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UROLOGICAL SURVEY

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STONE DISEASE

Kidney damage and renal functional changes are minimized by waveform control that suppresses cavitation in shock wave lithotripsy

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Purpose: In studies to understand better the role of cavitation in kidney trauma associated with shock wave lithotripsy we assessed structural and functional markers of kidney injury when animals were exposed to modified shock waves (pressure release reflector shock pulses) that suppress cavitation. Experiments were also performed in isolated red blood cells, an in vitro test system that is a sensitive indicator of cavitation mediated shock wave damage.

Materials and Methods: We treated 6-week-old anesthetized pigs with shock wave lithotripsy using an unmodified HM3 lithotriptor (Dornier Medical Systems, Marietta, Georgia) fitted with its standard brass ellipsoidal reflector (rigid reflector) or with a pressure release reflector insert. The pressure release reflector transposes the compressive and tensile phases of the lithotriptor shock pulse without otherwise altering the positive pressure or negative pressure components of the shock wave. Thus, with the pressure release reflector the amplitude of the incident shock wave is not changed but cavitation in the acoustic field is stifled. The lower pole of the right kidney was treated with 2,000 shocks at 24 kV. Glomerular filtration rate, renal plasma flow and tubular extraction of para-aminohippurate were measured in the 2 kidneys 1 hour before and 1 and 4 hours after shock wave lithotripsy, followed by the removal of each kidney for morphological analysis. In vitro studies assessed shock wave induced lysis to red blood cells in response to rigid or pressure release reflector shock pulses.

Results: Sham shock wave lithotripsy had no significant effect on kidney morphology, renal hemodynamics or para-aminohippurate extraction. Shock waves administered with the standard rigid reflector induced a characteristic morphological lesion and functional changes that included bilateral reduction in renal plasma flow, and unilateral reduction in the glomerular filtration rate and para-aminohippurate extraction. When the pressure release reflector was used, the morphological lesion was limited to hemorrhage of vasa recta vessels near the tips of renal papillae and the only change in kidney function was a decrease in the glomerular filtration rate at the 1 and 4-hour periods in shock wave treated kidneys. Red blood cell lysis in vitro was significantly lower with the pressure release reflector than with the rigid reflector.

Conclusions: These data demonstrate that shock wave lithotripsy damage to the kidney is reduced when cavitation is suppressed. This finding supports the idea that cavitation has a prominent role in shock wave lithotripsy trauma.

Editorial Comment

The Indiana group continues to demystify the phenomena of shock wave lithotripsy and to systematically elucidate the mechanism of shock wave-induced stone fragmentation and tissue injury. Although cavitation has been suggested as a mechanism of stone comminution in shock wave lithotripsy, it has also been implicated in vascular and tissue damage. By placing a pressure release reflector insert into the standard brass ellipsoid reflector of the unmodified Dornier HM3, these investigators were able to "uncouple" shock waves from their cavitation effect without otherwise altering the positive or negative pressure components of the shock wave.

Using a porcine model, they compared shock wave treatment using a standard rigid reflector with shock wave treatment using a pressure release reflector or sham control lithotripsy. They found that shock waves associated with the pressure release reflector resulted in only minor hemorrhage near the renal papillae and a mild decrease in GFR post-treatment in contrast to shock waves administered using the standard rigid reflector which demonstrated characteristic intraparenchymal hemorrhage and subcapsular hematomas as well as more pronounced decreases in renal plasma flow and GFR. Not only do these findings suggest a role for cavitation in shock wave-induced renal tissue injury, but they also imply that alteration of the shock waveform could potentially be used to maximize stone comminution effects or minimize tissue trauma.

Dr. Margaret S. Pearle

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Safety and efficacy of holmium: YAG laser lithotripsy in patients with bleeding diatheses Watterson JD, Girvan AR, Cook AJ, Beiko DT, Nott L, Auge BK, Preminger GM, Denstedt JD Division of Urology, University of Western Ontario, London, Ontario, Canada, and Comprehensive Kidney Stone Center, Division of Urology, Duke University Medical Center, Durham, North Caroline, USA J Urol. 2002; 168:442-5

Purpose: We assessed the safety and efficacy of ureteroscopy and holmium: YAG laser lithotripsy for treating upper urinary tract calculi in patients with known and uncorrected bleeding diathesis.

Materials and Methods: We retrospectively reviewed the charts at 2 tertiary stone centers to identify patients with known bleeding diathesis who were treated with holmium: YAG laser lithotripsy for upper urinary tract calculi. A total of 25 patients (29 upper urinary tract calculi) underwent ureteroscopic holmium laser lithotripsy. Bleeding diathesis involved warfarin administration for various conditions in 17 patients, liver dysfunction in 3, thrombocytopenia in 4 and von Willebrand's disease in 1. The mean international normalized ratio, platelet count and bleeding time were 2.3, 50×10^{9} /L and greater than 16 minutes in patients on warfarin and in those with liver dysfunction, thrombocytopenia and von Willebrand's disease, respectively.

Results: Overall the stone-free rate was 96% (27 of 28 cases) and 29 of 30 procedures were completed successfully without significant complication. In a patient treated concomitantly with electrohydraulic lithotripsy significant retroperitoneal hemorrhage required blood transfusion.

Conclusions: Upper tract urinary calculi in patients with uncorrected bleeding diathesis can be safely managed by contemporary small caliber ureteroscopes and the holmium laser as the only modality of lithotripsy. Ureteroscopic holmium laser lithotripsy without preoperatively correcting hemostatic parameters limits the risk of thromboembolic complications and costs associated with an extended hospital stay. Avoiding electrohydraulic lithotripsy is crucial for decreasing bleeding complications in this cohort of patients.

Editorial Comment

The patient with a symptomatic stone and an uncorrected bleeding disorder presents a challenging therapeutic dilemma. Traditionally, bleeding diatheses have been corrected pre-operatively before any surgical intervention, and treatment with shock wave lithotripsy or percutaneous lithotripsy are still contraindicated with any uncorrected bleeding disorder. However, the improved efficacy and efficiency of ureteroscopy in conjunction with Holmium:YAG laser lithotripsy as well as the increased margin of safety of the Holmium laser has expanded the indications of ureteroscopy for the treatment of upper tract stones to potentially include

treatment of patients with uncorrected bleeding diatheses. The authors reviewed their experience in 25 patients with known bleeding disorders undergoing 30 ureteroscopic procedures without correction of hemostatic parameters. A stone free state was achieved in 96% of cases, and a single bleeding complication (retroperitoneal hemorrhage) occurred in the only patient in whom electrohydraulic lithotripsy was used in addition to Holmium:YAG laser lithotripsy.

Although it is ideal to attempt to a correct bleeding disorder prior to surgical intervention thus maintaining all therapeutic modalities as options for treatment, this series demonstrates the safety of treating symptomatic stone patients with ureteroscopy without correction of their bleeding problems, thereby reducing cost and hospital length of stay and avoiding the risk of discontinuing anticoagulation therapy. Although it is difficult to draw conclusions based on a single bleeding complication, the known lower margin of safety of electrohydraulic lithotripsy suggests that this modality should be avoided in favor of the Holmium: YAG laser. It should also be noted that laser lithotripsy in these patients should be applied gently and judiciously to avoid forniceal or caliceal rupture with subsequent perinephric bleeding.

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ENDOUROLOGY & LAPAROSCOPY _

Laparoscopic linear cutting stapler failure

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Objectives: To characterize the frequency and nature of problems with linear cutting staplers to help prevent complications in the future. These devices are often used during laparoscopic urologic procedures.

Methods: We retrospectively reviewed the experience with laparoscopic linear cutting staplers at two institutions routinely performing urologic laparoscopy and analyzed the difficulties with any staplers. Data from the Food and Drug Administration Center for Devices and Radiological Health were also examined to determine the prevalence and types of reported problems.

Results: In performing approximately 460 laparoscopic cases, we encountered 5 problems (1%) with endovascular gastrointestinal anastomosis staplers. Fifty-five additional cases in 50 patients were documented in the Food and Drug Administration database. Of the 55 patients, 15 (27%) required open conversion to manage the problem, 8 (15%) received blood transfusions, and 2 (4%) died postoperatively. Twenty-two events occurred during 19 laparoscopic donor nephrectomies (35%) without associated graft dysfunction, damage, or loss. All phases of instrument use were subject to problems; however, abnormal firing of the stapler and improper staple formation were the most common and morbid aspects of device malfunction.

Conclusions: Despite the general reliability of linear cutting staplers, difficulties were encountered in every step of use. Most situations were successfully managed by prompt identification and appropriate

intracorporeal maneuvers. Nevertheless, significant morbidity may occur, and conversion to an open operation should be considered. Many potential problems can be avoided by surgeon and staff education, and one should be aware of the alternative methods of tissue ligation currently available.

Editorial Comment

This article follows a similar one by Chan and associates (1), from Johns Hopkins, published in 2000, which summarized 10 cases of linear cutting stapler failure in a series of 565 cases. An interesting feature of the current article is the use of the FDA database to identify an additional 55 cases of staplers malfunction. All the details of this additional group of events are not available, but it is likely, as in the personal series reported in this article, and in the one of Chan and associates (1), that operator error was responsible for many of the stapler malfunctions. Applying the stapler over a clip appears to be the most common mechanism of failure. The second most common problem appears to be bleeding from a staple line, without any apparent technical error. Although I have not reviewed the stapler malfunctions in my personal series (620 laparoscopic cases, including 443 nephrectomies) as carefully as have these authors, I certainly do not think that I've seen 6 to 10 stapler malfunctions (1 to 1.7%), the range noted in these 2 articles. Although I am not able to directly compare my technique to that of Deng and associates and Chan and associates (1), we generally use staplers only on a well dissected renal vein (very rarely on arteries), and we control branches into the vein to be stapled with bipolar electrocautery rather than clips (2). This obviates the most common mechanism of failure, that being the application of the stapler over a clip. The only significant stapler failure that I can recall in my series has been when, in an attempt to address a "sticky" renal hilum, we used the stapler over a mass of tissue that, in retrospect, was too thick to be handled by a stapler. This was an error in judgment; again, user error is the most common cause of stapler failure. The importance of this article and the previous one (1) is to highlight the importance of avoiding these technical errors, and to remind the laparoscopic surgeon that on very rare occasions there can be primary device failure. All laparoscopic surgeons using linear cutting staplers should have a plan worked out in advance in the event of stapler malfunction.

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One versus two proficient laparoscopic surgeons for laparoscopic live donor nephrectomy

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Urology 2002; 60:406-9

Objectives: To compare the laparoscopic donor nephrectomy (LDN) results obtained by two different surgical teams, one consisting of a proficient laparoscopic surgeon assisted by an inexperienced laparoscopic surgeon and another consisting of two proficient laparoscopic surgeons. With more centers embarking on LDN programs, it is important to identify the factors that can improve overall outcomes during the initial learning curve.

Methods: A retrospective review was performed of the initial 70 sequential LDNs performed between October 1998 and March 2001 at our institutions. The procedures were stratified into two groups. Group 1 consisted of LDN cases performed by one proficient laparoscopic surgeon and an inexperienced laparoscopic surgeon (resident, fellow, or faculty) as the first assistant; group 2 consisted of cases performed by two proficient laparoscopic surgeons.

Results: Twenty-six LDNs were performed by group 1 and 44 by group 2. The total operative time and estimated blood loss showed a statistically significant decrease in group 2 compared with group 1, 143 ± 32 minutes versus 218 ± 38 minutes (P<0.001) and 92 ± 115 mL versus 158 ± 148 mL (P=0.044), respectively. Two major complications occurred in group 1 (7.7%) and two major complications occurred in group 2 (4.5%). The 3-month postoperative recipient creatinine levels were similar for both groups, 1.6 ± 1.3 versus 1.4 ± 0.4 (P=0.408).

Conclusions: A surgical team composed of two proficient laparoscopic surgeons during the early learning curve of LDN may allow safe and efficient development of a laparoscopic live donor renal transplantation program.

Editorial Comment

Following this article is an excellent editorial by Cadeddu from Dallas, TX, USA. He correctly points out that, the only clinically significant advantage in this series of having 2 experienced laparoscopic surgeons performing the operation, was a shorter operative time. While this is certainly a reasonable goal, the more important endpoints, such as complications and transplant function, were no different between the two groups. I agree with Cadeddu that the availability of 2 experienced laparoscopic surgeons is a luxury not available at most centers. If such staffing is available, the data in this article confirms that this might decrease operative time, but the centers where such staffing is not available should be reassured by the data as well - in that the important endpoints of complications and transplant function were just as good when there was only one experienced laparoscopic surgeon performing the operation. This is not to say that starting a laparoscopic donor program should be taken lightly; there should be at least one experienced laparoscopic surgeon involved, and preparation should be thorough.

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PATHOLOGY_

Percent Gleason grade 4/5 as prognostic factor in prostate cancer diagnosed at transurethral resection Egevad L, Granfors T, Karlberg L, Bergh A, Stattin P Department of Pathology and Cytology, Karolinska Hospital, Stockholm, Department of Urology, Central Hospital, Västeras and Departments of Pathology and Urology and Andrology, Umea University Hospital, Umea, Sweden J Urol. 2002; 168:509-13

Purpose: To investigate the value of percent Gleason grade 4/5 as a predictor of long-term outcome in men with prostate cancer diagnosed at transurethral resection who received deferred treatment.

Materials and Methods: A series of 305 men with prostate cancer diagnosed at transurethral resection from 1975 to 1990 who had subsequent expectancy was analyzed. Mean patient age at diagnosis was 74 years (range 52 to 95). Slides were reviewed, and the Gleason score, percent Gleason grade 4/5 and modified Gleason score (the sum of the dominant and worst grades) were assessed.

Results: At followup 271 men (89%) had died, including 110 (36%) of prostate cancer. Gleason score, percent Gleason grade 4/5 and modified Gleason score were significant predictors of disease specific survival (p<0.001). Of all men 34% had tumors without any grade 4/5 pattern, of whom only 8% died of prostate cancer compared with 52% with any grade 4/5 pattern (p<0.001). Gleason score 6 tumors with focal grade 4 (less than 5%) had a worse prognosis than pure Gleason score 3+3=6 tumors (p=0.008). There was nonsignificantly shorter survival for Gleason score 4+3=7 than for Gleason score 3+4=7 disease (p=0.19). In Cox models including all possible pairs of Gleason score, percent Gleason grade 4/5 and modified Gleason score the percent Gleason grade 4/5 and modified Gleason score, although all 3 were independently significant prognosticators.

Conclusions: Percent Gleason grade 4/5, modified Gleason score and Gleason score are predictors of disease specific survival in patients with prostate cancer on deferred treatment. Our study indicates that any grade 4/5 pattern impairs the prognosis significantly.

Editorial Comment

The Gleason system is the gold standard for histologic grading of prostate cancer. In spite of an effort by the World Health Organization to combine nuclear anaplasia to the Gleason system, glandular differentiation alone has been strong enough to defer cytology. In his original study (J Urol. 1974;111:58-64), Gleason found that both first and second grades predicted prognosis for prostatic adenocarcinoma, but prognosis was better predicted when both numbers were combined. This fact is clearly shown in the paper commented. There was a non-significantly shorter survival for Gleason score 4+3=7 than for Gleason score 3+4=7 disease (p=0.19). In 1996, the Association of Directors of Anatomic and Surgical Pathology in the United States (Hum Pathol. 1996;27:321), recommended that on prostatic needle biopsies showing 3 grades, the second grade should be the worst, and not the most extensive. This recommendation is also in accordance with the Swedish study. There is not such recommendation for radical prostatectomy, but is worth that the pathologist informs in the report of the surgical specimen the existence of a third grade as well as the extent of grades 4 and/or 5.

Dr. Athanase Billis

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Phenotypic, molecular and ultrastructural studies of a novel low grade renal epithelial neoplasm possibly related to the loop of Henle

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Purpose: To study a novel renal epithelial neoplasm with tubular, spindled and mucinous morphology. This tumor has a female predominance and displays a low grade biologic behavior. The origin of this tumor and its relation to other types of renal carcinoma is poorly understood.

Material and Methods: 20 examples of this light microscopically neoplasm were studied using immunohistochemical (20 cases), molecular (10 cases) and ultrastructural (5 cases) techniques.

Results: The 20 tumors from patients' age 17-82 (mean 53 years) included 16 females and 4 males. The tumors consistently stained for cytokeratins (CAM 5.2, CK7, CK8 and CK 18), EMA, Ulex, peanut and soya bean agglutins. They displayed consistent negativity for CK20, CD10, villin and Tamm-Horsfall protein. 16 cases showed positivity for RCC, a proximal nephron marker. CGH revealed chromosomal alterations detected on 11q, 12q, 16q, 17 and 20q. FISH showed no evidence of VHL deletions and confirmed chromosomal monosomies in a subset of tumors. EM studies showed tightly packed, often elongated tubules composed in part of slender attenuated cells similar to those described in normal loop of Henle.

Conclusions: This novel renal neoplasm displays immunohistochemical heterogeneity with expression of proximal and distal nephronic markers. Molecular analysis allows separation of this tumor entity from common renal epithelial tumors of proximal nephron origin because the latter tumors frequently show 3p deletions (clear cell RCC) or chromosomal 7 gains (papillary RCC). While the immunohistochemical and molecular studies show considerable heterogeneity, the light and electron microscopic studies show a distinct morphologic pattern suggesting a possible histogenetic relationship to the loop of Henle.

Editorial Comment

This is a new comer to the classification of malignant renal cell tumors. Probably this neoplasia was classified by pathologists either as papillary renal cell carcinoma, or placed in the group of the unclassified tumors according to the Heidelberg (J Pathol. 1997; 183:131) or Rochester (Cancer 1997; 80:987) classifications. This tumor has a female predominance and displays a low grade biologic behavior. Pathologists must become aware of its existence. Its morphology is quite distinctive. This paper emphasizes that the histochemical and molecular studies show considerable heterogeneity, but light and electron microscopic studies show a distinct morphologic pattern, suggesting a possible histogenetic relationship to the loop of Henle. A postgraduate student collected 12 tumors of this kind for her doctoral thesis, all from female patients. We had the opportunity to analyze the electron microscopy from 7 of these cases. In all cases, we found discontinuation of the tubular basement membranes. This finding may be a distinct morphologic lesion in this tumor.

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IMAGING_

Evaluation of sonographically guided percutaneous core biopsy of renal masses Caoili EM, Bude RO, Higgins EJ, Hoff DL, Nghiem HV Department of Radiology, University of Michigan Medical Center, Ann Arbor, MI, USA *AJR Am J Roentgenol. 2002; 179:373-8*

Purpose: Our objective was to determine the utility of sonographically guided percutaneous core biopsy to evaluate renal masses.

Material and Methods: We conducted a retrospective analysis of our imaging-guided procedures from January 1999 to June 2001. We performed 26 sonographically guided percutaneous core biopsies of renal masses in 26 patients. From two to five specimens were obtained from a single mass in each patient using an 18-gauge automated biopsy system. We examined the patients' medical records, pathology results, and imaging studies. Core biopsy results were compared with surgical pathology (n=6) or clinical follow-up (n=20).

Results: All biopsies provided sufficient material for analysis. Biopsy findings were positive for malignancy in 19 (73%) of 26 masses. Histologic diagnoses included renal cell carcinoma were (n=11), metastasis (n=3), lymphoma (n=2), and transitional cell carcinoma (n=2). Specific cell type characterization could not be made on one biopsy, but the specimens were highly suspicious for malignancy. Biopsy revealed seven (27%) of 26 benign diagnoses: oncocytoma (n=3), angiomyolipoma (n=2), and fibrosis (n=2). The average follow-up period for patients with benign diagnoses was 10 months. One case of surgically proven necrotic pyelonephritis was mischaracterized as fibrosis at core biopsy. Sonographically guided percutaneous core biopsy of renal masses showed a sensitivity of 100% and a specificity of 100% for the diagnosis of malignancy. The core specimens yielded a specific diagnosis in 92% (24/26) of masses. No immediate complications occurred after the procedure. One patient developed a pseudoaneurysm that presented 3 months after the biopsy.

Conclusion: Sonographically guided percutaneous core biopsy is a reliable and accurate method for evaluating renal masses.

Editorial Comment

The use of percutaneous biopsy of a renal mass has a limited role in the current era of high-quality imaging procedures. The majority of renal masses are treated based on imaging tests (Ultrasound with power Doppler, Helical – CT, and Magnetic Resonance Imaging). By the use of strict radiologic criteria, and the indispensable correlation with clinical and laboratorial data, we can achieve a very high overall accuracy in distinguishing benign versus malignant disease. Although recently described as a useful procedure(1), fineneedle aspiration biopsies are not used routinely. This can be explained by its low sensitivity for detection of malignancy, and undesirable false-negative rates. This method, however, can occasionally be used for cytologic confirmation of an infected cyst or abscess. On the contrary, core biopsy of renal mass is a safe and accurate procedure that may be used in some special clinical and radiologic situations. The authors presented a retrospective review of the utilization of percutaneous ultrasound-guided renal biopsy in 26 patients. From each mass a mean of 3 cores was obtained, and although post biopsies radiologic imaging was not performed in all patients, small perinephric hematoma (1-3 cm) was observed in 19% of patients. One patient developed a pseudoaneurysm with gross hematuria, and a perinephric hematoma requiring arterial embolization. Among these 29 patients, 9 had a known extrarenal neoplasm; 4 had multiple renal masses, 2 had adrenal masses, 2 had suspected renal masses, but were not considered surgical candidates. As we can see by their results, core biopsy of renal masses has few indications, and is used routinely mainly for identifying lymphoma or metastasis from a non-renal primary tumor; this can be confirmed, since only 5 of 26 patients(19%) presented an indeterminate renal mass. The main value of this publication is to show that percutaneous renal biopsy guided by ultrasound is better than when guided by CT (2). Unlike CT, ultrasound allows continuous visualization of the needle as it enters the mass, with much better accuracy (95%). CT-guided biopsy has the drawbacks of occasional movement of the needle when it is manipulated outside the gantry, and the possibility of displacing the mass instead of puncturing it.

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Testicular microlithiasis: prospective analysis of prevalence and associated tumor Middleton WD, Teefey SA, Santillan CS Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, MO, USA Radiology 2002; 224:425-8

Purpose: To evaluate testicular microlithiasis (TM) prospectively with modern state-of-the-art equipment. Material and Methods: Information concerning indication for examination, presence and degree of TM, presence of testicular tumor, and patient age was prospectively recorded for all patients referred for scrotal ultrasonography between 1996 and 1999. High-frequency linear transducers (7.5 MHz or higher) were used. TM was divided into classic (CTM) and limited (LTM) on the basis of the presence of five or more microliths on one or more images of the testes. Fisher exact tests were used for determining significant differences in proportions.

Results: Data in 1,079 patients were analyzed. The overall prevalence of TM was 18.1% (195 of 1,079). Forty (3.7%) patients had CTM, and 155 (14.4%) had LTM; 15 (1.4%) had tumors visible at US. Tumors were present in three (8%) of 40 patients with CTM (seminoma in two, embryonal cell in one), nine (5.8%) of 155 with LTM (seminoma in six, mixed germ cell in one, Leydig cell in two), and three (0.3%) of 884 with no TM (seminoma in two, other in one). There was no difference between CTM and LTM (P = 72) in the rate of coexisting tumor. There was a significant difference between no TM and CTM or LTM (P <= .001) in the rate of coexisting tumor. Eighty percent (12 of 15) of patients with tumor at presentation had CTM or LTM.

Conclusion: Approximately one of 27 patients had CTM, and one of seven had LTM. Although a majority of patients with testicular tumors had coexistent TM, more than 90% with TM (both CTM and LTM) did not have tumor at presentation.

Editorial Comment

Testicular microliths (TM) occur in the lumen of seminiferous tubules, and represent calcified cores smaller than 1mm in diameter, surrounded by collagen fibers. TM is usually furthered categorized as classic microlithiasis (CTM), if at least one image of the scrotal US examination shows five or more microliths in either or both testes, and LTM, when the image show at least one microlith. TM has been considered in the last few years an imaging marker of testicular cancer, with several reports recommending serial scrotal ultrasound in order to detect testicular tumor in asymptomatic patients (1,2). Some authors reported that 30-40% of patients with TM had testicular tumors. However, others studies has shown that testicular microlithiasis is common in a screening in an asymptomatic population, with a prevalence of 5.6%, and a significant higher prevalence among afro-Americans, and that this entity is not likely associated with testicular cancer (3).

The authors presented a prospective study of one thousand seventy-nine patients which underwent scrotal US. TM was detected in 18.1% of patients; 3.7% had CTM, and 14.4% had LTM. The prevalence of testicular tumor was 1.4% (15 of 1,079), with 80%(12 of 15) associated with CTM or LTM at presentation. Only 8% (3 of 40) patients with CTM had tumors, and 5.8% (9 of 155) with LTM had tumors. On the other hand, only 0.3% (3 of 884) patients without TM had testicular tumor. This results shows that there is a significant difference in patients with and those without TM, and this fact emphasizes that TM and tumors are linked in some way. The authors concluded that the retrospective studies performed in the past have led to underestimation of the prevalence of TM, and overestimation of the risk of coexisting tumor. They estimated that CTM would be detected in one of every 27 patients, and LTM in one of every 7 patients. They also estimated that the risk of coexisting TM and testicular tumors is 5-10%, rather than 30-40% as previously reported.

As we can see, this subject has becoming less and less controversial, but a large long-term prospective study using high-resolution US for follow-up is needed. From a practical point of view, such study is necessary to demonstrate whether the patients with TM need or not serial US examination, or if they can be safely managed only by clinical follow-up.

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INVESTIGATIVE UROLOGY_

Autologous penile corpora cavernosa replacement using tissue engineering techniques Kwon TG, Yoo JJ, Atala A Department of Urology, Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA J Urol. 2002; 168:1754-8

Purpose: The availability of engineered tissues would be beneficial to patients undergoing penile reconstruction. We explored the possibility of replacing an entire cross-sectional segment of both corporal bodies with autologous engineered tissues in rabbits, and investigated the structural and functional integrity of the neo-corpora.

Materials and Methods: Acellular corporal collagen matrices were obtained from donor rabbit penis. Autologous corpus cavernosal smooth muscle and endothelial cells were harvested, expanded and seeded on the matrices. An entire cross-sectional segment of protruding rabbit phallus was excised, leaving the urethra intact. A total of 26 matrices, including 18 seeded with cells and 8 without cells, were interposed into the

excised corporal space. An additional 4 rabbits that did not undergo surgical intervention served as normal controls. Functional and structural parameters (cavernosography, cavernosometry, mating behavior and sperm ejaculation) were followed for 6 months. Gross examination, and histochemical, immunocytochemical and Western blot analyses were performed at 3 and 6 months after implantation.

Results: The experimental corporal bodies demonstrated intact structural integrity on cavernosography and decreased maximal intracavernosal pressures on cavernosometry compared to normal controls. Mating activity in animals with engineered corpora normalized by 3 months postoperatively. The presence of sperm was confirmed during mating and was present in all rabbits with engineered corpora but in only 2 with the matrix alone. Histologically sinusoidal spaces and walls lined with endothelial and smooth muscle cells were observed in the engineered grafts. Each cell type was identified immunocytochemically. Grafts without cells contained fibrotic tissue and calcifications with sparse corporal elements. Western blot analysis of engineered grafts showed nitric oxide synthase activity similar to normal controls.

Conclusions: Autologous corpus cavernosal smooth muscle and endothelial cells seeded on collagen matrices can form corpora cavernosa tissue structures in a rabbit model. Engineered corpora cavernosa achieved adequate structural and functional parameters. This technology may be applicable to patients who require additional tissue for phallic reconstruction.

Editorial Comment

The authors replaced in vivo entire cross-sectional segments of corpora cavernosa in the protruding penis in rabbits by interposing autologous engineered tissue, and provided encouraging data on erectile function and structural integrity. The authors should be commended for this wonderful work that represents a very important step towards the replacement of human penile tissue.

The authors have used acellular matrices obtained from homologous corpus cavernosum, seeded with autologous smooth muscle and endothelial cells. The engineered grafts had sinusoidal structures similar to normal controls, and were composed of multiple smooth muscle layers surrounding layers of endothelial cells. The functional evaluation showed that the present engineered corpora cavernosa may not achieve full erection, but it can show sufficient erectile activity for penetration and adequate sexual function.

Phallic reconstruction using conventional methods, such as free flaps or prosthetic devices, has not been uniformly satisfactory. Thus, a large number of congenital and acquired abnormalities of the genitalia would benefit from the availability of transplantable, autologous corpus cavernosum tissue for reconstructive procedures.

Dr. E. Alexsandro da Silva

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Effects of various nitric oxide donating agents on the contractility and cyclic nucleotide turnover of human seminal vesicles in vitro

Heuer O, Uckert S, Machtens SA, Stief CG, Tsikas D, Frolich JC, Jonas U Department of Urology, Hannover Medical School, Hannover, Germany Urology 2002; 59:958-62

Objectives: To evaluate the effects of the nitric oxide (NO)-donating drugs sodium nitroprusside, Snitroso-glutathione (GSNO), S-nitroso-N-acetylcysteineetylester (SNACET), and linsidomine (SIN-1), as well as the adenylyl cyclase-stimulating agent forskolin, on electrically induced contractions and on tissue levels of cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) of isolated human seminal vesicle strip preparations. The significance of the L-arginine-NO-cGMP pathway in the regulation of smooth muscle tone in the human genitourinary tract has been well established; however, information on the relevance of NO-mediated signal transduction in the functional control of mammalian seminal vesicles is still sparse.

Methods: Seminal vesicle strip preparations were applied to an organ bath system under standard conditions. Phasic contractions were induced by electrical field stimulation (frequency 80 Hz, amplitude 10 V, single pulse 1 ms, total pulse duration 1 second, pause 90 seconds). After stable contraction amplitudes had been reached, the drugs were added in a cumulative manner (0.001 to 10 microM), and the isometric responses were registered. After drug exposure, freezing, tissue homogenization, and extraction of cyclic nucleotides, cAMP and cGMP were measured by means of enzyme-linked immunosorbent assays.

Results: Electrical field stimulation-induced amplitudes were attenuated by the drugs in a dose-dependent manner. The rank order of potency was GSNO > sodium nitroprusside > forskolin > SNACET > or = SIN-1. The relaxing effect of GSNO was antagonized in the presence of 10 microM of guanylyl cyclase inhibitor methylene blue. The inhibitory effects of GSNO, sodium nitroprusside, and forskolin on the contractile activity were paralleled by an increase in tissue cGMP (2 to 100-fold) and cAMP (7 to 9-fold).

Conclusions: Our results strongly support the hypothesis that the contractility of human seminal vesicles is in part regulated by the NO-cGMP-cascade. This may give a rationale for the use of S-nitrosothiols, such as GSNO, in the pharmacotherapy of hyperexcitatory disturbances of ejaculation.

Editorial Comment

Ejaculation is a multifunctional process involving sympathetic neuronal input, release of the ductus ejaculatory closure resistance and coordinated contraction of seminal vesicle and ductus deferens smooth muscle. In this context, normal regulation of seminal vesicle smooth muscle tension contributes to the facilitation of seminal emission, and defects at the level of neuromuscular control may result in impaired ejaculatory function (i.e., anejaculation or premature ejaculation).

The authors provide interesting data regarding the role of NO-cGMP pathway in the regulation of seminal vesicle smooth muscle tone. In their results, neurogenic contractions of isolated seminal vesicle strips were most effectively reversed by the NO-donating drugs sodium nitroprusside (NNP) and S-nitroso-glutathione (GSNO). These attenuating effects were paralleled by an increase in tissue cGMP, but not cAMP. However, evidence that forskolin was not as effective as GSNO and NNP in the organ bath studies may highlight the fact that cAMP-mediated mechanisms of smooth muscle control are of inferior significance in the seminal vesicles. The increase in tissue cAMP mediated by linsidomine might be explained the as the increase in cGMP exerted by the activation of guanylyl cyclase may result in an inhibitory effect on phosphodiesterase (PDE) type 3 (cGMP-binding, cGMP-inhibited PDE), which in turn would induce an elevation of cellular cAMP. Although the expression of PDE3 has been demonstrated in human genitourinary tract tissues, such as the urinary bladder and corpus cavernosum penis, data on the presence of PDE isoenzymes in the human seminal vesicle are not yet available.

This is a potentially important paper because presents additional evidence for the hypothesis that the contractility of human seminal vesicle is regulated by the balance between the generation and degradation of NO and cGMP. These findings open new avenues for the clinical management of premature ejaculation.

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HUMAN REPRODUCTION_

Effect of cigarette smoking on levels of seminal oxidative stress in infertile men: a prospective study

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Fertil Steril. 2002; 78: 491-9

Objective: To investigate levels of seminal oxidative stress (OS) and sperm quality in a group of infertile men with a history of cigarette smoking.

Design: A prospective clinical study.

Setting: Male infertility clinic, Urological Institute, the Cleveland Clinic Foundation, Cleveland, Ohio. Patient(s): Infertile men who smoked cigarettes (n=20), infertile men who were nonsmokers (n=32), and healthy nonsmoking donors (n=13).

Intervention(s): Genital examination, standard semen analysis, sperm DNA damage.

Main Outcome Measure(S): Levels of seminal reactive oxygen species (ROS) and total antioxidant capacity (TAC) measured by a chemiluminescence assay and seminal OS assessed by calculating a ROS-TAC score. Sperm DNA damage was measured by sperm chromatin structure assay.

Result(s): Smoking was associated with a 48% increase in seminal leukocyte concentrations (P<.0001), a 107% increase in ROS levels (P=.001), and a 10-point decrease in ROS-TAC scores (P=.003). Differences in standard sperm variables and DNA damage indices between the infertile smokers and infertile nonsmokers were not statistically significant.

Conclusion(s): Infertile men who smoke cigarettes have higher levels of seminal OS than infertile nonsmokers. Given the potential adverse effects of seminal OS on fertility, physicians should advise infertile men who smoke cigarettes to quit.

Editorial Comment

Spermatozoa produce low levels of reactive oxygen species (ROS) as part of their aerobic metabolism. Under normal conditions, sperm ROS are physiologically important. However, nonmotile, abnormal spermatozoa, as well as normal ones that are functionally defective, and seminal plasma leukocytes, produce high amounts of ROS. Elevated seminal reactive oxygen species surpasses the seminal plasma total antioxidant capacity. Consequently, lipid peroxidation of sperm membrane polyunsaturated fatty acids may occur. Lipid peroxidation causes intense proteic damage, cytosqueletal modifications, and inhibition of many cellular mechanisms, thus decreasing the individual fertility status. Oxidative stress may damage sperm DNA, and such damage cannot be measured by any test of the conventional semen analysis.

This study advocates that smoking cigarettes places an additional risk to the already compromised fertility in infertile men. Seminal ROS levels in infertile smokers were very high, which can also be explained by an inflammatory reaction, as evidenced by an increase in the number of seminal leukocytes. It has been shown that leukocytes produce much higher amounts of ROS than spermatozoa. On the other hand, this study did not show any differences in conventional sperm parameters between infertile men who smoke or not. These results are expected, and reiterates what was said about oxidative stress and conventional sperm parameters in the last paragraph. Surprisingly, the authors could not show increased sperm DNA damage in infertile smokers, despite the elevated ROS levels in these individuals. The inclusion of an additional group of healthy smokers could strengthen the study by reiterating the negative impact of smoking cigarettes on the fertility potential of otherwise fertile men.

Besides the preventive approach as proposed by the authors, strategies to minimize oxidative stress have been studied. However, oral supplementation with antioxidants such as vitamin C and E, among others, is merely empirical to date (1).

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Dr. Sandro C. Esteves Androfert Campinas, SP, Brazil

Lack of standardization in performance of the semen analysis among laboratories in the United States

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Objective: To determine the level of standardization in performance of the semen analysis among clinical laboratories in the United States.

Design: A survey was mailed to laboratories requesting information about the laboratory and performance of the semen analysis. Responses were received from 536 laboratories.

Setting: Clinical laboratories enrolled in the American Association of Bioanalysts Andrology Proficiency Testing Program.

Patient(s): None.

Intervention(s): None.

Main Outcome Measure(s): Agreement among laboratories.

Result(s): Sixty-one percent of respondent laboratories were part of an assisted reproductive technology program. The laboratories perform less than 50 (53%), less than 10 (25%), or less than 5 (16%) andrology laboratory procedures per month. The laboratories routinely report sperm count (94% of laboratories), motility (95%), morphology (85%) and forward progression (69%), and semen volume (96%) as part of the semen analysis. Only 64% of laboratories routinely report abstinence, and 60% of laboratories indicate the criteria used for sperm morphology on the report form. The most common lower limits of normality for sperm count and motility were >20 x 10(6)/mL (77% of laboratories) and >50% (59% of laboratories), respectively. Few laboratories performed quality control for sperm counts (29%), motility (41%), and morphology (41%).

Conclusion(s): These data indicate a significant lack of standardization in the performance and reporting of semen analyses among laboratories in the United States.

Editorial Comment

This is a study based on a questionnaire's answers from U.S. clinical laboratories which perform semen analysis. It is interesting to observe that all laboratories participate in an accreditation and proficiency program. Therefore, it should be expected that such laboratories follow standardized guidelines. However, among many sperm parameters, only three microscopic ones (sperm count, percent motility, and morphology) are being performed by most laboratories. In addition, 61% of all laboratories are part of an assisted reproductive technology program. In such places, often considered as state-of-the-art laboratories, the careful laboratory evaluation of the male partner by the semen analysis is critical, since the semen analysis is the most important routine test in the male infertility work-up.

The semen analysis must be performed according to the World Health Organization (WHO) criteria. The WHO publishes guidelines which are frequently updated. The most recent one was published in 1999 (1), and it includes important information, such as the normal values for each sperm parameter, as well as the tests that should be performed during a routine semen analysis. In the present study, 1/3, and nearly half, of all laboratories are not updated regarding the normal values for sperm count and motility, respectively.

In Brazil, the situation is even worse, since most clinical laboratories do not participate in any accreditation or proficiency program. In addition, urologists often receive sperm analysis reports from different laboratories in which the values for normality and the tests performed are quite different. Therefore, the present study gives us an important alert. Setting rules and guidelines to perform routine semen analysis, as well as to report results, which should be followed by all laboratories, would help many urologists in dealing with infertile patients in their offices. It has to be emphasized the semen analysis has a direct impact on the therapeutical choices, as well as on couples counseling.

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RECONSTRUCTIVE UROLOGY

Phenotypic and functional characterization of in vivo tissue engineered smooth muscle from normal and pathological bladders

Lai J-Y, Yoon CY, Yoo JJ, Wulf T, Atala A From the Laboratory for Cellular Therapeutics and Tissue Engineering, Department of Urology, Children's Hospital and Harvard Medical School, Boston, Massachusetts *J Urol. 2002; 168:1853-8*

Purpose: The engineering of bladder tissue involves obtaining a biopsy from a host, expanding the cells, seeding them onto a matrix and implanting the cell-matrix composite back into the host. Clinically, cells used for these techniques may be harvested from abnormal bladders. It is not known whether abnormal bladder cells may be engineered into functionally normal tissue. We investigated the phenotypic and functional characteristics of tissue engineered bladder smooth muscle derived from patients with functionally normal bladders and functionally abnormal exstrophic and neuropathic bladders.

Materials and Methods: Human smooth muscle cells derived from functionally normal bladders, exstrophic bladders and neurogenic bladders were grown, expanded and seeded onto polymer scaffolds. Sixteen cell seeded scaffolds were analyzed in vitro and 40 cell seeded scaffolds were implanted in athymic mice. The tissue engineered constructs were retrieved and analyzed at 2 weeks and 2 months. The scaffolds were evaluated immunocytochemically, histologically, with organ bath studies and with Western blot analyses.

Results: Human bladder cells showed similar expression of smooth muscle marker proteins (alphaactin and myosin) in vitro and after 2 months in vivo, regardless of their origin. All scaffolds showed similar muscle formation in vivo. The cell seeded scaffolds demonstrated the typical "contraction-relaxation" response to supramaximal electrical field and carbachol stimulation. There were no statistical differences among the experimental groups (normal, exstrophic, neurogenic).

Conclusions: Tissue engineered muscle from normal and diseased bladders retain their phenotype in vitro and after implantation in vivo. The cells exhibited the same degree of contractility to electrical and chemical stimulation regardless of their origin. These results suggest that there are no phenotypic or functional differences between muscle cells obtained from urodynamically normal or pathological bladders, and that bladder muscle cells, regardless of their origin, may have the potential to be engineered into normal bladder tissues.

Editorial Comment

For reconstruction of neurogenic bladders gastrointestinal segments are the preferred substitution material. The authors of this manuscript belong to a group, which has tried to demonstrate in recent years that tissue engineering may be an option for bladder augmentation or even replacement, using in vitro cultivated urothelial cells with or without smooth muscle cells seeded onto a scaffold.

Whereas the biomaterials for cell seeding may be autologous, homologous, heterologous or artificial in the clinical setting, the cells to be seeded must be from the individual who needs bladder reconstruction. It is an ongoing debate where to obtain bladder cells for tissue engineering in patients with malignant or neurogenic disease of the lower urinary tract.

The current paper demonstrates that smooth muscle cells from patients with congenital or neurogenic diseases of the lower urinary tract had the same functional properties than engineered smooth muscle cells from normal patients. If this proves true in further studies it will not only widen the possibilities of using tissue engineered flaps for bladder reconstruction but may also give more clues as to the pathophysiology of neurogenic bladders. If there is no functional difference in the musculature of the bladder, the underlying pathomechanism could be e.g. a deficient mucosa (1) or a cerebrospinal disease.

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Tunica albuginea acellular matrix graft for penile reconstruction in the rabbit: a model for treating Peyronie's disease

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Objective: To evaluate the use of an acellular matrix graft of the tunica albuginea for functional penile reconstruction in severe cases of Peyronie's disease.

Materials and Methods: In 18 rabbits, an acellular matrix graft of the tunica albuginea was used to cover a 4x8 mm tunical defect, and six animals each were killed 1, 3 and 6 months later; four unoperated animals served as histological controls. Before death an erection was induced by papaverine, with the quality classified on a scale of 0–5, and cavernosography performed. After death the penis was prepared for histological study, and the cell number, collagen and elastic fiber content evaluated in the regenerated matrix, and in control specimens and four unimplanted matrices.

Results: Of 18 experimental animals, 11 had normal erections before death, four had slight penile deviation and three developed no erection. Failure was caused by severe postoperative haematoma, resulting in scar tissue. There was no graft rejection. Histologically there was no difference between natural and regenerated tunica. The collagen content and cell number were not significantly different in regenerated and control samples. There were significantly fewer elastic fibers in the unimplanted grafts and the 1-month group, but in later samples this difference was no longer evident.

Conclusion The homologous acellular matrix graft of the tunica albuginea warrants further evaluation as an alternative treatment in Peyronie's disease, despite some postoperative failures. The advantage of this orthotopic biomaterial is its rapid integration, with no rejection.

Editorial Comment

Various tissues and materials have been tried with variable success in the reconstruction or surgical repair of penile diseases. Many of the flaps are usually incorporated into the well vascularized surrounding of the penile structures. But apart from closing a defect of the corpus cavernosum after, e.g. excision of a plaque, none of them could reliably imitate all features of cavernous tissue. Strength, elasticity, venous tightness and controlled venous leakage are qualities which are difficult to substitute by tissues such as fascia or dermis.

Recently artificial biomatrices have proven to be successful clinically in closing surgical defects of patients suffering from Peyronie's disease. Among those a collagenous fleece usually used for surgical hemostasis seems to be a good scaffold along which cavernous tissue may regenerate (1). Another attempt, although not yet proven clinically to be useful, is tissue engineering.

Wefer and collaborators from San Francisco have previously shown the possibilities of using acellular matrix for reconstruction in the lower urinary tract. The advantage of acellular matrix would be that cellular regeneration is based on the native scaffold of the respective organ. This matrix therefore already has the qualities of resembling very closely the organ to be reconstructed. If tunica albuginea acellular matrix is a viable option for penile reconstruction, further interesting options may ensue. One could be the use of healthy corpus cavernosum from cadavers for the treatment of erectile dysfunction. However, before we are ready to speculate about future projects like that it has to be demonstrated that homologous penile acellular matrix craft works also in the human setting.

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UROLOGICAL ONCOLOGY _

Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma

Kaasinen E, Rintala E, Hellstrom P, Viitanen J, Juusela H, Rajala P, Korhonen H, Liukkonen T Hyvinkaa Hospital, Hyvinkaa, Finland *Eur Urol.* 2002;42:167-74

Objectives: To study the factors determining new recurrences in patients with frequently recurring superficial bladder tumors.

Methods: Of all 205 eligible patients, each received 5 weekly intravesical instillations of mitomycin C (MMC), with the first instillation given perioperatively. This was followed, according to randomization, by BCG instillations alone, or by alternating instillations of interferon-alpha and BCG monthly for up to 1 year. Impact of 12 variables on time to first recurrence, was retrospectively studied with the Cox multiple hazards regression and Kaplan-Meier analysis.

Results: Type of regimen was the most significant factor determining new recurrences, with preceding recurrence rate being the most important prognostic factor. Timing of the first MMC was the third significant predictor in the main multivariate analysis, with more than a two-fold relative risk for a new recurrence if the first MMC instillation was given later than on day 0.

Conclusion: Preceding recurrence rate, most accurately reflects, in patients with frequently recurring tumors, the inherent risk for new recurrences. This risk can be considerably reduced by use of an effective chemoimmunotherapy regimen, and in addition, by inclusion of an early perioperative chemotherapy instillation in such a regimen.

Editorial Comment

This study is a follow-up analysis of the trail that was previously published in the Journal of Urology. This late report provides interesting data that supports and emphasizes the previous results. The most important knowledge to gain from this publication is:

- 1. Single-shot instillation of cytotoxic drugs after the TUR should be given as early as possible, and not later than day 0, which is the day of TUR (preferably within 6 hours after the operation).
- 2. Adjuvant treatment with BCG is superior to alternating BCG and Interferon.
- 3. Preceding recurrence rate is the most important prognostic factor for superficial bladder cancer.

Within the context of further publications on that topic, a possible explanation of point 2 is obviously the number of instillations of BCG given, which was double in the BCG-group as compared to the BCG/ Interferon-group, thus making the number of BCG instillations an important therapeutic factor.

Dr. Andreas Böhle Professor and Deputy Chairman of Urology Medical University of Luebeck Luebeck, Germany

Perioperative single dose instillation of epirubicin or interferon-alpha after transurethral resection for the prophylaxis of primary superficial bladder cancer recurrence: a prospective randomized multicenter study — Finnbladder III long-term results

> Rajala P, Kaasinen E, Raitanen M, Liukkonen T, Rintala E; The Finnbladder Group Divisions of Urology, Turku University Hospital, Turku, Finland J Urol. 2002;168:981-5

Purpose: We evaluated the long-term efficacy of a single dose of interferon or epirubicin administered immediately after transurethral resection compared with transurethral resection alone for primary superficial bladder cancer recurrence.

Material and Methods: A total of 200 patients with primary superficial stages Ta to T1, grades 1 to 3 bladder cancer were randomized into 3 treatment groups, including transurethral resection alone, transurethral resection plus 50 milliunits interferon-alpha2b and transurethral resection plus 100mg epirubicin. The primary end point was time to first recurrence.

Results: At a median followup of 72 months, we observed a sustained effect of a single epirubicin instillation compared to other treatments. To date only 46% of the patients in group 3 have experienced recurrence, in contrast to 73% and 68% in groups 1 and 2, respectively (p=0.002). At 72 months, the Kaplan-Meier disease-free estimates were 24%, 31%, and 51%, in groups 1 to 3, respectively (p=0.002). The Cox multivariate model revealed a more than 2-fold relative risk of recurrence in group 1 versus group 3 (p<0.001). Other significant variables predicting recurrence were grade and the number of tumors.

Conclusions: A single perioperative instillation of 100mg epirubicin causes a significant and sustained decrease in primary superficial bladder cancer recurrence, whereas a single dose of 50 milliunits interferonalpha2b is ineffective for prophylaxis.

Editorial Comment

This study provides the long-term results of 3-armed study of TUR *versus* TUR + Interferon *versus* TUR + Epirubicin. After a median follow-up of 22 months, the results are rather clear, showing clinical effectiveness of a single short instillation of Epirubicin after TUR. Both the Kaplan-Meier estimates after 72 months, and the Cox multivariate hazard regression, support the use of a cytotoxic drug to prevent implantation of floating tumor cells. Two comments are to be made with this study:

- 1. The authors used 100mL physiological together with 100mg Epirubicin, and refer to the dose and not to the concentration, which might be more relevant in this context.
- 2. Furthermore, the instillate remained for 2 hours in the bladder, which might involve problems if given immediately after a transurethral resection. Thus, the results of a further sub-evaluation regarding the timing of the instillation would be very interesting.

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Correlation of cystoscopy with histology of recurrent papillary tumors of the bladder Herr HW, Donat SM, Dalbagni G Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA J Urol. 2002;168:978-80

Purpose: We correlated individual urologist impressions of tumor stage, and grade of recurrent papillary bladder tumors at cystoscopy, with histological findings after transurethral resection to determine whether cystoscopy can reliably identify low grade, noninvasive papillary tumor for outpatient fulguration.

Materials and Methods: A total of 144 recurrent papillary bladder tumors identified on outpatient flexible cystoscopy were classified as low grade and noninvasive (stage Ta grade 1), high grade and noninvasive (stage Ta grade 3), or invasive (stage T1). Voided urine cytology was also performed. The cystoscopic impression

of each tumor was correlated with the final histological findings of tumor stage and grade after transurethral resection.

Results: Cystoscopy classified 97 tumors as stage Ta grade 1, and 47 as stage Ta grade 3 or stage T1. Cystoscopy correctly predicted the tumor stage and grade of 93% of stage Ta grade 1, and 99% of stage Ta grade 1 lesions associated with negative urine cytology.

Conclusions: Urologists can usually identify noninvasive, low grade recurrent papillary tumors on follow-up cystoscopy, and these may be treated safely with outpatient fulguration.

Editorial Comment

This paper addresses the important point of how reliable the urologist's endoscopic evaluation is as compared to histology obtained after TUR. The authors performed flexible cystoscopy in a number of patients with non-invasive bladder cancer, and concluded that the prediction of superficial bladder tumors was reliable enough to recommend fulguration and did not require resection. Several comments, however, have to be made. The reliability of cystoscopy only comes with the help of cytology. Stage Ta grade-1 tumors were misdiagnosed in 7 of 97 cases, in that 6 tumors had grade-3 and one tumor had stage T1 in final histology. Furthermore, in cystoscopically stage Ta grade-3 tumors (37), 8 in fact were T1 tumors. In both situations, only cytology significantly improved the predictive value of cystoscopy. Thus predictive reliability will depended on a good cytologist. Finally, this paper was generated by 3 of the world's most experienced urologists, whereas in daily outpatients practice, the individual urologist's performance, including mine, might be significantly lower. In conclusion, it is nice to see that urologists can indeed predict superficial bladder cancer with high reliability, which to my opinion does not justify fulguration only.

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FEMALE UROLOGY _

Long-Term Results of Ingelman-Sundberg Denervation Procedures for Urge Incontinence Refractory to Medical Therapy

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Purpose: Urge incontinence refractory to anticholinergic medication and behavioral techniques is a therapeutic challenge. We evaluated the durability of the modified Ingelman-Sundberg detrusor denervation procedure as minimally invasive surgical therapy for intractable urge incontinence.

Materials and Methods: Patients presenting with severe urge incontinence unresponsive to medical and/or behavioral therapy were injected subtrigonally with 10mL 0.25% bupivacaine. The patients were contacted 24 hours later to determine whether they experienced a decrease in urgency and urge incontinent episodes. The 28 patients with temporary resolution of symptoms were offered operative management. All patients were evaluated with history, physical examination, and fluoroscopic urodynamics. The procedure consists of transvaginal dissection of the perivesical fascia from the area of the trigone, including sharp division of the terminal branches of the pelvic nerve.

Results: A total of 28 patients 28 to 83 years old (mean age 54.6), underwent the Ingelman-Sundberg procedure from April 1993 to September 1997. All patients presented with a history of urge incontinence, 10 reported concomitant stress incontinence and 10 had documented unstable detrusor contractions on urodynamic evaluation. Needle suspension and the pubovaginal sling procedure were performed with the Ingelman-Sundberg procedure in 1 case each. Mean follow-up was 44.1 months (range 14 to 67). Of the patients 15 (54%) achieved the complete durable resolution of urge incontinence, 4 (14%) were improved and 9 (32%) were unchanged.

Conclusions: Ingelman-Sundberg bladder denervation resulted in a 68% long-term cure or improved rate in a difficult patient population, namely those with intractable urge incontinence. This brief, minimally invasive procedure is an excellent alternative to more aggressive surgical options.

Editorial Comment

The authors describe the technique of the Ingleman-Sundberg transvaginal denervation, as well as their long-term data in the treatment of patients with this surgery.

The value of this paper is heightened secondary to the increasing discussion of the treatment of this population of patients with peripheral or sacral nerve neuromodulation.

The materials and methods section is very clear and to the point. With regard to the anesthetic block description, previous publications on this topic by the senior author have provided the reader with a little more concise direction on the actual injection (1). In addition, care must be taken when injecting the test block, secondary to the vascular nature of the area and the potential for calamity if the patient over absorbs the bupivicaine (2). The operative technique mirrors very closely the dissection used for a pubovaginal sling. In addition, the response rate for the cure of associated urge incontinence mirrors very closely the success rate of the I-S (69% vs. 54%), (3). One must ponder the degree of denervation that takes place during classic transvaginal dissection. For readers that have not previously performed the I-S denervation, having had the privilege of operating with the senior author, I can attest that the operation in experienced hands is as rapid as described. Other authors have discussed the need for bilateral *versus* unilateral transection, using parameters such as post void residual, but this paper does not broach this subject (4,5). In addition, a potential topic of interest would have been a cost analysis of this technique *versus* sacral nerve neuromodulation in a set of patients with similar diagnoses.

This technique may differ from neuromodulation in that it is neuroablative, and does not really strive to modulate neural response to bladder physical changes. A potential danger in neural ablation may be the long term effects of the down stream denervated tissue; for example, will later neuroplastic changes leave the end organ in a more pathologic state than before the performance of the procedure?

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Outcome of the Artificial Urinary Sphincter in Female Patients Thomas K, Venn SN, Mundy AR St. George's Hospital and Institute of Urology and Nephrology, London, and St. Richard's Hospital, Chichester, United Kingdom J Urol. 2002; 167:1720-2

Purpose: We reviewed the outcome in female patients at our unit in whom an artificial urinary sphincter was inserted.

Materials and Methods: We reviewed notes on 68 patients and mailed a questionnaire to those without recent followup.

Results: Median time since insertion was 12 years. Overall 25 patients (37%) had the original artificial urinary sphincter *in situ* and were dry at a median followup of 7 years. The artificial urinary sphincter was replaced for loss of function in 12 patients, of whom 11 were dry with the replaced device. The device was removed for erosion or infection in 31 patients, of whom 19 underwent successful replacement or were continent after removal. Overall 55 of 68 patients (81%) were continent. Those with neuropathic bladder dysfunction achieved a continence rate of greater than 90%, although half required sphincter removal initially. When the indication for insertion was stress incontinence, 70% of the patients had the original or a replaced artificial urinary sphincter in situ and 82% were continent. All patients with previous pelvic irradiation had the sphincter removed and urinary diversion was done.

Conclusions: The overall continence rate in female patients after insertion of an artificial urinary sphincter is satisfactory. A satisfactory outcome was achieved in terms of stress incontinence and we would recommend an artificial urinary sphincter after an adequate anti-stress incontinence operation fails. Continence in patients with neuropathic bladder dysfunction is excellent and the artificial urinary sphincter should be considered first line treatment in this group, although the risk of revision surgery is high. Pelvic irradiation is a contraindication to the artificial urinary sphincter in female patients.

Editorial Comment

The authors review the outcome of the use of artificial urinary sphincter in the female patient. This manuscript is important secondary to the volume of patients reviewed (n=68), as well as their observation of the role of pelvic radiation pre-operatively, and its use in the neuropathic population. This is a valuable review, since the use of the artificial urinary sphincter in women is still not as common as its use in the male incontinent patient population. The artificial urinary sphincter in women differs from the traditional urethropexy or suburethral sling in that it tends to not elevate the bladder neck to a high retropubic position, nor to provide a backboard of urethral support; it attempts to mimic the sphincter mechanism of the urethra with a circumferential compression (1). Though in this study the patients had their device placed transabdominally, transvaginal approach may be used as well (2). Of note, in Appell's transvaginal series, no woman suffered from any erosion. Findings of this paper included that the observation of the risk of erosion in the neuropathic bladder population is approximately 50%, but the authors did use a 71-80cm water pressure reservoir, which is somewhat higher than the traditional 61-70cm pressure reservoir used in patients treated for male post-prostatectomy incontinence. In addition, the investigators were able to identify pelvic irradiation as a significant risk factor to morbidity with the artificial urinary sphincter placement in the female population. At the time of placement of an artificial urinary sphincter in the female, bladder, urethral, or vaginal injury should not lead to abandonment of the procedure. The injured area should be identified and closed in layers, if possible with absorbable suture (3).

Of interest would have been the authors' comments on the impact of the artificial urinary sphincter on female sexuality, fecundity, and parturition. The placement of artificial urinary sphincter in the woman should not interfere with the sexual aspect of her life, or with potential fertility (2,4). If the female patient should

become pregnant, consideration should be given towards deactivation in the third trimester, to diminish the excessive pressure on the cuff and bladder neck (5). Whether to utilize a vaginal delivery or Cesarean section at the time of delivery, can be left to the discretion of the obstetrician, with both methods having been described in the literature (4,5).

With regards to these authors study, facets which may warrant further exploration include review of potential complications experienced by those patients who underwent enterocystoplasty. It has been found that approximately 30% of patients with mild meningocele and an artificial urinary sphincter will need an augmentation enterocystoplasty (6,7). A point of debate in the literature is whether the artificial urinary sphincter should be placed at the time of the augmentation, or initially in a staged manner (6,8). In addition, another point to review, which may further add to this excellent article, is the rate of clean intermittent catheterization experienced by the patients.

The authors should be applauded for their adding to the urologic literature of their findings in female patients with the artificial urinary sphincter. Their experience with pelvic irradiation and later, artificial urinary sphincter, may help the reader avoid potential complications with this population.

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PEDIATRIC UROLOGY _

46,XY Intersex individuals: phenotypic and etiologic classification, knowledge of condition, and satisfaction with knowledge in adulthood

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Objectives: The objective of this study was to identify and study adults who have a 46,XY karyotype and presented as infants or children with variable degrees of undermasculinization of their genitalia (female genitalia, ambiguous genitalia, or micropenis). Participants' knowledge of their condition, satisfaction with their knowledge, and desire for additional education about their intersex condition were assessed.

Methods: Participants were classified according to the cause underlying their intersex condition based on review of medical and surgical records. Knowledge of medical condition, satisfaction with that knowledge, and desire for additional education were assessed with a written questionnaire and a semistructured interview.

Results: Patients were ineligible for recruitment because of death (9%), because of developmental delay (12%), or because they were not located (27%). Among the 96 eligible patients, 78% participated. Approximately half of the men (53%) and women (54%) exhibited a good understanding of their history. Fewer women who have a 46,XY chromosome complement and were born with female genitalia were informed about their intersex condition (36% with complete androgen insensitivity syndrome) than were women who were born with masculinized genitalia such as micropenis (50%) or ambiguous genitalia (72%). More women (66%) than men (38%) were satisfied with their knowledge of their medical and surgical history.

Conclusions: Almost half of the patients, reared male or female, were neither well informed about their medical and surgical history nor satisfied with their knowledge.

Editorial Comment

The management of patients with intersex is highly complex. Care should be multidisciplinary and should, at a minimum, include input from surgeons, endocrinologists, geneticists, psychologists and bioethics experts. Urgent decisions are made in the nursery that will have significant effects on patients for years to come. Most concerning is the fact that there are only limited long-term outcome data on these neonatal decisions. Some of the first outcome studies, flawed as they may be, are just being published at this time.

Among the most important points that patient activists make is the accusation that intersex individuals and their families are poorly informed about their medical conditions and therefore can not make optimal decisions regarding their own healthcare. This study reviews adults with intersex due to under-masculinization despite a 46, XY karyotype. Using questionnaires and semi-structured interviews the authors assessed patient knowledge of their history and satisfaction with their knowledge.

Although not surprising, it was still disturbing to find that only 50% of patients (both male and female) were informed adequately about their condition. Interestingly, fewer women were informed about their condition if they had Complete Androgen Insensitivity (36%) than men with micropenis (80%). On the other hand, women were more satisfied than men (66% vs. 38%) with their state of knowledge.

The importance of neonatal decisions in these patients is considerable and there are still too few studies of outcome to assess how we are doing. Perhaps more important, factors that could improve outcome have not been studied enough. Studies like the one summarized above are to be encouraged strongly.

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The single testis: paternity after presentation as unilateral cryptorchidism Lee PA, Coughlin, MT Penn State University College of Medicine, Hershey, Pennsylvania, USA J Urol. 2002; 168:1680-3

Purpose: We determine if paternity is reduced among men with monorchidism (absent or removed testis) compared to men with unilateral cryptorchidism corrected during childhood by orchiopexy and controls. The group of men with an absent testis was determined among males presenting during childhood with only 1 descended testis.

Materials and Methods: Data were obtained by medical record review and a detailed questionnaire. Only men who had been successful at or attempted paternity for whom we had complete data were included in the study from the entire cohort of 584 men with former cryptorchidism, 23 with absent testis, 26 treated with orchiectomy and 706 controls.

Results: Percentages of men reporting success after attempting paternity did not differ among men with an absent testis (15 of 15, 100%), treated with orchiectomy (17 of 20, 85.0%), with corrected unilateral cryptorchidism (313 of 349, 89.7%) and controls (412 of 442, 93.2%). There was no difference for a subgroup of men with cryptorchidism judged to have an atrophic testis at orchiopexy (17 of 20, 85%) or those who underwent orchiectomy at initial attempted orchiopexy (8 of 10, 80%) and men who had subsequently undergone orchiopexy (9 of 10, 90.0%). Paternity was also not reduced in the group of men with only 1 testis (32 of 35, 91.4%) (monorchism plus orchiectomy) compared to either the corrected unilateral cryptorchid group or the control group. Of 637 testes 183 were recorded as impalpable on examination before surgery and 23 testes were absent, including 7 recorded as palpable. In fact, 12.1% (23 of 190) of testes that should have been recorded as impalpable were absent.

Conclusions: This study failed to indicate that paternity is diminished among men with a single testis compared with the general population, regardless of the origin of the loss. About 12% of unilateral impalpable testes judged to be impalpable on examination before surgery were found to be absent after surgical exploration.

Editorial Comment

Cryptorchidism is one of the most common urological conditions, affecting almost 1% of the male population (1). The etiology of the condition remains unclear, but it may be due to a mechanical problem (abnormal gubernaculum) or a hormonal problem (hypogonadism). Anatomical anomalies (an abnormal epididymis) coexist and studies in adults have suggested that even after appropriate surgical intervention, the previously undescended testis contributes little to long-term sperm production (2). Questions remain about the long-term follow-up of these patients.

The authors reviewed paternity in these patients (and in a control population) by questionnaire. Their findings were that patients with a history of unilateral cryptorchidism had a paternity rate of 90% vs. 93% in controls and 91% in patients with unilateral anorchia. None of these differences were statistically significant.

Despite a focus on early orchiopexy and hormonal therapy (even after successful orchiopexy) it is unclear if we are really making a difference for these patients (3,4). The fact that there is little difference in paternity in patients undergoing orchiopexy should be very reassuring to parents and surgeons.

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