mortality, ICU, and hospital stay) were analyzed. Multiple and logistic regression analyses were used to examine the relationship between type of management and hospital outcomes.

Results: Of a total of 945,326 blunt trauma admissions, 517 patients (0.05%) had injuries to the renal artery. Of the 517 patients, the kidney was not explored in 376 (73%), 95 (18%) patients had immediate nephrectomy, and 45 (9%) patients underwent surgical revascularization. In 87 of 517 (17%) patients, renal artery injury was the only intraabdominal injury. Of the 87 patients with isolated renal artery injuries, 73 (84%) were observed, 7 (8%) underwent surgical revascularization, and 7 (8%) had early nephrectomy. Multiple regression analysis demonstrated that patients who had surgical revascularization had a considerably longer ICU and hospital stay than observed patients. Patients who had nephrectomy had a considerably longer hospital stay than observed patients.

Conclusions: Blunt renal artery injury is rare. Nonoperative management should be considered as an acceptable therapeutic option.

Editorial Comment

The National Trauma Data Bank (NTDB) is a very useful and powerful database tool for which one can perform outcomes research of urological trauma. Access to the data is free and can easily be accessed over the internet. The NTDB is a nation wide trauma registry from trauma centers across the United States and Puerto Rico, and contains over 2 million records. The goal of the NTDB is to inform the medical community, the public, and decision makers about a wide variety of issues that characterize the current state of care for injured persons. The information contained in the data bank has implications in many areas including epidemiology, injury control, research, education, acute care, and resource allocation. The NTDB is a very useful and powerful database tool for which one can perform outcomes research of urological trauma. Access to the data is free and easily accessed over the internet.

As to blunt renal artery injuries that result in intimal injury and subsequent arterial thrombosis, Sangthong et al report on their review of renal injuries from across the US. Clearly, when there are two normal kidneys and the patient has normal renal function, renal artery thrombosis is best managed conservatively. Even when recognized promptly, exploration and renal artery repair is often not successful, and when successful, typically preservation of renal function is very poor. Exploration is indicated, however, in cases of injured solitary kidneys or in the very rare instance of bilateral renal artery thrombosis.

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PATHOLOGY

Positive-Block Ratio in Radical Prostatectomy Specimens Is an Independent Predictor of Prostate-Specific Antigen Recurrence

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Background: Tumor volume has been considered an important variable in determining the probability of disease progression in prostatic adenocarcinoma. There have been many studies that have tried to determine an appropriate method of calculating tumor volume, but no single methodology has been agreed upon. We tested the hypothesis that the ratio of tumor positive tissue blocks to the total number of blocks submitted (positive-block ratio) can be used as an independent prognostic indicator for disease recurrence.

Design: We analyzed 504 patients who underwent total radical retropubic prostatectomy between 1990 and 1998. None of the patients had preoperative radiation or androgen-deprivation therapy. Clinical records were reviewed.

Results: The mean positive-block ratio was 0.44 (median, 0.43; range, 0.05-1.0). The positive block-ratio was significantly associated with Gleason score, pathologic stage, surgical margin status, extraprostatic extension, seminal vesical invasion, lymph node metastasis, perineural invasion, and preoperative serum PSA level (all $P < 0.001$). Using a multivariate Cox regression model, controlling for pathological stage, Gleason score, and surgical margin status, positive-block ratio was an independent predictor of PSA recurrence (hazard ratio, 2.4; 95% confidence interval, 1.1-5.1; $P = 0.02$). Five-year PSA recurrence-free survival was 67% for those patients with positive-block ratio 0.43, as compared to 42% those with positive-block ratio > 0.43 ($P < 0.001$).

Conclusions: Positive-block ratio is an independent predictor of PSA recurrence and we recommend that this variable be recorded in radical prostatectomy specimens.

Editorial Comment

One of the most controversial aspects of the pathologic assessment of radical prostatectomy specimens is the measurement of tumor volume (1). No accepted standard exists for reporting cancer volume in prostatectomy specimens (2). Some institutions have calculated tumor volume accurately using computer-assisted image analysis systems. Because this method is not feasible for routine clinical practice, other investigators have proposed alternative simpler means of measuring tumor volume including diameter of largest tumor focus, number of tumor foci, number of involved blocks, percentage of blocks involved, use of a grid with 3.0 mm squares, or naked eye examination of the glass slides after the pathologist had circled all microscopically identifiable foci of carcinoma with a marking pen (the pathologist's percentage estimate) (3-7). The method for evaluating tumor extent applied and proposed in the study by Marks et al. is based in the positive-block ratio and is a simple one and accessible to all general pathologists. Actually is easier than the one we proposed based on a point count method (8).

Numerous studies have documented that tumor extent, volume and percentage of prostatic tissue involved by tumor within the prostate gland are important prognostic indicators. Tumor extent has been correlated with histologic grade, clinicopathologic stage, extraprostatic extension, seminal vesicle invasion, metastasis, tumor progression, and patient survival rate (6).

Although most authors agree that tumor size (percentage of carcinoma or tumor volume) in patients with prostate carcinoma should be reported in radical prostatectomies because of its prognostic importance, in some analyses, tumor size has not been considered to be an independent predictor of tumor recurrence (1,9). In the study surveyed, Marks et al. have shown that the 5-year biochemical-free progression was 67% for those

patients with positive-block ratio 0.43, as compared to 42% for those with positive-block ratio > 0.43 ($p < 0.001$) and that the positive-block ratio is an independent predictor of biochemical progression.

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Utility of ALK-1 Protein Expression and ALK Rearrangements in Distinguishing Inflammatory Myofibroblastic Tumor from Malignant Spindle Cell Lesions of the Urinary Bladder

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Inflammatory myofibroblastic tumor of the urinary bladder is an unusual spindle cell neoplasm that displays cytologic atypia, infiltrative growth and mitotic activity mimicking malignant tumors, such as leiomyosarcoma, rhabdomyosarcoma and sarcomatoid carcinoma. The objective of this study was to determine if anaplastic lymphoma kinase (ALK-1) protein expression detected by immunohistochemistry and ALK rearrangements detected by fluorescence in situ hybridization (FISH) were useful in distinguishing inflammatory myofibroblastic tumor from malignant spindle cell tumors of the urinary bladder. In inflammatory myofibroblastic tumor, ALK-1 expression was identified in 13 of 21 cases (62%) and ALK rearrangements in 14 of 21 cases (67%). All cases of inflammatory myofibroblastic tumor demonstrating ALK-1 expression, carried ALK rearrangements.

One case negative for ALK-1 expression exhibited ALK rearrangement. ALK rearrangements were more common in women ($P=0.0032$). Leiomyosarcoma, sarcomatoid carcinoma, embryonal rhabdomyosarcoma and reactive myofibroblastic proliferations were negative for ALK-1 protein and ALK rearrangements. Immunohistochemistry using markers of muscle, epithelial, neural, and follicular dendritic cell differentiation showed overlap between inflammatory myofibroblastic tumor with and without ALK gene rearrangements, and between inflammatory myofibroblastic tumor and spindle cell malignancies. However, coexpression of cytokeratin and muscle-specific antigens was unique to inflammatory myofibroblastic tumor, observed in approximately half the tumors. This study indicates that detection of ALK protein and ALK gene rearrangements are useful in distinguishing inflammatory myofibroblastic tumor from spindle cell malignancies in the urinary bladder. Additionally, our findings suggest that ALK rearrangement is the primary mechanism for ALK activation and that inflammatory myofibroblastic tumor likely represents a heterogeneous group of spindle cell proliferations with the majority associated with ALK translocations, and the remaining associated with other etiologies.

Editorial Comment

Inflammatory myofibroblastic tumor is a rare lesion occurring at a number of anatomic sites, including the urinary bladder. The vast majority of these tumors behave in a benign fashion, although occasionally tumors can recur following surgical excision. Due to the fact that displays cytologic atypia, infiltrative growth and mitotic activity, the tumor mimics aggressive malignant tumors, such as leiomyosarcoma and sarcomatoid carcinoma.

The differential diagnosis is of utmost importance and particularly difficult for the pathologist. The sarcomatoid variant of urothelial carcinoma is a very aggressive tumor. In a study by Lopez-Beltran et al., 70% of patients died of cancer at 1 to 48 months (mean 17 months) (1). Leiomyosarcoma is a rare malignant mesenchymal tumor that arises from urinary bladder smooth muscle and is the most common sarcoma of the urinary bladder. Although previous reports suggest that 5-year survival after partial or radical cystectomy approaches 70%, the largest recent study indicates that 70% of patients with leiomyosarcoma developed recurrent or metastatic disease, resulting in death in nearly half (2).

The study by Sukov et al. emphasizes the importance of immunohistochemistry as a help for the pathologist in the differential diagnosis of spindle cell lesions of the urinary bladder. In inflammatory myofibroblastic tumor there is a clonal aberration typically involving chromosome 2p (3). This results in rearrangement of the ALK gene which codifies a receptor of tyrosine-kinase and hence over-expression of ALK-1 protein which is disclosed by immunohistochemistry in up of 62% of the cases.

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INVESTIGATIVE UROLOGY

Digital Three-Dimensional Modeling of the Male Pelvis and Bicycle Seats: Impact of Rider Position and Seat Design on Potential Penile Hypoxia and Erectile Dysfunction

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Objective: To digitally model (three-dimensional, 3D) the course of the pudendal arteries relative to the bony pelvis in the adult male, and to identify sites of compression with different bicycle riding positions as a potential cause of penile hypoxia and erectile dysfunction.

Subjects and Methods: 3D models were made from computed tomography scans of one adult male pelvis (a healthy volunteer) and three bicycle seats. Models were correlated with lateral radiographs of a seated rider to determine potential vascular compression between the bony pelvis and seats at different angles of rider positioning. **Results:** Pelvis/seat models suggest that the most likely site of compression of the internal pudendal artery is immediately below the pubic symphysis, especially with the rider leaning forward. For an upright rider, the internal pudendal arteries do not appear to be compressed between the seat and the bony pelvis. Leaning partly forward with arms extended, the seat/symphysis areas were reduced to 73 mm(2) with standard seat and 259 mm(2) with a grooved seat. Leaning fully forward, the seat/symphysis areas decreased (no space with standard seat; 51 mm(2) with a grooved seat) and both the ischial tuberosities and the pubic symphysis might be in contact with the seat.

Conclusion: A grooved seat allows better preservation of the seat/symphysis space than a standard seat, but the rider's position is more important for preserving the seat-symphysis space (and reducing compression) than is seat design alone. Any factors which influence the seat-symphysis space (including an individual's anatomy, seat design and rider position) can increase the potential for penile hypoxia and erectile dysfunction/perineal numbness.

Editorial Comment

The first published article associating bicycling with erectile dysfunction appeared 20 years ago and referred to a man riding a stationary bicycle that experienced transient tight sensations around the glans penis during the exercise and progressive impairment of sexual potency over a period of more than one year. After lowering the bicycle seat the attacks of impaired penile sensation disappeared, and one month after the patient discontinued the bicycle exercises, sexual potency returned (1). The authors proposed a vascular compression for explain the abnormal penile sensation and a neural compression for impotence (1). Ten years later, a study included 260 participants in a Norwegian annual bicycle touring race of 540 km. Thirty-five of 160 responding males (22%) reported symptoms from the innervation area of the pudendal or cavernous nerves. Thirty-three had penile numbness or hypoesthesia after the tour. In 10, the numbness lasted for more than one week. Impotence was reported by 21 (13%) of the males. It lasted for more than one week in 11, and for more than one month in three. The symptoms afflict both experienced cyclists and novices. In some, the complaints may last up to eight months. The authors concluded that changing the hand and body position on the bike, restricting the training intensity, and taking ample pauses might also be necessary in prolonged and vigorous bicycle riding to prevent damage to peripheral nerves (2). Since then, many studies showed the association of bicycling with erectile dysfunction and genital numbness as well as associated the symptoms with the body position and bicycle characteristics (3,4).

The present study by Gemery et al. created digital 3-dimensional models of pelvis, pudendal arteries and bicycle seats to evaluate potential sites of compression of the vessels. The authors hypothesized that the

type of seat in conjunction with the rider's position differentially affects the orientation and compression of the pudendal arteries. This precise morphological study supports the hypothesis that the compression occurs between the top of the forward portion of the bicycle seats and the undersurface of the pubic symphysis, and is associated with the rider's position. Based on their results, the authors suggested that the rider's position has a greater role than seat design in potential compression.

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Comparative Study of Degree of Renal Trauma between Amplatz Sequential Fascial Dilation and Balloon Dilation during Percutaneous Renal Surgery in an Animal Model

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Urology. 2007; 69: 586-9

Objectives: To compare two commonly used methods of dilation, the Amplatz sequential fascial (ASF) and the balloon dilator, in a porcine model.

Methods: Fourteen kidneys from 9 female pigs were used for this experiment. One kidney of each pig underwent ASF dilation and the other underwent balloon dilation using the Nephromax balloon. This was achieved after percutaneous renal puncture with an 18-gauge needle under fluoroscopic guidance. The effects of both methods of dilation were assessed immediately in 1 pig, after 24 hours in 3 pigs, at 4 weeks in 4 pigs, and at 6 weeks in 1. The animals were killed, and the kidneys were removed for gross and histologic examination.

Results: Grossly, the ASF dilated tracts appeared rounded and the balloon dilated tracts appeared V-shaped with lateral fragmentation within 24 hours. No obvious gross differences were noted at 4 to 6 weeks between the two methods of dilation, with both appearing as fine scars. Histologically, minor differences were seen at 4 to 6 weeks, with slightly more abscesses and larger scar formation in the kidneys that underwent ASF dilation than in the balloon dilation group.

Conclusions: In this porcine animal model, the degree of renal trauma induced by the ASF dilators and the balloon dilators during percutaneous renal surgery seems to be comparable. The acute and chronic renal parenchyma effects of both methods of tract dilation were almost similar. The choice of nephrostomy tract dilation should be by physician preference.

Editorial Comment

This is an interesting animal model study comparing the two most common methods of nephrostomy tract dilation in USA; Amplatz sequential fascial (ASF) dilators and balloon dilators. The study aimed to determine whether any significant differences in renal trauma were present between the two techniques both acutely (immediate to 24 hours) and chronically (at 4 to 6 weeks) in pigs. The authors chosen the best animal model for this kind of analysis, since the renal collecting system, the intrarenal arteries and the kidney morphometric parameters are very similar between pigs and humans (1,2).

The analysis was macroscopic and microscopic. The histologic examination at 24 hours showed no apparent differences, except for the degree of hemorrhage, which was slightly more in the ASF dilated tracts. However, in the specimen removed at 4 to 6 weeks after ASF dilation, slightly more inflammation with abscess formation was present in the ASF dilated tracts than in the balloon-dilated tracts.

The slight differences were not significant and the authors demonstrated that the use of either method of dilation had no difference in terms of the degree of renal parenchymal trauma. Therefore, they concluded that the method of dilation is a matter of physician preference and experience.

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RECONSTRUCTIVE UROLOGY

New Technique of Total Phalloplasty with Reinnervated Latissimus Dorsi Myocutaneous Free Flap in Female-to-Male Transsexuals

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From December 2001 to September 2005, the technique of total penile reconstruction with a reinnervated free latissimus dorsi myocutaneous flap was used in 22 patients (24-38 years old) with gender dysphoria. These patients were followed up for at least 11 months (range, 11-44 months). All flaps survived. Complications include hematoma (7 cases), vascular thrombosis (2 cases), partial necrosis (1 case), excessive swelling of the

neophallus (3 cases), and skin graft loss at the donor site (1 case). Of the 19 patients included in the final evaluation, the transplanted muscle was able to obtain contraction in 18 (95%) cases and 8 patients (42%) had sexual intercourse by contracting the muscle to stiffen and move the neopenis. The described technique of neophalloplasty proved to be a reliable technique and the muscle movement in the neophallus can be expected in almost all cases. The muscle contraction in the neophallus leads to “paradox” erection-stiffening, widening, and shortening of the neopenis, which allows for sexual intercourse in some patients. Subsequent reconstruction of the urethra is possible.

Editorial Comment

Functioning free muscle flaps have recently been shown to successfully restore volitional voiding in patients with acontractile bladders (1). Apart from the anastomosis of the flap, vasculature to suitable vessels at the recipient site function is achieved by microsurgical coaptation of the motor nerve supplying the flap muscle to a recipient motor nerve supplying an abdominal muscle. The transferred muscle starts acting as a “piggyback” muscle to the same muscle with which it shares its new innervation.

The authors of this paper have applied the same principle for phalloplasty in female-to-male transsexuals. In addition to obtaining a neophallus, the majority of patients were able to contract the muscle after a mean of 4 months. Almost half of the patients used the muscle contraction to stiffen the penis and were thus able to have intercourse.

Contrary to the sole use of latissimus dorsi muscle in detrusor, myoplasty phalloplasty needs a large portion of the overlying skin similar to musculocutaneous flaps used for breast reconstruction. Therefore, the rate of donor site morbidity was larger than previously reported (2), but according to the authors, 83 % considered donor site morbidity as acceptable.

The fact that no urethral reconstruction was done in these patients may be seen as a downfall. However, the possibility of actively stiffening the neophallus may be appealing for some patients. The mean follow-up of almost two years with some patients just followed for a year is too short. Some patients apparently had considerable shrinkage of the graft and this number might get larger with a longer follow-up. However, the concept of using a functioning muscle transfer for phalloplasty is worth to be considered and shows furthermore the possible versatility of this technique applicable in various fields of urology.

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Porcine Small Intestinal Submucosa Graft for Repair of Anterior Urethral Strictures

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Eur Urol. 2007; 51: 1702-8

Objectives: We evaluated porcine small intestinal submucosa (SIS) used in the treatment of inflammatory, iatrogenic, posttraumatic, and idiopathic strictures of bulbar and penile urethra. Midterm maintenance of urethral patency was assessed.

Methods: Fifty patients aged 45-73 yr with anterior urethral stricture underwent urethroplasty using a porcine SIS collagen-based matrix for urethral reconstruction. Stricture was localized in the bulbar urethra in 10 patients, the bulbopenile area in 31 cases, and in the distal penile urethra in nine patients. All patients received a four-layered SIS patch graft in an onlay fashion. A voiding history, retrograde and antegrade urethrography, and cystoscopy were performed preoperatively and postoperatively. Failure was defined as stricture confirmed on urethrogram.

Results: After a mean follow-up of 31.2 mo (range: 24-36 mo), the clinical, radiological, and cosmetic findings were excellent in 40 (80%) patients. Restricture developed in one of 10 bulbar, five of 31 bulbopenile, and four of nine penile strictures. These all occurred in the first 6 mo postoperatively. All patients with recurrences needed further therapy, but there has been no additional recurrence observed to date. No complications such as fistula, wound infection, UTI, or rejection were observed.

Conclusions: Use of inert porcine SIS matrix appears to be beneficial for patients with bulbar and bulbopenile strictures. Midterm results are comparable to skin flaps and mucosal grafts.

Editorial Comment

Several recent reports have used porcine small intestinal submucosa (SIS) produced either commercially or by individual laboratories as a substitute for autologous flaps in urethral stricture surgery. The initial experimental results were promising (1,2), however, clinical results were mixed (3).

When using porcine acellular matrix, it might be applied either alone functioning as a scaffold for the ingrowths of the neighboring healthy urethra or together with cultivated urothelial cells as urethral wall substitute.

The authors of this contribution used commercially available porcine SIS in an onlay fashion for bulbar, bulbopenile, and distal penile urethral defects after careful excision of strictured urethral segments. The results were acceptable for bulbar strictures but clearly unsatisfactory for penile and bulbopenile strictures. One should be cautious with the interpretation of the results in bulbar strictures: one of ten patients with bulbar stricture surgery recurred after 24 – 36 months. Considering the small number in this subgroup and the possibility of further recurrences with longer follow-up one has to question the use of xenogenic acellular matrices over autologous free flaps such as buccal mucosa. Recent experimental studies have shown that at least in commercial products there are nuclear remnants identifiable within the matrix of the presumably acellular small intestinal submucosa suggesting possible remnant donor DNA (4). Under in vitro conditions, it was also seen that human urothelial cell growths was grossly impaired. Furthermore, SIS so far did not yield any other obvious benefit for patients nor does it help to reduce any surgical costs. We therefore have to continue our search for suitable biomaterials in urethral reconstructive surgery. Until we succeed to find something current standard techniques such as buccal mucosa are the best and safest choice.

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UROLOGICAL ONCOLOGY

Delay of Radical Prostatectomy and Risk of Biochemical Progression in Men with Low Risk Prostate Cancer

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J Urol. 2006; 175: 1298-302; discussion 1302-3

Purpose: Men newly diagnosed with prostate cancer are faced with multiple treatment options. Understanding these options and their associated side effects, and making a decision often requires time, resulting in a delay before receiving treatment. This is particularly pertinent in men with low risk disease who may be considered candidates for watchful waiting and, thus, may not experience strong pressure to undergo treatment promptly. Whether delays and especially prolonged delays, eg greater than 180 days, before RP negatively impact the disease outcome is unclear.

Materials and Methods: We examined the association between time from diagnosis to surgery, and pathological features of the RP specimen and risk of biochemical progression in 895 men with low risk prostate cancer (prostate specific antigen less than 10 ng/ml and biopsy Gleason sum 6 or less) treated with RP between 1988 and 2004 in the Shared-Equal Access Regional Cancer Hospital Database using logistic regression and Cox proportional hazards, respectively.

Results: Time from biopsy to surgery was not significantly related to high grade disease in the RP specimen, positive surgical margins or extraprostatic extension (all p-trend >0.05). After adjustment for multiple clinical covariates a longer time from biopsy to surgery was significantly associated with an increased risk of biochemical progression (p-trend = 0.002). However, this increased risk of progression was only apparent in men with delays greater than 180 days (median 263, vs 90 or fewer days RR 2.73, 95% CI 1.51 to 4.94).

Conclusions: Our data suggest that patients with low risk prostate cancer can be reassured that immediate treatment is not necessary. Whether long delays (greater than 180 days) decrease the likelihood of curability in some patients requires further study.

Editorial Comment

In contrast to the detrimental effects of delaying radical therapy in bladder cancer too long, the effect in prostate cancer treatment is different. Here, the window is open for a longer time, but still begins to close

measurably after half a year. The practical advice is to give the patient time enough to evaluate his treatment options and not proceed in a hurry. Then do your job thoroughly.

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Complications and Other Surgical Outcomes Associated with Extended Pelvic Lymphadenectomy in Men with Localized Prostate Cancer

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Eur Urol. 2006; 50: 1006-13

Objectives: More-extensive pelvic lymph node dissection (PLND) may be associated with a higher rate of complications and a longer hospital stay than more limited PLND.

Methods: Before radical retropubic prostatectomy, PLNDs were performed in 963 patients. Of these, 767 (79.6%) had ≥ 10 lymph nodes removed and examined (extended PLND [ePLND]), while 1-9 nodes (limited PLND [lPLND]) were removed in the remaining 196 (20.4%). Limits included external iliac, obturator, internal iliac, and iliac bifurcation. PLND-related complications and the length of hospital stay were recorded prospectively and analyzed according to the extent of PLND.

Results: In patients subjected to ePLND, the overall rate of complications was 19.8% versus 8.2% in those treated with lPLND ($p < 0.001$). In individual analyses of specific complications, only the lymphocele rate was significantly higher after ePLND (10.3% vs 4.6%; $p = 0.01$). Similarly, ePLND translated into a longer hospital stay (9.9 vs 8.2 d; $p < 0.001$). These differences persisted when adjustment was made for prostate-specific antigen and either clinical or pathologic tumor characteristics.

Conclusions: Our data indicate that, even in the hands of experienced urologic surgeons, ePLNDs are associated with higher complication rates and longer hospital stay. These detriments need to be taken into account when the staging benefit associated with ePLND is considered.

Editorial Comment

This is a timely article suitable into the actual discussion on the extend of lymph node dissection in radical prostatectomy (RP). The authors state clearly that extended lymph node dissection (eLND) leads to more complications and prolongs hospital stay. Therefore they caution against a too generous use of eLND before the benefits of this approach is clearly established.

Lymphoceles occurred in 10.3% vs. 4.6% of patients and blood loss was higher in eLND (median 1200 mL) vs. Limited LND (median 1000 mL). The drawbacks of this article are its obvious retrospective approach and the very few numbers of lymph nodes in both arms (median 7 in the “limited” vs. 17 in the “extended” LND).

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NEUROUROLOGY & FEMALE UROLOGY

Displacement and Recovery of the Vesical Neck Position during Pregnancy and After Childbirth

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Neurourol Urodyn. 2007; 26: 372-6

Aims: (i) To describe the displacement and recovery of the vesical neck position during pregnancy and after childbirth and (ii) to discriminate between compliance of the vesical neck supporting structures with and without pelvic floor contraction.

Methods: We focussed on the biomechanical properties of the vesical neck supporting structures during pregnancy and after childbirth by calculating the compliance and the hysteresis as a result from of abdominal pressure measurements and simultaneous perineal ultrasound.

Results: This study shows that compliance of the supporting structures remains relatively constant during pregnancy and returns to normal values 6 months after childbirth. Hysteresis, however, showed an increase after childbirth, persisting at least until 6 months post partum.

Conclusions: Vaginal delivery may stretch and or load beyond the physiological properties of the pelvic floor tissue and in this way may lead to irreversible changes in tissue properties which play an important role in the urethral support continence mechanism.

Editorial Comment

This manuscript reviews the effects of vaginal delivery on the biomechanical properties of the bladder neck and the pelvic tissues that support same. The authors found that the dynamic properties of the pelvic floor tissue only undergo a transient change and by six months, the dynamic component has returned to normal. In contrast, the effects of childbirth on hysteresis (failure of tissue to follow the same course during relaxation as during distention) are permanently altered with pregnancy. It is stated in the manuscript that the changes are potentially secondary to the delivery overwhelming the intrinsic properties of the pelvic floor tissues thus leading to permanent alteration. Along these same lines, the effectiveness of cesarean section in preventing the development of post-partum stress urinary incontinence has already been reported in the literature and reviewed in this journal (1).

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Parameters of Bladder Function in Pre-, Peri-, and Postmenopausal Continent Women without Detrusor Overactivity

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Neurourol Urodyn. 2007; 26: 356-61

Aims: To determine normative data for lower urinary tract function in asymptomatic continent women without detrusor overactivity (DO) across the age span.

Methods: Healthy female volunteers aged ≥ 20 years were recruited from the community. Comprehensive assessment included bladder diary, physical examination, uroflowmetry, and video-urodynamics. Continent women without history of frequent urgency and without DO were selected. Data on bladder storage, voiding and urethral sphincter function, urine output and frequency are presented for pre-, peri-, and postmenopausal women. **Results:** Twenty-four asymptomatic women (mean age 50.2 years, range 22-80 years) met the inclusion criteria, including 7 pre- (29.2 years), 7 peri- (48.8 years), and 10 postmenopausal (66.0 years) women. For all subjects, maximum single voided volume in bladder diary was 500 ml and maximum cystometric capacity was 580 ml (median values). Strong desire to void (SDV) was reported at 287, 366, and 425 ml for pre-, peri-, and postmenopausal groups, respectively. The maximum flow rate was 25, 32, and 23 ml/sec in uroflowmetry and 23, 24, and 18 ml/sec in pressure-flow study, respectively. Median post-void residual volume (PVR) was below 20 ml in all groups. At maximum flow rate subjects voided with detrusor pressures of 29, 26, and 24 cm H₂O, respectively. Maximum urethral closure pressure was 94, 74, and 42 cm H₂O, respectively.

Conclusions: We provide normative data on bladder function in asymptomatic, continent, pre-, peri-, and postmenopausal women without DO.

Editorial Comment

As stated by the authors “this is the first comprehensive evaluation of voiding storage and urethral sphincter function in carefully selected asymptomatic continent, pre-, peri-, and post-menopausal women without DO”. A well-written manuscript that deserves to be included in one’s file of reference articles. Of note is that the rigid criteria used combined with the prevalence of detrusor overactivity and urodynamic/voiding abnormalities yielded a very small study population distilled from a much larger population of volunteers: of the 396 women that initially responded and were interviewed over the telephone only 24 patients met the selection criteria and in addition only 3 of these were over the age of 73 years of age. This finding solidly raises the question of what really is normal with regards to bladder function and voiding habits as opposed to what is physiologic perfection.

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PEDIATRIC UROLOGY

Evolution of Endoscopic Management of Ectopic Ureterocele: A New Approach

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J Urol. 2007; 177: 1118-23; discussion 1123

Purpose: We report the evolution of endoscopic treatment of ectopic ureteroceles from the unroofing technique to a novel approach using concomitant ureterocele double puncture and intraureterocele fulguration. We also compare the results of different endoscopic modalities at a single center.

Materials and Methods: We reviewed the records of 46 children with ectopic ureteroceles who were treated endoscopically between 1995 and 2005. The patients were divided into 2 main groups. Group 1 included 17 patients who underwent common endoscopic treatments, including ureterocele incision (4 patients), single ureterocele puncture (4), and single puncture with insertion of a Double-J stent (9). Group 2 included 29 children who underwent ureterocele double puncture and fulguration of the anterior and posterior walls of the collapsed ureterocele after insertion of a Double-J stent into both punctured sites. We also managed concomitant vesicoureteral reflux by endoscopic injection of tricalcium phosphate ceramic into the subureteral region.

Results: Total success rates in group 1 were 0%, 25% and 33% in patients who underwent ureterocele incision, single ureterocele puncture and single puncture with insertion of a stent, respectively. Total success rate in group 2 was 90% ($p < 0.05$). New onset vesicoureteral reflux developed in 8 patients (47%) in group 1, of which 6 were in ureterocele moieties, and in 8 patients (28%) in group 2, with none in a ureterocele moiety ($p < 0.01$). A total of 13 patients (76%) in group 1 required open surgical intervention, compared to 3 (10%) in group 2 ($p < 0.05$).

Conclusions: This new endoscopic approach is highly effective in the treatment of children with ectopic ureteroceles.

Editorial Comment

The treatment of ureteroceles has for the last decade and a half has swung towards endoscopic incision with subsequent management as necessary. Success rates vary significantly and there are articles such as Ben Meir et al. (1) suggesting that intravesical ureteroceles do very well with incision techniques while ectopic ureteroceles do not have such good results.

I think this manuscript is remarkable in that only 10% of the patients with the new approach needed open surgery and the remainder of the ectopic ureteroceles could be managed endoscopically. Preoperative and postoperative reflux can be a problem. These authors successfully managed it with injection therapy in many patients. There is concern that the ureteroceles have poor muscular backing and that this procedure in the long-term may lead to bladder diverticula. One would expect with 8 years follow up in some of their patients that perhaps some of those would have been seen by now. Presumably, the longest term follow up patients were the ones with incisions were not the ones with the two incisions and the double-J stent placement.

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Initial Trial of Timed Voiding is Warranted for All Children with Daytime Incontinence

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Objectives: To analyze the relationship between potential prognostic factors and early success after treatment of childhood daytime urinary incontinence without anticholinergic medication.

Methods: A total of 63 patients with daytime urinary incontinence met the inclusion criteria for a retrospective review of the effect of a timed voiding regimen. The severity, duration, and frequency of wetting, along with age, sex, and uroflow parameters, were recorded. Statistical analysis was used to determine the factors predictive of improvement in wetting without anticholinergic treatment.

Results: Of 315 children evaluated with daytime incontinence, only 24% were treated with nonanticholinergic methods. At the first follow-up visit, 6.3% of patients treated without anticholinergics became dry, 38.1% showed significant improvement, 36.5% were slightly improved, and 19.0% were unchanged. Age, sex, duration or severity of wetting, constipation, bladder capacity, and uroflow pattern and parameters were not predictive of early improvement with timed voiding. Patients with good compliance with timed voiding were significantly more likely to improve than those with poor compliance ($P = 0.014$).

Conclusions: The results of our study have indicated that anticholinergic therapy appears to be overused as a first-line treatment for children with daytime urinary incontinence in our clinic population. The lack of reliable predictive factors regarding the response to nonanticholinergic treatment suggests a trial of timed voiding should be used as an initial treatment for all children with daytime urinary incontinence. Almost 45% of our patients had significant improvement in the frequency of wetting within 4 months without anticholinergics.

Editorial Comment

It is interesting in this study to have nearly 45% of the patients have significant improvement without pharmacotherapy and this study would suggest that patients who come to the office for evaluation of daytime incontinence should all have an initial treatment of timed voiding and elimination diaries and a follow up visit prior to instituting drug therapy. Since compliance was the only positive correlate, it would suggest that all efforts in a urologists' office to encourage parental and patient compliance should be attempted to gain the best outcome.

It is surprising in this manuscript that constipation did not have any correlation. Other studies suggest that this is highly correlated but perhaps with the highly selective group and small numbers the authors were not able to find this correlation.

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