The July - August 2004 issue of the International Braz J Urol presents interesting contributions and as usual the Editor’s Comment will be close to the list of contents and will highlight some important papers.

Doctor Kim and colleagues, from Chungbuk National University, South Korea, and University of Pittsburgh School of Medicine, Pennsylvania, USA, world-recognized experts in the field, presented on page 275 their experience with the use of gabapentin to treat symptoms of overactive bladder (OAB) and nocturia in patients who have failed conventional anticholinergic therapy. The authors studied 31 patients receiving gabapentin doses ranging from 100-300 mg at bedtime. Fourteen of 31 patients with refractory OAB and nocturia improved with oral gabapentin. Six patients stopped taking the drug within one month due to side effects mostly described as drowsiness or lethargy. The authors concluded that gabapentin was generally well tolerated and can be considered in selective patients when conventional modalities have failed.

Doctor Faria and co-workers, from McGill University, Montreal General Hospital, Canada, assessed the experience of following without immediate treatment patients presenting biochemical failure as single abnormality after radical external beam radiation for prostate cancer (page 289). After a median follow-up of 77 months, of the 78 patients with biochemical failure followed without initial therapy, 7 died from other causes than prostate cancer and the remaining 71 cases were alive and asymptomatic in the last follow-up. The most significant aspects for considering delayed hormone therapy were low PSA (median 3.9 ng/mL) and a slow PSA doubling time (median 22.5 months). The authors concluded that there seems to be space for expectant management, without initial hormone therapy, in patients with prostate cancer who present biochemical failure and are asymptomatic after radical external beam radiation.

Doctor Mittal and co-workers, from Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India, analyzed on page 279 whether the NAT2 genotypes are risk factors for bladder cancer and studied the possible association of tobacco usage with NAT2 genotype of these patients. A case control study was undertaken over a period of 19 months and included 101 bladder cancer patients and 110 controls. The NAT2 genotypes were identified by PCR-RFLP method in peripheral blood DNA samples. The authors found that the NAT2 fast or slow acetylators genotype did not associated with the risk of developing bladder cancer in North Indian population when compared with controls. Doctor Ingolf Cascorbi, from University Hospital Schleswig-Holstein, Kiel, Germany, Doctor David W Hein, from University of Louisville School of Medicine, USA, and
Doctor Ralph de Vere White, from University of California Davis, USA, well-known authorities in this topic, provided editorial comments on this article.

Doctor Romero and colleagues, from Santa Casa School of Medicine, São Paulo, Brazil, studied on page 296 the coexistence of prostate neoplasia in patients undergoing radical cystoprostatectomy due to vesical neoplasia. The authors also analyzed if the characteristics of the bladder neoplasia influenced the prostatic involvement. They found that the coexistence of prostatic neoplasia in patients operated for bladder neoplasia was frequent in their sample (55%). Also, it was observed that the prostatic infiltration by bladder tumors occurs more frequently with tumors located in the trigone, with associated in situ carcinoma and with high histological grade. There was no correlation between neoplastic infiltration of the prostate and multifocality or size of the bladder tumor.

Doctor Almeida and colleagues, from State University of Londrina, Paraná, Brazil, through a multivariate analysis, studied the variables predictive of voiding dysfunction following aponeurotic sling surgery (page 302). They reviewed 130 patients ranging in age from 41 to 83 years (mean 56.7) and found that pre-operative presence of post-voiding residual urine higher than 100 mL was the only variable predictive of voiding dysfunction.

Dr. Francisco J.B. Sampaio
Editor-in-Chief
GABAPENTIN FOR OVERACTIVE BLADDER AND NOCTURIA AFTER ANTIMUSCARINIC FAILURE

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Department of Urology; Chungbuk National University Hospital Chungbuk, South Korea (1), and Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA (2)

ABSTRACT

Introduction: We reviewed our experience with the use of gabapentin to treat symptoms of overactive bladder (OAB) and nocturia in patients who have failed conventional antimuscarinic therapy.

Methods: Thirty-one patients referred to us with refractory (OAB) and/or nocturia were treated with oral gabapentin. All the patients had tried or remained on antimuscarinic drugs during treatment. Twenty-four of 31 complained of bothersome symptoms during day and night and the other seven had primary complaints of nocturia. Initial gabapentin doses ranged from 100-300 mg at bedtime. Dose was slowly titrated up to 3,000 mg based on patients’ symptomatology and tolerability.

Results: The mean age was 51 years old (range 27-78). There were 13 men and 18 women. The median steady state dose chosen by the patient after initial titration was 600 mg/day. Fourteen of 31 patients reported subjective improvement of their frequency and 8 have been on the medication for over 12 months with persistent efficacy. For the 14 improved patients, mean frequency/24 hours decreased from 14.1 ± 2.2 to 10.0 ± 2.1. Three patients with primary nocturia reported improvement from a mean of 4.0 ± 1.3 to 1.0 ± 0.3 episodes/night. Six patients stopped taking the drug within one month due to side effects mostly described as drowsiness or lethargy.

Conclusions: Fourteen of 31 patients with refractory (OAB) and nocturia improved with oral gabapentin. Gabapentin was generally well tolerated and can be considered in selective patients when conventional modalities have failed.

Key words: bladder; nocturia; urination disorders; prostate; neuromodulation

Int Braz J Urol. 2004; 30: 275-8

INTRODUCTION

Gabapentin is approved as an anticonvulsant but it has significant pain control properties. It has been widely used in neurology for the treatment of peripheral neuropathic pain. In animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures similar to other marketed anticonvulsants (1,2). Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not interact with GABA receptors, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation (3).

The mechanism of gabapentin’s action for neuropathic pain has not been fully elucidated but it appears to have inhibitory activity on afferent C-fibers nerve activity (4). Because of demonstrated clinical safety and efficacy over the past decade, gabapentin appears to have attractive properties for
consideration to treat refractory lower urinary tract symptoms. We have previously reported on the successful use of gabapentin in patients with interstitial cystitis (5). Up-regulation of bladder C-fiber afferent nerve function may also play a role in certain cases of urge incontinence, overactive bladder (OAB) and sensory urgency (6). Therefore, gabapentin is a rational drug to consider in cases of refractory (OAB).

We hereby reviewed our experience with gabapentin as a method of treating symptoms of (OAB) and nocturia in patients who have failed conventional anticholinergic therapy. Gabapentin is not FDA indicated for urologic dysfunction and the patients treated in this series were explained that this was an off label used of the drug.

MATERIALS AND METHODS

Thirty-one patients referred to our university urology clinic with refractory (OAB) and/or nocturia were treated with oral gabapentin. The mean age was 51 years old (range 27 - 78). Mean duration of symptoms was 6.3 years. There were 13 men and 18 women. Twelve of the women had multiple sclerosis and had neurogenic detrusor hyperreflexia. The other 6 women had mixed urge and stress incontinence with urge as the predominate component. In the 13 men, 7 have had prior transurethral resection of the prostate and 3 had microwave of the prostate. Six patients smoked and none had more than social alcohol consumption.

Baseline evaluation included exclusion of urethral outlet obstruction. None of the men had bladder outlet obstruction as documented on pressure-flow videourodynamics. None of the patient had neurogenic detrusor-sphincter dyssynergia as noted on multichannel videourodynamics.

All the patients had tried oral tolterodine or oxybutynin for at least 8 weeks prior to their referral. During the gabapentin trial, the patients were instructed to not change any of their prior or present medications. Sixteen of the patients remained on their usual dosage of antimuscarinic drug during gabapentin therapy. None of the patients discontinued or modified antimuscarinic treatment.

Twenty-four of 31 complained of bothersome symptoms during day and night and the other seven had primary complaints of nocturia. Initial gabapentin (Pfizer, New York, USA) doses ranged from 100 mg or 300 mg at bedtime. Dose was slowly titrated up to 3,000 mg based on patients’ symptomatology, all taken at bedtime.

After a routine history and physical examination, including a measurement of bladder diary, the patients were started on gabapentin. Micturition frequency was measured after 12 weeks and additional follow-up of up to 12 months was available in ten of the 14 patients who reported improvement.

Data Analysis: All values are presented as mean ± standard error. Statistical analyses and comparisons between groups were performed using student t-test. A probability level of < 0.05 was accepted as significant.

RESULTS

No patient had a history of seizures or convulsions, nor had any ever been treated with an anticonvulsant or antiepileptic agent. The mean dose of gabapentin was 600 mg/day (range 100 - 3,000 mg). Fourteen of 31 patients reported subjective improvement of their frequency and 8 have been on the medication for over 12 months with persistent efficacy (Table-1). For the 14 improved patients, mean frequency/24 hours decreased from 14.1 ± 2.2

<table>
<thead>
<tr>
<th>Table 1 – Bladder diary of patients who did or did not improve in frequency and nocturia groups.</th>
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</thead>
<tbody>
<tr>
<td><strong>Frequency</strong> (n = 31)</td>
</tr>
<tr>
<td>Improved (n = 11)</td>
</tr>
<tr>
<td>No improvement (n = 20)</td>
</tr>
<tr>
<td><strong>Nocturia</strong> (n = 7)</td>
</tr>
<tr>
<td>Improved (n = 3)</td>
</tr>
<tr>
<td>No improvement (n = 4)</td>
</tr>
</tbody>
</table>

*p = 0.01; ** p = 0.03
to 10.0 ± 2.1. Three patients with primary nocturia reported improvement from a mean of 4.0 ± 1.3 to 1.0 ± 0.3 episodes/night.

Gabapentin was well tolerated with only six patients stopping the drug within one month due to side effects mostly described as drowsiness or lethargy.

The side effects were transient and resolved promptly after the gabapentin was discontinued. Three of the patients who improved also reported lethargy but described them as tolerable and continued with the medication.

**COMMENTS**

Gabapentin has been widely used in the neurologic field for the treatment of focal neuropathic pain. Pain resulting from diffuse and focal neuropathies, such as painful diabetic neuropathy and post herpetic neuralgia, is a common but difficult clinical problem to manage (1). Neuropathy occurs in more than 50% of patients with diabetes who have been hyperglycemic for more than 15 years (7). Unfortunately, drug treatment for neuropathic pain is often unsatisfactory, as demonstrated by the large number of drugs that patients will have taken in an attempt to seek pain relief.

Rowbotham et al (1) and Backonja et al. (2), reported 2 clinical series on gabapentin for chronic neuralgesic pain. Gabapentin was titrated from 900 mg/d to 3,600 mg/d or the maximally tolerated dosage over 8 weeks. Both studies demonstrated significant and clinically substantive amelioration of daily pain severity and improvement in important secondary end points, including sleep interference scores and quality-of-life measures.

Gabapentin was well tolerated, with similar numbers of treated and placebo patients withdrawing because of adverse effects (8% in gabapentin group and 6% in placebo group), Table-1.

The most common adverse effects were dizziness and drowsiness. Gabapentin may be a safer drug choice for the older patient who is prone to orthostatic hypotension and cardiac arrhythmias.

Gabapentin has been used in urology for the treatment in patients with refractory interstitial cystitis (5). In that study ten of 21 interstitial cystitis patients reported subjective improvement of their pain. Why did we consider using gabapentin to treat refractory (OAB)? We hypothesize that certain cases of (OAB) may share a similar pathophysiology of up-regulation ofafferent C-fiber sensory neurons as in interstitial cystitis (6) stimulated us to consider using gabapentin for (OAB) and nocturia. Overall 14 of 31 (45%) of patients reported improvement. It was rewarding to see that gabapentin was able to help certain cases of nocturia, which has been a difficult symptom for oral antimuscarinic agents to help. There did not appear to be a difference in efficacy in patients with or without multiple sclerosis.

**CONCLUSIONS**

Although only 14 of 31 patients improved with oral gabapentin, one should consider that these were patients with refractory (OAB) and nocturia. Gabapentin was generally well tolerated and can be considered in selective patients with (OAB) when conventional modalities have failed.

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**REFERENCES**


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NAT2 GENE POLYMORPHISM IN BLADDER CANCER: A STUDY FROM NORTH INDIA

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ABSTRACT

Purpose: This study was conducted to examine: 1) whether the NAT2 genotypes are risk factors for bladder cancer, 2) to study possible association of tobacco usage with NAT2 genotype of these patients.

Materials and Methods: This case control study was undertaken over a period of 19 months and included 101 bladder cancer patients and 110 controls. The NAT2 genotypes were identified by PCR-RFLP method in peripheral blood DNA samples. Genotypes frequencies and the association of the genotypes among patients and controls group were assessed by $\chi^2$ test and Fisher exact test.

Results: The NAT2 fast acetylator genotype frequency of slow or fast acetylator genotypes was not significant in bladder cancer patients alone (OR = 1.18, 95% CI: 0.69 - 2.03, p value = 0.583) or combination with tobacco users (OR = 0.84, 95% CI: 0.328 - 2.125, p value = 0.813) when compared with controls.

Conclusion: These data demonstrate that the NAT2 fast or slow acetylators genotype did not associated with the risk of developing bladder cancer in North Indian population when compared with controls.

Key words: bladder neoplasms; risk; tobacco; arylamine N-Acetyltransferase; polymorphism genetics

INTRODUCTION

N-acetyltransferases 2 (NAT2) is one of the phases II enzyme that participate in the bioconversion of heterocyclic arylamines into electrophilic nitrenium ions, which are important ultimate carcinogens that are directly implicated in tumor initiation process (1,2). It expresses at high level in liver, and encoded by a polymorphic gene presenting several nucleotide substitutions. Consequently the presence of the different alleles in each individual genome produces a broad range of metabolic phenotypes that vary from fully active rapid metabolizers to the less active alleles of slow metabolizers (3).

Enzymatic activation and detoxification of carcinogens is a major principle in chemical carcinogenesis (4,5). Many chemical and dietary carcinogens, such as nitrosoamines and arylamines derived from dietary fat as well as tobacco users’ product, acquire bioactivation and deactivation by NATs enzymes. N-acetyltransferase-2 catalyze the activation and for deactivation of a wide variety of aromatic amines, heterocyclic amines, and hydrazine drugs. This suggests that polymorphism of genes encoding metabolic enzymes may represent potential risk factors (6-8).

Recent molecular epidemiological studies have analyzed the relationship between various metabolic enzymes, such as N-acetyltransferases (NATs), cytochrome P450 (CYP) and glutathione S-
transferases (GSTs) in bladder and prostate cancer to determine as biomarkers (9,10). In humans, hereditary differences in N-acetylation activity have lead to phenotypic classification of individual as rapid or slow acetylators.

It has been reported that genetically variable NATs, CYP P450 and GSTs are involved in the metabolism of drugs, carcinogens and natural products; and therefore act as candidate genes for cancer susceptibility (8,11). It is known that human express two forms of N-acetyltransferases: NAT1 and NAT2; both genes are polymorphic. Thus for 24 NAT1 and 26 NAT2 alleles have been identified in humans. A recent review describes the nucleotide and amino-acid changes associated with various alleles and deduced phenotype from genotype. It also summarized results of molecular epidemiologic studies assessing the association of NAT1 and NAT2 genotypes with cancer risk of bladder, colon, breast, lung, head and neck and prostate (12,13).

Although, some of these studies suggest that NAT1 and NAT2 polymorphisms may or may not be influence the susceptibility with these cancers. Recent studies have not supported a relationship between NAT1 genotypes and N-acetylation activity (14,15). Furthermore, NAT2 has been reported to exhibit a polymorphism (16,17), resulting in the potential expression of four mutant alleles (M1, M2, M3, M4), which can be identified by RFLP analysis following NAT2 PCR. NAT2 activity is predicted from the detected combination of these NAT2 alleles. Presence of at least one wild type alleles results in rapid acetylators where as the carriage of 2 mutant alleles results as a slow acetylator (16). The slow allele is present in up to 90% in some Arab population, 40-60% of Caucasians including Indians, 5-25% East Asian (18-20) and 74% in South Indians (21). It has been reported that slow acetylators may be at increased risk of bladder and prostate cancer when exposed to environmental arylamines carcinogens, due to their slower inactivation.

The present study was undertaken to examine NAT2 polymorphism and to evaluate whether, fast or slow acetylator phenotype is associated with increased risk of bladder cancer when compared with the controls. We also try to examine the association between NAT2 polymorphism with clinical stage and pathological grade of bladder cancer.

MATERIALS AND METHODS

Subjects: The study group consisted of 101 bladder cancer patients (all were transitional cell carcinoma, out of them 32% were grade 1 tumor, 20% were grade 2 and 48% were grade 3 tumor) with mean age ± SD (57.29 ± 13.40) and 110 controls with mean age ± SD (56.71 ± 13.95). Ethnic origin of cases and controls were rural area (not industrial area). There were no statistical differences in age of patient and control group.

Blood samples were obtained between December 2001 and December 2003 from patient group and control group, and patient data were obtained from medical records of patients. This study was approved by ethical committee of health care and research, of SGPGI under the guidelines of ministry of education, culture and science and technology.

The diagnosis of prostate cancer and bladder cancer patients was confirmed histopathologically in the study group. The control group consisted of age matched 110 normal healthy individuals. Serological (prostate serum antigen), physical (digital rectal examination) and radiological examination were performed in all controls individuals in order to exclude the possibility of malignancy. The inclusion criteria for the controls were absence of prior history of cancer or pre-cancerous lesions.

The consumption of tobacco in any form (cigarette bidi - a kind of cigarette used in rural area by the villagers) smoking, chewing tobacco in beetle leaf or gutka etc.) in both groups (cases and controls) was noted through a detailed questionnaire.

PCR-RFLP and Alleles Genotyping

Genomic DNA was isolated from peripheral leucocytes by Proteinase -K digestion and phenol/ chloroform method (22). The NAT genotypes were determined using the PCR-RFLP as described previously by Vatsis et al. 1995 (3). 1093 bp PCR product was generated by polymerase chain reaction (Figure-1) using the following primer:
Forward 5’-TCTAGCATGAATCACTCTGC-3’
Reverse 5’-GGAACA AATTGG AC TTGG -3’

Genomic DNA 200 ng to 500 ng was added to a PCR mixture, composed of 18.5 pmol of each primer, 200 micromol dNTP (Banglore Gennai, India), 1.5 unit of Taq polymerase (Banglore Gennai, India), and PCR buffer (Banglore Gennai, India) composed of 10 mmol/mL Tris HCl pH = 8.4, 50 mmol/mL KCl and 2.5 mol/mL MgCl2) in a total volume of 50 µL. We used PTC-100 (Programmable Temperature Control System) for polymerase chain reaction. The reaction mixture was subjected to initial denaturation at 94°C for 5 min, followed by 35 cycles performed at denaturation (94°C, 1 min), annealing (58.5°C, 1 min) and extension (72°C, 1 min). The final extension was done at 72°C for 10 min. Following PCR, 7µL of PCR products were taken in 4 different tubes and digested with 4 separate enzymes including Kpn1 for NAT2*5 (M1) allele, at 37°C for 2h; Taq1 for NAT2*6 (M2) allele, at 56°C for 4h; BamH1 for NAT2*7 (M3) allele at 37°C for 2h; and Msp1/Alu1 for NAT2*14 (M4) allele at 37°C for 2h. Digested product runs on 2% agarose gels for M1, M3, M4 alleles and 3% agarose gels for M2 allele (3). If the allele could not be identified as M1, M2, M3 or M4 after digestion, then the remaining allele were identified as a NAT2*4 (wild type) allele: since the wild type allele possess the entire restriction site. The NAT rapid acetylator genotypes are wild type (WT) allele, homo or heterozygotes (WT/WT, WT/M1, WT/M2, WT/M3 or WT/M4), whereas the slow acetylator genotypes are those with 2 mutant alleles (M1/M1, M1/M2, M1/M3, M1/M4, M2/M2, M2/M3, M2/M4, M3/M3, M3/M4 and M4/M4).

**Statistical Analysis**

Statistical analysis was done with SPSS software. Difference in genotype prevalence and association between case and control group were assessed by the Chi square and Fisher exact tests. Odds ratios (OR) and its 95% confidence interval (CI) were obtained by summarizing data over 2 habit strata (tobacco users / non-users). Multivariate analysis, correlation coefficient, odds ratios, p value (two-sided tests) and 95% CI were used to describe the strength of association.

**RESULTS**

The frequency of NAT2 slow or fast acetylator genotypes was not significant in bladder cancer patients (OR = 1.18, 95% CI: 0.69 - 2.03, p value = 0.583) in comparison to controls (Table-1).

![Figure 1 – PCR product from amplification of NAT2 analyzed on 2% agarose. Lane M-100 bp ladder, lane 1, 2, 3, and 4 are in control samples and lane 5, 6, 7 and 8 are in bladder cancer patients. Lane 1 and 5 indicate BamH1 digestion (NAT2*7), lane 2 and 6 Kpn1 digestion (NAT2*5), lane 3 and 7 Alu1 digestion (NAT2*14), lane 4 and 8 Taq1 digestion (NAT2*6).](image)

<table>
<thead>
<tr>
<th>Patients</th>
<th>NAT2 phenotype</th>
<th>Chi-square</th>
<th>p Value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slow-acetylators</td>
<td>Fast-acetylators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls (n = 110)</td>
<td>59 (53.64%)</td>
<td>51 (45.36%)</td>
<td></td>
<td>1.0 (Ref.)</td>
</tr>
<tr>
<td>Bladder cancer (n = 101)</td>
<td>51 (50.5%)</td>
<td>50 (49.50%)</td>
<td>0.36</td>
<td>0.583</td>
</tr>
</tbody>
</table>

Table 1 – Frequency of NAT2 phenotypes in bladder cancer patients in comparison to controls.
We analyzed the effect of NAT2 genotypes and tobacco users on the risk of bladder cancer in comparison to controls. We did not observe association between slow phenotypes and tobacco users with bladder cancer in our population (Table-2).

We divided clinical stage of tumor into 2 groups: T1 group (Ta-b and Ti) and T2 in another group (T2a-b + T3 + T4); and we found that NAT2 slow acetylator genotype was not significant in these groups when compared to controls (Table-3).

We also divided pathological findings into 3 groups: well differentiated (Grade-1), moderately differentiated (Grade-2) and poorly differentiated (Grade-3). We observed that NAT2 slow acetylator genotype were insignificant with any grade when compared with controls (Table-4).

The results presented demonstrated that NAT2 genotype show no relationship to bladder cancer risk when considered alone (OR = 1.18, 95% CI: 0.69-2.03, p value = 0.583) or in combination with smoking (OR = 0.84, 95% CI: 0.328-2.125, p value = 0.813) in comparison to controls. We also tried to correlate clinical stage and pathological grade with NAT2 genotype in bladder cancer, but no association was found.

Our findings agree with previous studies (23) that showed no relationship of NAT2 genotype to bladder cancer risk when considered alone or in combination with smoking. But several studies have demonstrated that low activity is doubtless a risk

<table>
<thead>
<tr>
<th>Tobacco users</th>
<th>Controls (n = 110)</th>
<th>Ca Bladder (n = 101)</th>
</tr>
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<tbody>
<tr>
<td>Non-users</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow-phenotype</td>
<td>45 (56.3%)</td>
<td>28 (48.3%)</td>
</tr>
<tr>
<td>Fast-phenotype</td>
<td>35 (43.7%)</td>
<td>30 (51.7%)</td>
</tr>
<tr>
<td>P value</td>
<td>1.0 (Ref.)</td>
<td>1.378 (0.669 - 2.715)</td>
</tr>
<tr>
<td>Tobacco-users</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow-phenotype</td>
<td>14 (46.6%)</td>
<td>22 (51.2%)</td>
</tr>
<tr>
<td>Fast-phenotype</td>
<td>16 (54.4%)</td>
<td>21 (48.8%)</td>
</tr>
<tr>
<td>P value</td>
<td>0.813</td>
<td>0.835 (0.328 - 2.125)</td>
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</table>

**Table 3 – Frequency of N-acetyltransferase-2 genotypes of bladder cancer patients categorized by stage of the disease.**

<table>
<thead>
<tr>
<th></th>
<th>NAT2 phenotype</th>
<th>p Value</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Slow-acetylators</td>
<td>Fast-acetylators</td>
<td></td>
</tr>
<tr>
<td>Controls (n = 110)</td>
<td>59 (53.64%)</td>
<td>51 (45.36%)</td>
<td>1.0 (Ref.)</td>
</tr>
<tr>
<td>Bladder cancer (n = 101)</td>
<td>29 (47.55%)</td>
<td>32 (52.45%)</td>
<td>0.523</td>
</tr>
<tr>
<td>T1 stage (n = 61)</td>
<td>21 (52.50%)</td>
<td>19 (47.50%)</td>
<td>1</td>
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</table>
factor for bladder cancer, particularly for those individuals who smoke or who are exposed to specific occupational hazards (24,25). According to the current theory of the role of N-acetyltransferases (NAT1 and NAT2) in bladder cancer etiology, a decrease of arylamine N-acetylation rates in the liver enforces N-hydroxylation mediated by CYP4501A2, which in turn leads to increased concentrations of hydroxylamines in the urinary bladder (26).

Polymorphisms of NAT and CYP enzymes that activate or detoxifying carcinogens and mutagens were believed to play crucial role in carcinogenesis. NAT2 enzyme has been shown to activate carcinogenic aromatic amines, which can arise from tobacco products or dietary intakes or environmental exposures (8,10). Human acetylation polymorphism influences both the metabolic activation (O-acetylation) and deactivation (N-acetylation) of aromatic amines via the polymorphic expression of NAT2. It has been hypothesized that the increased susceptibility to urinary bladder cancer for slow acetylators is associated with the decreased deactivation of aromatic amines in the liver, so that excess hydroxylated aromatic amines reach the bladder epithelium where they can induce further activation step (27). The deactivation pathway can compete with activation pathway (N-hydroxylation and O-acetylation) (6). Whether NAT serves as an activating or deactivating enzyme depends on the final consequence of the competition of all these pathways, which is related to the polymorphism of CYP enzymes. Therefore, without studies on pharmacogenetics and cancer epidemiology, predicting any association of acetylator status with certain cancer is difficult.

This suggests that the association of metabolic enzyme gene polymorphisms with bladder cancer may differ according to the metabolic enzymes (NAT, CYP or GST) and ethnic population under study. Perhaps different environmental carcinogens in different countries determine whether O-acetylation or N-acetylation is the major pathway of that type of disease. However, because of limited data on metabolic pathway of various aromatic amines, further studies are mandatory to address this discrepancy.

In conclusion, this study indicates that NAT2 genotype exhibits non-significant association with the risk of developing bladder cancer, either alone or with tobacco users, or pathological grade, or clinical stage of disease.

Table 4 – Frequency of N-acetyltransferase-2 genotypes of bladder cancer patients categorized by pathologic grade of differentiation.

<table>
<thead>
<tr>
<th>NAT2 phenotype</th>
<th>p Value</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Slow-acetylators</td>
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</tr>
<tr>
<td>Bladder cancer (n = 101)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade-1 (n = 40)</td>
<td>18 (45%)</td>
<td>22 (55%)</td>
</tr>
<tr>
<td>Grade-2 (n = 26)</td>
<td>14 (53.85%)</td>
<td>12 (46.15%)</td>
</tr>
<tr>
<td>Grade-3 (n = 35)</td>
<td>18 (51.43%)</td>
<td>17 (48.57%)</td>
</tr>
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</table>

The Director of Sanjay Gandhi Post Graduate Institute of Medical Science provided the necessary facilities.
Daya Shankar Lal Srivastava is research fellow supported by the Council of Scientific and Industrial Research, New Delhi, India.
REFERENCES


EDITORIAL COMMENT

There is a long-lasting discussion, whether foreign-compound-metabolizing enzymes may modify the risk of chemically induced cancer. Phenotyping studies in the late sixties provided evidence that slow acetylators are at increased risk for bladder cancer (1-3). It was hypothesized that in rapid acetylators arylamines, as contained in aniline dyes or cigarette smoke (e.g. 4-aminobiphenyl), are detoxified by N-acetylation in the liver and excreted in the urine. In contrast, low N-acetylation activity leads to increased formation of N-hydroxylated products. These hydroxylamines may undergo further O-acetylation in the urinary bladder preferentially by arylamine N-acetyltransferase 1 (NAT1), which was found to be expressed in the urinary epithelium (4). The product, arylamine acetoxyesters are unstable in the acid environment and disintegrate spontaneously to aryl nitrenium ions. These highly reactive radicals may well interact with proteins and DNA of bladder epithelial cells forming adducts (5). A number of in vitro studies gave evidence for this theory. However to date, occupational exposure is fortunately decreasing.

The current carefully performed study of Mittal et al. (6) published in this issue, showed in a sample of 101 North-Indian bladder cancer patients and 110 controls that the NAT2 polymorphism did not play a role as susceptibility factor. Also after stratification to smoking habits, differences did not reach statistical significance.

A meta-analysis of 22 published case-control phenotyping and genotyping studies conducted in a total of 2496 cases and 3340 controls in different populations, however, revealed that slow acetylators had a 40% increased risk compared to rapid acetylators (odds ratio 1.4, 95% confidence interval 1.2-1.6) (7). In particular, the largest genotyping studies showed gene-environment interactions. Slow acetylators with a smoking history of more than 50 pack years had a 2-fold higher risk of bladder cancer, as did subjects with typical risk occupations. Subjects meeting both criteria showed the highest risk (8). Differences observed between different ethnicities and locations were thought to be due to distinct tobacco blends preferred by the consumers.
In the new study of Mittal et al. in Northern India, only 43 out of 101 bladder cancer patients and 30 out of 110 controls were classified as tobacco-users (6). In contrast, in the large European study showing NAT2 gene-environment interactions, 70% of all patients were smokers (7). However, in this study also no significant association of NAT2 to bladder cancer risk was observed without consideration of smoking or occupational exposure.

Therefore, as correctly stated by Mittal et al. (6), NAT2 may not be considered as a single individual risk factor for urinary cancer. There is strong evidence that the environmental influence is of essential impact and possibly the interaction with other genes e.g. NAT1 should be investigated to estimate the overall risk of a large sample. Indeed, Bell et al. (9) reported two important facts: NAT1*10 was found to provide enhanced activity in bladder tissue compared to NAT1*4 and moreover, the frequency of NAT1*10 was increased among bladder cancer patients. However, these results are conflicting (10) and recently we were able to show that NAT1*10 does not alter enzyme activity towards ex-vivo formation of N-acetyl p-amino benzoic acid (11). We observed a significant decrement of NAT1*10 genotypes among 425 bladder cancer patients; the odds ratio, adjusted for age, gender, and smoking was 0.65 (95%-C.I. 0.46-0.91; p = 0.013) (12). Considering the NAT2 genotype, a clear under-representation of NAT1*10 genotypes among rapid NAT2 genotypes in the cases studied (odds ratio 0.39; 95%-C.I. 0.22-0.68; p = 0.001), and a gene-gene-environment interaction was observed. NAT2*slow/NAT1*4 genotype combinations with a history of occupational exposure were 5.96 (2.96-12.0)-times more frequent in cancer cases than in controls without risk occupation (p < 0.0001), suggesting that individuals with NAT2*4 and NAT1*10 alleles are at a significantly lower risk for bladder cancer, particularly when exposed to environmental risk factors.

Due to inter-ethnical differences of polymorphic traits, smoking and dietary habits, investigations on the role of polymorphic genes as susceptibility factor for complex diseases like cancer may lead to different results in different populations. There is also some evidence for the predominance of rapid acetylators among colon cancer patients. The role of NAT1 however, is still the subject of considerable investigation. The functional significance of the diverse point mutations in NAT1 is not yet fully understood and there are a growing number of distinct haplotypes being identified. Therefore, studies of NAT1 and NAT2 are sometimes difficult to compare, since different methodologies and numbers of alleles were investigated. However, consideration of gene-gene-environment interactions and the possibility of identifying in parallel a number of SNPs, using modern genotyping techniques, will help to elucidate the impact of these interesting genes particularly in the etiology of cancer.

REFERENCES

8. Brockmöller J, Cascorbi I, Kerb R, Roots I: Combined analysis of inherited polymorphisms in arylamine N-acetyltransferase 2, glutathione S-transferase M1 and


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EDITORIAL COMMENT

The subject of this study is a fundamentally interesting and of highly relevant to public health. It provides an opportunity to test the hypothesis that individuals with slow acetylator NAT2 genotypes have increased susceptibility to bladder cancer, particularly individuals exposed to aromatic amine carcinogens deactivated by NAT2 (such as those present in tobacco smoke). As the authors discuss, many previous studies (many cited in their manuscript), both individually and collectively (through metaanalyses) have reported this relationship and indeed it is one of the most consistently reported gene-environmental relationships identified. However, some small individual studies did not find a significant association, and the present study adds one more to these. As discussed in a review of this subject (reference 1 below and cited by the authors as reference 12), many of these studies have insufficient sample size and power in order to observe the effect. As the authors acknowledge in the introduction to this paper, over 25 NAT2 alleles have been identified in human populations. Yet, the authors used a NAT2 genotype method designed to distinguish only 4 alleles (M1, M2, M3, and M4). NAT2 genotype misclassification can greatly confound these analyses and bias them towards the null hypothesis (1). A study to appear shortly (2) provides more details on the effects of NAT2 genotype misclassification on sample sizes required to detect the association with bladder cancer in smokers. The authors are encouraged to continue these interesting studies with larger sample sizes and more comprehensive NAT2 genotype procedures.

REFERENCES


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EDITORIAL COMMENT

The issue about whether acetylation rates are important in bladder cancer has been discussed for a long time, and different reports have come out. There also is considerable literature about the effect of smoking on bladder cancer so to make the assumption that the two might be additive is very reasonable. This paper looks at 101 bladder cancer patients and 110 controls. The studies have been done very carefully, and they conclusively show that there is no link between fast and slow acetylators and the development of bladder cancer and that smoking does not tip the balance. It is hoped this will lay to rest these questions.

The authors are to be commended on their paper.

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Professor and Chair, Department of Urology
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BIOCHEMICAL FAILURE AS SINGLE ABNORMALITY IN PATIENTS WITH PROSTATE CANCER FOLLOWING RADICAL TREATMENT WITH EXTERNAL RADIOTHERAPY: FOLLOW-UP WITHOUT IMMEDIATE TREATMENT

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ABSTRACT

Introduction: Biochemical failure has been defined as 3 consecutive increases in PSA following curative treatment of prostate cancer. The appropriate management in such cases is controversial. The most usual treatment has been early introduction of hormones. Such patients will live for many years and hormone therapy causes important secondary effects and increases costs. The guideline in our Department of Radiotherapy has been to follow up, with no initial therapy, cases with low PSA and short PSA doubling time. The present study reports this experience.

Materials and Methods: 528 patients with localized prostate cancer were treated by radical approach between 1992 and 1999, with external radiotherapy, with or without adjuvant hormone therapy. After a median follow-up of 77 months, there were 207 (39%) cases with biochemical failure, 78 of which were followed without therapy after the identification of biochemical failure. All of them were asymptomatic patients and had negative radiographic examinations or did not have imaging exams requested since they presented a favorable outcome. The follow-up included at least 2 annual visits with physical examination and PSA.

Results: Of the 78 patients with biochemical failure followed without initial therapy, 7 died from other causes than prostate cancer and the remaining 71 cases were alive and asymptomatic in the last follow-up. Prognostic factors previous to radiotherapy such as stage and Gleason score were not considered when deciding for follow-up without initial therapy in these cases. The most significant aspects considered for this decision were low PSA value (median PSA on the last visit for the 78 cases was only 3.9 ng/mL) and a slow PSA doubling time (in the present experience the median PSA doubling time was 22.5 months).

Conclusion: There seems to be space for expectant management, without initial hormone therapy, in patients with prostate cancer who present biochemical failure and are asymptomatic after radical external radiotherapy. This decision is important, since early introduction of hormones brings late effects and is expensive. Prospective and randomized studies are required to define this issue.

Key words: prostate cancer; radiotherapy; prostate-specific antigen; hormones

INTRODUCTION

Prostate cancer is the most common malignant tumor in men in several countries (1). External radiotherapy is a potentially curative alternative and has been largely used for more than 30 years (2). Serum prostate specific antigen (PSA) is a traditional and well-established marker to monitor the follow-
up of such patients (3). In 1997 the American Society for Therapeutic Radiology and Oncology (ASTRO) published its definition of biochemical failure as being 3 consecutive increases in PSA (4). Though it has not been proved, biochemical failure has been largely used as a marker that anticipates death due to prostate cancer (5). Many patients with prostate cancer, following external radiotherapy, remain asymptomatic, but present a slow increase in PSA as an isolated abnormality. There is no definitive answer about what to do after biochemical failure and thus management in these cases is controversial (6). The most frequently used treatment, even if there is no convincing evidence, has been the introduction of hormones, but there is a concern in relation to costs and side effects (7). Patients with prostate cancer, who are asymptomatic following radiotherapy radical, but with biochemical failure, should live for many years and present clinical progression of cancer only after 8 to 10 years, and eventually die as a consequence of this cancer approximately 12 to 13 years after the diagnosis of biochemical failure (8). This slow evolution has been documented in patients undergoing radical prostatectomy and followed without immediate introduction of therapy following biochemical failure (9).

Initiating the treatment immediately after biochemical failure means that these patients are going to receive hormones for a long time. It is known that long periods of hormone therapy cause significant secondary effects such as loss of libido, impotence, increase in osteoporosis, fractures, and muscle atrophy (8). Not less important, with the exception of orchietomy, all other alternatives for anti-androgenic treatment are quite expensive. Considering this situation, it is useful to know how patients with biochemical failure evolve when they are uniquely observed without an initial treatment. Our hypothesis is that some patients will die with, but not due to prostate cancer, as in cases of low-risk untreated prostate cancer.

The Department of Radiotherapy, in Montreal, tends to follow asymptomatic cases with biochemical failure, without initial treatment. The present work performs a retrospective assessment of such experience.

**MATERIALS AND METHODS**

Between January 1992 and February 1999, 910 cases of prostate cancer were seen in our radiotherapy service, with histological confirmation of adenocarcinoma. Patients included in this review should have localized tumors clinically staged as T1-3N0M0, have been treated with external radiotherapy (without surgery or brachytherapy), with or without neoadjuvant hormone therapy. These patients should have at least 1 year of follow-up in our service. In accordance to these features, 528 cases were reviewed.

Follow-up was performed at least twice a year, with physical examination and serum PSA. Tomography and bone mapping were required according to clinical need based on judgment by the attending doctor. Patients were treated with a 6MV- to 18 MV-energy linear accelerator, with 3 or 4 daily fields. Until 1995, planning was traditionally made in 2 dimensions (2D). Since the end of 1995, conformal planning in 3 dimensions (3D) was introduced in the radiotherapy service. The most recent pre-treatment PSA value was considered as the initial PSA value. Overall follow-up time was considered from the date of last radiotherapy application until the last visit or event. The date of biochemical failure was considered as the date in which the first increase in PSA occurred (among 3 consecutive increases). PSA doubling time (or PSADT) was calculated by linear regression considering all PSA values subsequent to the lowest value following radical radiotherapy (called nadir PSA), through mathematical software that automatically finds the curve that better fits PSA values.

Among the 528 patients analyzed, 207 (39%) had biochemical failure, defined as 3 consecutive increases in PSA separated at least by 4-month interval. When this review was concluded in 2002, of these 207 cases with biochemical failure, 8 did not have data in their records because they had been followed in other institutions, 59 other patients had positive bone mapping and/or pelvic computerized tomography (CT) and received hormone therapy. The remaining 140 patients with biochemical failure were asymptomatic, had negative bone mapping and/or tomography, or these testes were not requested by the attending doctors because they were regarded as
unnecessary. The decision about initiating treatment for these patients or not was individual, with no specific guideline. It was due to fast increase in PSA, decision by the patient himself, decision by the urologist and/or radiotherapist or case inclusion in clinical trials. Thus, 62 (44%) of these 140 cases received hormonal treatment following biochemical failure and 78 (56%) were only followed, without receiving any hormonal treatment following biochemical failure. This last group of 78 asymptomatic patients, with biochemical failure and untreated, is the main object of this retrospective analysis.

RESULTS

Median follow-up times for these 78 patients with biochemical failure and exclusively followed were 77 months. Median age was 70 years (between 49 - 78), median total dose of radiotherapy was 67 Gy (between 61 Gy - 72 Gy), median Gleason score = 6 (between 2 - 10), 12 patients were stage T1, 45 were T2 and 21 were T3. Median initial PSA value = 14 ng/mL (between 3.1 - 65.0). Median nadir PSA value = 0.4 ng/mL (between 0 - 2.8). Median PSA value at the time of diagnosis of biochemical failure was 1.2 ng/mL (between 0.2 - 20). Median PSA value on the last follow-up was only 3.9 ng/mL (between 0.7 - 91.1). Median time until the occurrence of biochemical failure was 30 months (between 4 - 72). Median time until PSA nadir value was reached was 12 months. Median follow-up time after biochemical failure was 43 months (between 0 - 112). Finally, median PSA doubling time (PSADT) was 22.5 months (between 6 - 60).

None of these 78 patients died from prostate cancer in the period under evaluation. Seven died from other causes and the remaining 71 were asymptomatic in the last follow-up.

In relation to the initial radiotherapeutic planning, 59% of cases exclusively followed after biochemical failure were treated with a traditional 2D planning. Table-1 gives a summary of this information and compares data from these 78 untreated patients with those from 62 patients who were treated following biochemical failure. None of these 140 patients died from prostate cancer in the period under evaluation. Comparison between patients, with

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treated (N = 62)</th>
<th>Untreated (N = 78)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>70</td>
<td>70</td>
<td>0.82</td>
</tr>
<tr>
<td>Median RT dose</td>
<td>65 Gy</td>
<td>67 Gy</td>
<td>0.08</td>
</tr>
<tr>
<td>Gleason score (median)</td>
<td>6</td>
<td>6</td>
<td>0.21</td>
</tr>
<tr>
<td>Median of initial PSA (ng/mL)</td>
<td>17</td>
<td>14</td>
<td>0.69</td>
</tr>
<tr>
<td>More frequent stage</td>
<td>T2b</td>
<td>T2b</td>
<td>0.86*</td>
</tr>
<tr>
<td>Without neoadjuvant hormone therapy</td>
<td>60%</td>
<td>63%</td>
<td>0.59</td>
</tr>
<tr>
<td>Median nadir PSA after RT</td>
<td>1.1 (0 - 6.1)</td>
<td>0.4 (0-2.8)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Median PSA in biochemical failure</td>
<td>2.2 (0.3 - 15)</td>
<td>1.2 (0.2-20)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Deaths not due to prostate cancer</td>
<td>2/62</td>
<td>7/78</td>
<td></td>
</tr>
<tr>
<td>Median time of overall follow-up</td>
<td>81 months</td>
<td>77 months</td>
<td>0.36</td>
</tr>
<tr>
<td>Median time until biochemical failure</td>
<td>23</td>
<td>31</td>
<td>0.003</td>
</tr>
<tr>
<td>Median follow-up after biochemical failure</td>
<td>60</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Median PSA on the last follow-up</td>
<td>1.8</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Time until nadir was reached (months)</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

* Mann-Whitney test; all others were χ²
biochemical failure and asymptomatic, both treated and untreated, as summarized in Table-1, is merely an exercise, since patients from the untreated group could have received hormone therapy and vice-versa. Additionally, the process is a dynamic one. Patients without initial treatment can be started on hormone therapy at any time. As shown in Table-1, practically there were no differences between the 2 groups. The few significant differences found suggest that treated patients had a slightly more aggressive PSA kinetics, when compared with untreated patients, with a higher median nadir PSA value (1.1 ng/mL versus 0.4 ng/mL), as well as a higher median PSA value at the time of biochemical failure (2.2 ng/mL versus 1.2 ng/mL) and a slightly shorter median time until occurrence of biochemical failure (23 versus 31 months).

Since they were given radical radiotherapeutic treatment at the same time, at the same radiotherapy service, remained always asymptomatic and had negative examinations or did not undergo any radiological examination (CT or scintigraphy), we tried to figure out why 62 patients were treated while other 78 cases did not receive any treatment. This decision was not clear in all records, but basically it was determined by the urologist’s decision and/or preference of the patients themselves, who were disturbed by seeing their PSA increasing without therapy. Some initiated treatment because they participated in the prospective trial NCIC-PR 7, still ongoing in Canada, aimed to asymptomatic patients with biochemical failure following radical radiotherapy and with PSA greater than 3 ng/mL. The protocol PR 7 randomizes patients comparing immediate intermittent versus continuous hormonal treatment.

COMMENTS

The present paper reviews 528 cases of patients with localized prostate cancer treated with external radiotherapy, with or without neoadjuvant hormone therapy. Two hundred and seven (39%) patients had biochemical failure and 78 of these cases were exclusively followed without any treatment. All these cases were asymptomatic and had negative radiographic examinations or were not required to perform imaging tests. During this period, 7 of these patients died from several causes, but not in consequence of prostate cancer. This is the intention of the “watchful waiting” politics. Why were some patients treated while others were not? There is an idiom in the English language that has been used to justify the current indication of hormone therapy for such cases: “chicken switch”. The expression refers to the point where patient and doctor are frightened (“chicken”) when they see PSA increasing and they activate a device (“switch”) in order to decide taking hormones, even if there is no evidence supporting this decision (10).

Some studies have suggested that early hormone therapy can be better than a late approach, but most of this studies included patients with locally advanced or clinically metastatic disease, that form a group that is different from the one featured in the present review. Messing et al., for example, compared initial androgenic treatment versus observation in a small group of 98 cases with prostate cancer following radical prostatectomy and with positive lymph nodes (11). After a median follow-up of 7.1 years, significantly more men died in the group that was initially observed than in the group with early hormonal treatment. However, the study was terminated before the initially stipulated deadline, there was no central review of the Gleason score (so that there was the possibility of an unequal distribution between both groups) and the cancer-specific survival rate was only 62% in the observed group, when other contemporary publications reported rates of 80% in similar situations (12). The English group “MRC Prostate Cancer Working Party Investigators” compared, in a prospective and randomized manner, the effect of early versus late endocrine therapy also in patients with locally advanced extensive disease, or clinically metastatic disease, but with no symptoms (13). 934 patients took part in this study. The follow-up method and subsequent therapy were not standardized. They were decided upon the usual practice of each participating doctor. As a result, a significant number of patients with late therapy had more pathological fractures and other symptoms, compared with
PSA INCREASE IN PROSTATE CA FOLLOWING RADIOTHERAPY

patients that received early hormone therapy. However, some patients from “late” group never received hormonal treatment in any moment, suggesting that the treatment was initiated too late or it was never offered. These 2 studies have been also referred in an attempt to warrant immediate hormonal treatment following biochemical failure also for asymptomatic patients, after radical radiotherapeutic treatment. We understand that, in addition to methodological criticism, these are completely different clinical situations.

In the present study, which assessed biochemical failure following radiotherapy, the 78 patients were asymptomatic, had no metastases and presented as their only abnormality a slow increase in serum PSA, forming, thus, a selected population that is different from the 2 studies previously mentioned. In our Department of Radiotherapy, there is a trend towards the non-introduction of initial treatment in cases that present low PSA and a slow increase over time, that is, a long PSADT time. Hormone therapy has been initiated basically when PSA values exceed 10 or 20 ng/mL or PSADT > 8 months. In the present experience, after 77 months of follow-up, median PSA in the last visit of 78 cases followed without therapy was only 3.9 ng/mL. Prognostic tables for prostate cancer include PSA values < 10 ng/mL or 20 ng/mL as a good prognostic factor (14) and consequently these have been our reference values for initiating therapy after biochemical failure.

In the present review, median PSADT time of the 78 patients that were followed without treatment was 22.5 months, reflecting the selection of cases with slow tumoral evolution. The group from MD Anderson hospital, in Houston, has several publications concerning PSA kinetics in patients with prostate cancer following radical external radiotherapy (15). They conclude that the metastasis rate significantly ranges depending on PSADT. Actuarial metastasis rates in 7 years were 54% and 7%, for cases with PSADT > 8 months and PSADT < 8 months, respectively.

Patients with newly diagnosed prostate cancer can be exclusively followed without initial therapy (“watchful waiting”) with good results for cases with low risk or early stages (16,17). In the present experience, initial prognostic factors such as Gleason score or staging (T), were not considered for deciding whether initiate hormone therapy or not after biochemical failure. Thus, there were more T3 (21 cases) than T1 cases (12 cases) in the group of 78 patients who were exclusively followed. Similarly there were patients with all levels of Gleason score, ranging from 2 to 10.

Finally, the request of radiographic examinations for assessing metastases, particularly bone scintigraphy, in asymptomatic patients with biochemical failure, is not well defined and varies among institutions and even among their professionals. The probability of a positive bone scintigraphy is close to zero in patients with PSA < 15 ng/mL (18). Recent guides (“guidelines”) for prostate cancer (19) suggest that in patients who are not under anti-androgenic therapy, the risk of positive bone scintigraphy is lower than 5% of cases when PSA is lower than 40 - 50 ng/mL, and consequently this examination should not be routinely requested in asymptomatic patients with low PSA. More than 1/3 of our patients with biochemical failure were not requested to perform bone scintigraphy because they were asymptomatic and had low PSA value.

CONCLUSION

This retrospective analysis found 207 (39%) out of 528 patients with localized prostate cancer and treated with radical radiotherapy, between 1992 and 1999, with biochemical recurrence after 77 months of median follow-up. There is a lot of controversy about what to do, and when, after biochemical failure. The most common treatment has been the introduction of early anti-androgenic therapy, though there is no evidence that this approach offers better survival than a slightly later treatment.

Our hypothesis is that asymptomatic patients with low PSA and long PSADT after biochemical failure can undergo an expectant management in a first moment, without worsening the final outcome. The present retrospective analysis showed that among the 78 (39%) patients who were exclusively followed
without any therapy following biochemical failure, there was no death from prostate cancer or metastasis, suggesting that there is room for delay when initiating the treatment in selected cases. Patients were not treated because they had low PSA level (in general PSA < 10 ng/mL) and long PSADT (in general > 8 months) during follow-up, without major concern with early prognostic factors such as staging or Gleason score.

Selecting patients with biochemical failure so they can be exclusively followed, and initiating hormone therapy only when the tumor shows signs of higher aggressiveness, is the most cost-effective alternative that should offer better quality of life, since these patients will not suffer the secondary effects caused by anti-androgenic therapy over long periods. As usual, the only way to know if there is a difference between early or late hormonal therapy in this particular group of patients, is through prospective and randomized studies. This concept has been previously published (20). Our suggestion, for an eventual study in Canada, is to compare immediate hormone therapy versus a selective delay. In the latter case, asymptomatic patients with biochemical failure would initiate treatment only with PSA > 10 ng/mL and PSADT < 8 months, or upon clinical progression of the tumor, confirmed by some radiological examination.

REFERENCES

18. Yap BK, Choo R, Deboer G, Klotz L, Danjoux C, Morton G: Are serial bone scans useful for the follow-
Editorial Comment

Biochemical recurrence following monotherapy for prostate cancer with external radiotherapy is a problem commonly found by the urologist in daily practice and its management is not always easy, since there is controversy in the literature about what should be done in such situation. The institution of adjuvant hormone therapy (continuous or intermittent) is associated with high costs and several changes that interfere in the patient’s quality of life, such as loss of libido, impotence, depression, osteoporosis and loss of muscular mass.

Thus, the authors report the experience with a recent series of patients treated by external radiotherapy, with or without neoadjuvant hormone therapy, where biochemical recurrence following treatment was observed in 39% of cases. Among the asymptomatic cases with no clinical, tomographic or scintigraphic evidence of progressive disease, the decision of initiating adjuvant hormone therapy was individual, but one group of 78 selected patients, based on the absence of clinical evidence of disease and slow increase in PSA (long doubling time), was followed without receiving adjuvant hormone therapy. The results in this group (with a median of 77 months of follow-up) were excellent, with no case of clinical metastasis or specific mortality to the moment. In the described series, the value of nadir PSA, the PSA upon detection of biochemical failure and the mean time until the occurrence of biochemical failure seem to have been determinant for selecting the group that was treated exclusively with observation. The paper strongly demonstrates that there is really room for careful observation of a selected group of patients with post-radiotherapy biochemical recurrence, especially if they do not present clinical or radiological signs of progression, and if the PSA doubling time is long (> 8 months). However, absolute results concerning these issues will be revealed only after the conclusion of prospective and randomized studies, as the authors personally stress.

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COEXISTENCE OF PROSTATE NEOPLASIA IN PATIENTS UNDERGOING RADICAL CYSTOPROSTATECTOMY DUE TO VESICAL NEOPLASIA

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ABSTRACT

Objective: To assess the incidence of bladder carcinoma infiltrating the prostate and prostate adenocarcinoma in patients undergoing radical cystoprostatectomy due to bladder cancer, as well as to assess if the characteristics of the bladder neoplasia influence the prostatic involvement by this neoplasia.

Materials and Methods: We retrospectively assessed 60 male patients, who underwent radical cystoprostatectomy between July 1997 and December 2003. Mean age was 66.7 years (40 and 93 years). The product of radical cystoprostatectomies was checked for involvement of urethra and prostate parenchyma by the primary neoplasia, and for the presence of associated prostate adenocarcinoma. Bladder neoplasia characteristics, such as localization, size, multifocality, association with in situ carcinoma and histological grade, were studied in order to assess the possibility of using such characteristics as predictive factors of prostate infiltration by bladder urothelial carcinoma.

Results: We observed the presence of 20% of patients with bladder carcinoma infiltrating the prostatic urethra, 23.3% of patients with infiltration of the prostate parenchyma and 28.3% of patients with associate prostate adenocarcinoma, resulting in a total of 55% of patients with prostatic involvement (infiltrative bladder carcinoma and/or adenocarcinoma). We also observed a statistically significant correlation between tumor location in the trigone, the presence of in situ carcinoma and the histological grade of the bladder tumor with prostatic infiltration by the vesical neoplasia.

Conclusion: The coexistence of prostatic neoplasia in patients operated for bladder neoplasia was frequent in our sample (55%). We observed that the prostatic infiltration by bladder tumors occurs more frequently with tumors located in the trigone, with associated in situ carcinoma and with high histological grade. There was no correlation between neoplastic infiltration of prostate and multifocality or size of the bladder tumor in the studied sample.

Key words: bladder neoplasms; neoplasm invasiveness; prostatic neoplasms; cystectomy

INTRODUCTION

Radical cystoprostatectomy with urinary reconstruction represents the most efficient treatment for invasive or refractory bladder cancer, with cure indexes up to 80% of treated cases (1). However, due to the high incidence of complication with this procedure, alternative techniques have been recently described, preserving the prostate apex, or even the prostate capsule, aiming to preserve sexual and urinary functions of operated patients (1-3).

Due to the increasing number of patients undergoing procedures with urethral preservation, more attention has been given to prostatic invasion by bladder neoplasia, which certainly increases the risk of urethral recurrence and death from the neoplasia (4),
PROSTATE CA IN PATIENTS WITH VESICAL NEOPLASIA

particularly in those patients with invasion of the prostate parenchyma (5).

Additionally, several studies have shown the high incidence of incidental prostate adenocarcinoma in specimens from cystoprostatectomies performed for treating bladder cancer (3,6-9). Some of them reported a predominance of tumors in the prostate apex (3,6). Patients with bladder neoplasia can present prostate neoplasia with a relative risk up to 19 times higher than what would be expected (10). However, incidental prostate tumors present characteristics that are similar to latent tumors found in autopsy series, some have a proven potential of progressive disease (3).

The objective of this work is to verify the incidence of tumoral infiltration (urethra and/or parenchyma) in the prostate of patients who underwent radical cystoprostatectomy for bladder urothelial carcinoma, as well as the presence and histological grade of the incidental prostate adenocarcinoma. The characteristics of bladder tumors invasive to urethra or prostate parenchyma were also assessed, in separate groups, with the objective of predicting those patients with higher predisposition to associated prostatic disease.

MATERIALS AND METHODS

We conducted a retrospective study of all patients undergoing radical cystoprostatectomy for management of bladder urothelial (or transitional cell) carcinoma during the period from July 1997 to December 2003. The inclusion criteria comprised male patients, who underwent radical cystoprostatectomy for management of bladder urothelial carcinoma, whose surgical specimens were histologically examined.

Female patients were excluded, as well as patients undergoing partial cystectomy, patients with different histological diagnosis other than bladder urothelial carcinoma and/or patients with irresectable tumors. Among a total of 84 patients who underwent open surgery for management of bladder carcinoma between 1997 and 2003, 60 fulfilled the inclusion criteria. Mean age of patients was 66.5 years, with age limits ranging between 40 and 93 years. All patients underwent radical cystoprostatectomy.

Staging and histological grading, according to the TNM system of the International Union Against Cancer (UICC) and grading system of the World Health Organization (WHO), respectively, are illustrated in Table-1. In relation to urinary reconstruction, 48 (80%) patients underwent ileal conduit, 11 (18.3%) orthotopic neobladder, 2 (3.3%) ureterosigmoidostomy and 2 (3.3%) wet colostomy.

The product from the radical cystoprostatectomies was fixed in 10% formalin solution and processed according to the usual standards for fixation and inclusion routinely employed in pathology services.

The specimens were weighted and measured. The majority of specimens were opened through the anterior bladder wall. In average, 2 to 5 sections were made to each tumor (depending on the size), in addition to random sections in the following bladder regions: dome, right and left lateral walls, posterior and anterior walls, triangle and urethral margin of the bladder.

The prostate was sectioned in quadrants, similar to the processing for radical prostatectomy specimens. Sections from transitional and peripheral zones of the prostate, and from apical, middle and basal regions in both lobes were included, resulting, in average, in 6 blocks per case. The margin of prostatic urethra was represented separately. The blocks were sectioned in slices with 3- to 5-micrometers in thickness and the resultant histological slides were stained by hematoxylin-eosin.

| Table 1 – Staging and histological grade of bladder tumors. |
|-------------|-----|-----|-----|-----|-----|-----|
|             | Ta  | T1  | T2  | T3  | T4  | Total |
| Low grade   | 3   | 5   | 3   | 4   | 1   | 16   |
| High grade  | 0   | 1   | 11  | 14  | 18  | 44   |
| Total       | 3   | 6   | 14  | 18  | 19  | 60   |

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In relation to the characteristics of bladder neoplasias, the variables included in the analysis were tumoral location in bladder, assessing invasion, or not, of the vesical triangle, tumoral multifocality, presence or absence associated in situ carcinoma in the adjacent vesical mucosa, and histological grade, according to the classification system of the WHO (11).

The correlation between these characteristics and the incidence of neoplastic infiltration of bladder carcinoma to prostate were assessed by Fisher’s exact test.

RESULTS

Of the 60 who underwent radical cystoprostatectomy for bladder neoplasia, we observed that 18 (30%) patients presented urethral (20%) and/or parenchymal (23.3%) invasion of the prostate. Due to the extremely distinct prognostic connotations between the infiltration of urethra and prostate parenchyma, since parenchymal invasion results in poorer survival (5), we separated the groups and assessed the characteristics of bladder tumors with these different forms of invasion. Among the total of assessed patients, 36 (60%) presented tumor in the trigone, including 9 (25%) with infiltration of the prostatic urethra and 12 (33.3%) with infiltration of prostatic parenchyma by the bladder urothelial carcinoma.

On the other hand, 3 (12.5%), of the 24 patients with tumors sparing the trigone, presented urethral infiltration, while only 2 (8.3%) of them presented parenchymal infiltration. This result did not show statistically significant differences in relation to invasion of the prostatic urethra, but was significant in relation to infiltration of the prostatic parenchyma (Table-2). Similar results were observed when the presence of in situ carcinoma was observed in the adjacent mucosa vesical.

Of the 18 (30%) patients with in situ carcinoma in vesical mucosa, 8 (44.4%) presented invasion of prostatic urethra and 7 (38.9%) presented infiltration of prostatic parenchyma, while only 4 (9.5%) of 42 patients without associated in situ carcinoma showed prostatic urethral involvement and, 7 (16.6%), prostatic parenchymal involvement (Table-3). Additionally, patients with high-grade bladder carcinoma also presented higher incidence of prostatic infiltration, both urethral and parenchymal, when compared with those with low-grade tumor. Of the 44 (73.3%)

<table>
<thead>
<tr>
<th>Prostate Infiltration</th>
<th>Present - N (%)</th>
<th>Absent - N (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethra</td>
<td>9 (25)</td>
<td>3 (12.5)</td>
<td>0.197</td>
</tr>
<tr>
<td>Parenchyma</td>
<td>12 (33.3)</td>
<td>2 (8.3)</td>
<td>0.023</td>
</tr>
<tr>
<td>Absent</td>
<td>22 (61.1)</td>
<td>20 (83.3)</td>
<td>0.058</td>
</tr>
<tr>
<td>Total</td>
<td>36 (60)</td>
<td>24 (40)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor in Trigone</th>
<th>Absent - N (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>18 (30)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>42 (70)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In Situ Bladder Carcinoma</th>
<th>Present - N (%)</th>
<th>Absent - N (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethra</td>
<td>8 (44.4)</td>
<td>4 (9.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Parenchyma</td>
<td>7 (38.9)</td>
<td>7 (16.6)</td>
<td>0.065</td>
</tr>
<tr>
<td>Absent</td>
<td>8 (44.4)</td>
<td>34 (81)</td>
<td>0.005</td>
</tr>
<tr>
<td>Total</td>
<td>18 (30)</td>
<td>42 (70)</td>
<td></td>
</tr>
</tbody>
</table>
patients with high-grade tumors, 12 (27.3%) presented infiltration of prostatic urethra and 14 (31.8%) infiltration of parenchyma, while none of the 16 patients with low-grade tumor, presented this particularity (Table-4). Prostatic involvement was evaluated in patients with multifocal bladder tumors as well (Table-5), but there was no statistically significant difference in this sample. Similarly, the association between size of the vesical tumor (smaller, equal or larger than 3 cm) and the presence of prostatic infiltration was not statistically significant, as shown in Table-6.

Prostatic adenocarcinoma was an incidental finding in 17 (28.3%) patients. Of these, 16 (94.1%) had a combined Gleason score lower or equal to 6 and only 1 (5.9%) presented Gleason score equal to 7 (3 + 4).

When grouping all patients with infiltrative urothelial carcinoma in prostate and/or primary prostate adenocarcinoma, 33 (55%) presented coexisting prostatic neoplasia.

**COMMENTS**

It was determined that 20 to 40% of patients undergoing radical cystoprostatectomy due to bladder urothelial carcinoma can present infiltration of urethra and/or prostatic parenchyma by the bladder neoplasia (4,12). In our series, 30% of patients were diagnosed with tumoral invasion of prostate, and this

**Table 4** – Correlation between the presence of prostate infiltration and histological grade of the bladder urothelial carcinoma.

<table>
<thead>
<tr>
<th>Prostate Infiltration</th>
<th>Histological Grade</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High grade - N (%)</td>
<td>Low grade - N (%)</td>
</tr>
<tr>
<td>Urethra</td>
<td>12 (27.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Parenchyma</td>
<td>14 (31.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Absent</td>
<td>26 (59.1)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>44 (73.3)</td>
<td>16 (26.7)</td>
</tr>
</tbody>
</table>

**Table 5** – Correlation between the presence of prostate infiltration and tumor multifocality.

<table>
<thead>
<tr>
<th>Prostate Infiltration</th>
<th>Multifocality</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present - N (%)</td>
<td>Absent - N (%)</td>
</tr>
<tr>
<td>Urethra</td>
<td>5 (19.2)</td>
<td>7 (20.6)</td>
</tr>
<tr>
<td>Parenchyma</td>
<td>5 (19.2)</td>
<td>9 (26.5)</td>
</tr>
<tr>
<td>Absent</td>
<td>19 (73.1)</td>
<td>23 (67.6)</td>
</tr>
<tr>
<td>Total</td>
<td>26 (43.3)</td>
<td>34 (56.7)</td>
</tr>
</tbody>
</table>

**Table 6** – Correlation between the presence of prostate infiltration and size of bladder urothelial carcinoma.

<table>
<thead>
<tr>
<th>Prostate Infiltration</th>
<th>Size</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 3 cm - N (%)</td>
<td>≤ 3 cm - N (%)</td>
</tr>
<tr>
<td>Urethra</td>
<td>8 (18)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Parenchyma</td>
<td>11 (25)</td>
<td>3 (18.7)</td>
</tr>
<tr>
<td>Absent</td>
<td>31 (70.4)</td>
<td>11 (68.7)</td>
</tr>
<tr>
<td>Total</td>
<td>44 (73.3)</td>
<td>16 (26.7)</td>
</tr>
</tbody>
</table>
incidence reached 55.5%, in patients with associate in situ carcinoma.

Additionally, we found an increase in the incidence of prostatic infiltration in patients with tumors located in the vesical triangle and in those with high-grade urothelial neoplasias, with incidences of 41.6% and 41%, respectively. The high risk of prostatic involvement by bladder tumors located close to the bladder neck, multifocal or associated with in situ carcinoma has been previously reported (5,13). The assessment of such factors is important because it can help when deciding whether to partially preserve or to completely resect the prostate, when treating patients with infiltrative bladder neoplasia.

Recent reports indicate that the invasion by urothelial carcinoma to the prostatic urethra does not alter survival, contrarily to parenchymal invasion of the prostate (5).

However, the infiltration of prostatic urethra can be associated with higher risk of urethral recurrence. In the present study, we observed a statistically significant correlation between urethral infiltration of the prostate and the presence of in situ carcinoma of vesical mucosa as well as a high histological grade. On the other hand, the incidence of infiltration of the prostatic parenchyma was significantly higher in patients with tumor located in the trigone and in those with high-grade urothelial neoplasia.

The diagnosis of incidental prostate adenocarcinoma in these patients was reported in 16% to 46% in cases, in the reviewed works (3,6-9). In our patients, 28.3% of operated patients presented prostatic adenocarcinoma.

Though the discrepancies between studies could be related to the method of pathologic evaluation employed, all indicate the presence of a significantly high incidence of associated disease (3). Several authors observed a relative risk of patients with bladder cancer developing prostate cancer that is 9 to 19 times higher than the expected rate (3,4). These incidental tumors are usually small, well or moderately differentiated and limited to the prostate. Almost all our patients (94.1%) presented combined Gleason score lower or equal to 6.

Only one patient (5.9%) presented Gleason 7 (3 + 4). These studies represent the closest correlation as possible between living patients and autopsy series that study incidental or latent prostate adenocarcinoma. However, in the modern age of orthotopic bladder replacement, where some authors have proposed preservation of prostatic tissue or prostatic capsule, the precise location, histological grade and size of these tumors are important factors to be considered. Several studies observed a high frequency of prostate tumors close or located in the prostate apex, so that an incomplete radical surgery of prostate could impair the principles of oncologic surgery (3,6). In our sample, it was impossible to determine the precise location of tumors due to the relatively recent standardization of surgical specimens processing.

When assessed together, invasive urothelial carcinoma in prostate and adenocarcinoma can be found in 40 to 80% of patients (2). In the present work, we found prostatic involvement in 55% of patients, by prostatic invasion either by the bladder tumor (30%), or by the presence of an associated prostate adenocarcinoma (28.3%).

Thus, in addition to a proper patient selection in order to rule out prostate adenocarcinoma in patients who are candidates to surgery with preservation of the prostate apex, through clinical examination, serum levels of prostate specific antigen, transrectal ultrasound and prostate biopsy, a detailed assessment of the bladder neoplasia’s characteristics must be performed, with urethrocystoscopy, endoscopic resection and randomized biopsy of bladder. In this way, the possibility of missing a diagnosis of coexisting prostate neoplasia is reduced (3,6-9). Additionally, it is possible to perform an intra-operative freezing biopsy of the urethral margin in order to further reduce this possibility (13,14).

Though several works have concluded that the resection of the prostate apex is mandatory during cystoprostatectomy for bladder cancer (3,6,9), the preservation of the prostate apex can reduce the morbidity and significantly improve the patients’ quality of life through improving social, sexual and psychological implications of the radical cystectomy (1). The proper selection of patients through a detailed preoperative evaluation can allow this procedure to be performed, but prospective studies will be required.
to follow these patients’ outcome in order to assess if the preservation of prostate apex really impairs survival and the risk of urethral recurrence in these patients.

CONCLUSION

The presence of prostatic involvement by local infiltration of bladder neoplasia and/or synchronous prostate adenocarcinoma was frequent in our sample (55%). We observed that the infiltration of prostatic urethra by bladder urothelial tumors occurs more frequently in tumors with in situ carcinoma in the adjacent vesical mucosa and in those with high histological grade. The parenchymal infiltration of prostate by urothelial carcinoma was more common among tumors located in the trigone and in high-grade tumors as well. We found no association between multifocality and size of bladder tumor with the presence of urothelial carcinoma in the prostate.

REFERENCES


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VARIABLES PREDICTIVE OF VOIDING DISFUNCTION FOLLOWING APONEUROTIC SLING SURGERY: MULTIVARIATE ANALYSIS

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ABSTRACT

Introduction: Aponeurotic sling surgeries can evolve with obstruction or voiding dysfunction in 5 to 20% of patients. There are few studies on factors that could possibly predispose to voiding difficulties or urinary retention. The objective of this work is to identify these potential clinical or urodynamic factors.

Materials and Methods: Records from 130 patients who underwent aponeurotic sling surgeries were reviewed. All patients underwent a throughout urodynamic study during pre-operative investigation. The variables studied were age above 65 years, previous pelvic surgeries, concomitant surgeries, post-voiding residue higher than 100 mL, vesical obstruction (according to Blaivas-Groutz nomogram) and urinary flow under 12 mL/s. Post-voiding residue was assessed on the seventh post-operative day through vesical catheterization. Recovering of spontaneous voiding after 7 post-operative days or with a residue higher than 100 mL, was regarded as voiding dysfunction. Univariate analysis was performed with qui-square test and Fisher’s exact test, and multivariate analysis was performed by logistic regression with $\alpha = 5\%$.

Results: Age in the studied group ranged from 41 to 83 years (mean 56.7 years), with 69 (53%) patients having urethral hypermobility and 61 (47%) having intrinsic urethral lesion. Normal voiding occurred in 97 (75.6 %) women with 7 post-operative days. The only significant variable in the univariate ($p = 0.014$) and multivariate ($p = 0.017$) analysis was post-voiding residue higher than 100 mL.

Conclusion: Pre-operative presence of a post-voiding residual urine higher than 100 mL was the only variable predictive of voiding dysfunction.

Key words: urinary incontinence; surgery; voiding dysfunction; urethra; bladder


INTRODUCTION

Pubovaginal sling surgery has been used for treating urinary incontinence due to sphincteric lesion for decades and with good results (1). Some years ago, some reports showed up demonstrating good results for all types of female stress urinary incontinence as well (2-4). This major indication of the technique has been accompanied by incidences of prolonged urinary retention of 5 to 20% (4-6).

The urethrovesical junction undergoes, due to the fibrotic process, a change in position during the postoperative period for synthetic and autologous slings (7). Such change could exert an obstructive effect on the urethra, increasing voiding pressure and decreasing the urinary flow, which could explain the
outcome with retention. However, videourodynamic studies have demonstrated that a band carefully placed with no tension, would not have an obstructive effect (8,9).

A number of factors are suggested as carrying a risk for voiding dysfunction, such as advanced age, concomitant surgeries, previous surgeries for urinary incontinence, urinary flow below 12 mL/s, large post-voiding residual urine and voiding with low contractility or with Valsalva’s maneuver, among others (6,10-13).

The objective of this study is to analyze the importance of some of these clinical and urodynamic factors for predicting the difficulty to obtain normal voiding following aponeurotic sling surgeries, using multivariate analysis.

MATERIALS AND METHODS

One hundred and thirty patients with urinary incontinence due to urethral hypermobility or intrinsic sphincteric lesion, who underwent sling surgery with aponeurosis of the rectus muscle of abdomen, between 1998 and 2003, had their medical records reviewed. All patients underwent a throughout urodynamic study with 2 vesical fillings previously to surgery.

The exam was performed according to the standards of the International Continence Society, using 0.9% saline solution at a temperature of 37° Celsius, with a 7F two-way urethral catheter and a 10F rectal catheter (14).

The abdominal leak point pressure under stress was measured at half cystometric capacity, in upright position, with the presence of a 7F two-way catheter inside the urethra, considering the lowest value for vesical pressure in the absence of detrusor contraction (15). Patients were initially asked to perform repeated Valsalva’s maneuvers for 3 times. In the absence of leakage with Valsalva, the patient was asked to cough. Those patients with abdominal leak point pressure under stress above 60 cm of H₂O were regarded as having urinary incontinence with some degree of urethral hypermobility.

The same surgeon performed all surgeries, using segments of aponeurosis of the rectus abdomi-
VOIDING DIFFICULTY FOLLOWING SLING SURGERY

Table 1 – Frequency of observed variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of other diseases</td>
<td>62</td>
<td>47.7</td>
</tr>
<tr>
<td>Previous surgeries</td>
<td>89</td>
<td>68.5</td>
</tr>
<tr>
<td>Concomitant surgeries</td>
<td>45</td>
<td>34.6</td>
</tr>
<tr>
<td>Age above 65 years</td>
<td>50</td>
<td>38.5</td>
</tr>
<tr>
<td>Urethral hypermobility</td>
<td>69</td>
<td>53.1</td>
</tr>
<tr>
<td>Urinary flow &lt; 12 mL/s</td>
<td>26</td>
<td>20.0</td>
</tr>
<tr>
<td>Obstruction</td>
<td>20</td>
<td>15.4</td>
</tr>
<tr>
<td>Residual urine &gt; 100 mL</td>
<td>67</td>
<td>51.5</td>
</tr>
</tbody>
</table>

Table-1 shows the frequencies for each variable. Table-2 demonstrates the results obtained in univariate analysis, with the only significant variable being post-voiding residual urine, which was also observed in the multivariate analysis (p = 0.017).

A post-voiding residual urine superior to 100 mL occurred in 67 patients, and 16 of them were obstructed, 22 had large prolapses, 15 presented contractility deficiency, and in 14 it was not possible to suppose any cause for the increased residual urine.

COMMENTS

Even if videourodynamics does not demonstrate obstruction following sling surgeries, the literature stresses that decreasing the tape tension reduces the risk of voiding dysfunction, but reduces therapeutic efficacy as well. Flood et al. (17) compared the presence of early voiding dysfunction in 2 groups where the only variable was tape tension. Voiding efficiency (smallest post-voiding residue) was significantly lowest in the group of tension-free tapes, however the failure indexes (any leakage at 3 months after surgery) were also significantly higher in this group (17). Petrou & Broderick demonstrated that urethral position changes in a retropubic direction after surgery, and that occurs progressively as the remodeling of aponeurotic tape takes place (18). Such change would lead to the necessity of voiding adaptation, which would be more efficient and prompter depending on each patient’s functional characteristics.

Voiding with weak detrusor contraction or with Valsalva’s maneuver has been associated with a higher risk of urinary retention and even surgical failure (12,19,20). Miller et al. (12) observed that of 21 women that voided without contraction on the pre-operative test, 4 (23%) presented postoperative urinary retention, versus none among other 48 women with normal contraction. Still in the same study, no patient with contraction superior to 12 cm of H2O presented retention.

Among the parameters tested for voiding dysfunction, only the post-voiding residue was a significant factor. However, the authors stress that the small sample limits the conclusions of the study (12).

Table 2 – Univariate analysis for different risk factors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant diseases</td>
<td>0.99</td>
<td>0.610 – 1.614</td>
<td>0.891</td>
</tr>
<tr>
<td>Previous surgeries</td>
<td>1.89</td>
<td>1.010 – 3.535</td>
<td>0.052</td>
</tr>
<tr>
<td>Concomitant surgeries</td>
<td>1.45</td>
<td>0.899 – 2.361</td>
<td>0.183</td>
</tr>
<tr>
<td>Age above 65 years</td>
<td>1.24</td>
<td>0.771 – 2.024</td>
<td>0.462</td>
</tr>
<tr>
<td>Urethral hypermobility</td>
<td>0.78</td>
<td>0.486 – 1.277</td>
<td>0.422</td>
</tr>
<tr>
<td>Urinary flow &lt; 12 mL/s</td>
<td>1.48</td>
<td>0.886 – 2.481</td>
<td>0.211</td>
</tr>
<tr>
<td>Urinary obstruction</td>
<td>1.51</td>
<td>0.887 – 2.591</td>
<td>0.213</td>
</tr>
<tr>
<td>Residual urine &gt; 100 mL</td>
<td>2.00</td>
<td>1.158 – 3.486</td>
<td>0.014</td>
</tr>
</tbody>
</table>
tical analysis. Kobak et al. (13) studied 3 groups of patients undergoing Burch surgery, anterior colporrhaphy and vaginal wall sling with multivariate analysis, and observed that advanced age, previous cystopectomy, larger vesical volume on the first voiding desire and high post-voiding residual urine were risk factors for postoperative voiding dysfunction. The authors did not associate pre-operative voiding mechanism, intensity of contraction and use of Valsalva’s maneuver, with risk of voiding dysfunction. The closest comparison to our group of patients would be only those 34 sling surgeries performed in this study, even if they were made on the vaginal wall. However, the type of surgery was not stratified by the authors (13).

Advanced age is the clinical information most frequently related to the risk of urinary retention following aponeurotic sling surgeries and even following “tension-free vaginal tape” (TVT), probably due to the higher risk of dysfunctional pelvic nervous plexuses and detrusor muscle (6,19). In this work, clinical factors were not predictive of voiding difficulties, reinforcing the theory that pre-operative urodynamic results are more important.

There is no universally accepted urodynamic criterion for diagnosing vesical obstruction in women. We used the Blaivas-Groutz nomogram, which classifies the obstruction levels in non-obstructed, slightly obstructed, moderately and severely obstructed (6). However this nomogram has not been shown able to predict postoperative dysfunction. In a randomized study between Burch surgery and TVT, it was observed that the nomogram did not show differences either between patients with objective cure of incontinence, failure or voiding dysfunction in both groups (20).

The methodology used in trials, usually retrospective, with limited statistical methods and samples, as well as different definitions of urinary retention and voiding dysfunction, grouping different types of surgery, explain the discordant results found in literature. Though we have not studied the voiding mechanism and the presence of involuntary contractions, the statistical analysis, the sample volume, and the selection of patients who underwent surgeries with aponeurotic slings only, strengthen the results of this work.

Urethral obstruction probably is not the only causal agent, both for achieving surgical success and for postoperative voiding dysfunction. Factors related to voiding dynamic and efficacy and to changes in the periurethral collagen, may act as well. Our results reinforce the notion that the pre-operative presence of significant post-voiding residual urine is not a contra-indication for performing the aponeurotic sling; however, it alerts the surgeon to the risk of any difficulty concerning the adaptation to a new voiding dynamics and consequently the recovery of normal voiding.

CONCLUSION

Voiding residual urine above 100 mL was the only variable predictive of voiding dysfunction in the postoperative period of aponeurotic sling surgery in a multivariate analysis.

REFERENCES


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LONGITUDINAL URETHRAL SLING WITH PREPUBIC AND RETROPUBIC FIXATION FOR MALE URINARY INCONTINENCE

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ABSTRACT

Objective: Description and early results of a new urethral sling technique for treatment of postprostatectomy urinary incontinence, which combines efficacy, low cost and technical simplicity.

Materials and Methods: From May 2003 to April 2004, 30 patients with moderate or total urinary incontinence, following radical prostatectomy or endoscopic resection of the prostate, underwent the new technique. The technique is based on the placement of a longitudinal-shaped sling in the bulbar urethra, measuring 4 cm in length by 1.8 cm in width, made of Dacron or polypropylene mesh, fixed by 4 sutures on each side, with 2 sutures passed with Stamey-Pereira needle by retropubic approach and 2 by prepubic approach, which are then tied over the pubis.

Pressure control was determined by interrupting the loss of infused water through a suprapubic cystostomy 60 cm from the pubis level.

Results: Pre-operative assessment excluded vesical instability, urethral stenosis and urinary infection. Suprapubic cystostomy was removed when the patient was able to satisfactorily void with urinary residue lower than 100 mL, which occurred in 29 of the 30 cases. In 2 cases, there was infection of the prosthesis, requiring its removal. In 3 cases, there was the need to adjust the sling (increasing the tension), due to failure of the urinary continence. Overall, 20 of 30 (66.7%) operated patients became totally continent, and did not require any kind of pads. Four of 30 (13.3%) patients achieved partial improvement, requiring 1 to 2 pads daily and 6 of 30 (20%) patients had minimal or no improvement. There was no case of urethral erosion.

Conclusion: This new sling technique has shown highly encouraging preliminary results. Its major advantage over other surgical techniques for treatment of moderate or severe stress urinary incontinence is the simplicity for its execution and low cost. A long-term assessment, addressing maintenance of continence, detrusor function and preservation of the upper urinary tract, is still needed.

Key words: urinary incontinence; men; urinary sphincter; prostheses and implants; surgical technique

INTRODUCTION

Stress urinary incontinence (SUI) is one occasional complication following radical prostatic surgery or transurethral resection of the prostate (TURP), however, when it occurs, the consequences in terms of quality of life are dramatic to patients. Urinary incontinence following radical prostate surgery has a variable incidence, which can reach more than 30% of cases, depending on the technique employed and the criteria for its definition (1).

When the SUI is moderate or severe, surgical treatment is required. Among the techniques currently accepted and available in our setting, we have injection of periurethral bulking agents, the Silimed®
periurethral constrictor (4,5), the artificial sphincter AMS-800® and other urethral sling techniques previously described (2). The artificial sphincter AMS-800® is considered the “gold standard” for treatment of moderate and severe SUI, however many patients continue with some degree of SUI and the need for surgical revision, after 5 years, can reach up to 50% of cases (3). Urethral bulking agents have high costs and produce quite modest results if the SUI is severe (2,4). There are no published results to the moment concerning the use of the periurethral constrictor Slimed®, idealized by Lima et al. (4,5), for treatment of urinary incontinence following radical prostate surgery, and in the authors’ experience, total continence was not achieved or the devices had to be removed due to urethral erosion.

The urethral sling surgery for treating urinary incontinence following radical prostate surgery was described by Schaeffer et al. (7), using 3 segments of vascular grafts, placed transversally to the urethra, fixed on the aponeurosis of rectus abdominis muscle, and using the leak point pressure of 150 cm of water as a parameter. With this technique, 56% of patients became totally continent. Several other sling techniques were proposed, using synthetic materials, cadaveric fascia or dermis, porcine skin collagen or autologous fascias. All techniques used fixation on the aponeurosis of rectus abdominis muscle or on ischiopubic rami, through bone screws (2,6-10).

The technique described here differs of the others concerning the following aspects; it uses low-cost material that is available at all hospitals, it does not require special training and is based on the principle of large extension of low-pressure urethral compression, which should improve the results and minimize the risk of urethral erosion. Additionally, it uses a bone basis for its fixation (the pubis), which reduces the risk of the sling’s supporting sutures to drop over time and reduces the chance of osteitis or osteomyelitis, since no screws are introduced in the pubis.

MATERIALS AND METHODS

From May 2003 to April 2004, 30 patients with moderate or severe SUI were operated using the described technique. 27 had urinary incontinence following radical prostate surgery and 3 had post-TURP stress urinary incontinence. Age ranged from 50 to 78 years (median 68 years) and follow-up from 2 to 12 months (median 4 months). Pre-operative assessment included urodynamic study or cystometry, cystoscopy and urine analysis in order to exclude infection. All patients had at least one year from prostate surgery and used geriatric pads or external urine collectors. Patients with urethral stenosis and patients with reduced bladder capacity or severe vesical instability were excluded.

SURGICAL TECHNIQUE

The patient is admitted on the surgery’s day. A 16F Foley catheter is inserted in the urethra to fill the bladder for puncture cystostomy and for better urethral identification during dissection. An 8-cm transverse incision is performed close to the upper pubic margin and a puncture cystostomy is performed. The perineum is longitudinally incised, in an extension of approximately 5 cm and the bulbar urethra is dissected, preserving the bulbospongious muscle. The central perineal tendon is incised in order to allow better contact between the bulbar urethra and the sling and thus prevent the muscle from providing an opposing force to the sling (8).

The sling is prepared using 2 superposed segments of polypropylene or Dacron mesh, in order to assure higher steadiness, because the suture thread can easily break if it is located too close to the sling margin. The final size is 4 cm in length by 1.8 cm in width. Four nylon or 0-prolene sutures are fixed to these superposed flaps, in order to better distribute the tension (Figure-1). With a Stamey-Pereira needle, the 2 posterior sutures are passed, parallel to the urethra and next to the pubis, by posterior approach (retropubic). The other 2 anterior prepubic sutures are passed closed to the pubis as well, taking care so that the spermatic cords are not included (Figures 2 and 3).

Retropubic sutures must be passed the closest to the pubis as possible, in order to prevent bladder perforation and to assure that soft tissues do not get interposed between the suture and the bone, which can cause pain in the postoperative period, as well as progressive loss of the sling tension due to tissue ne-
urethral sling with for male urinary incontinence

Figure 1 – Aspect of the sling ready for implantation.

Figure 2 – Sling already fixed on the bulbar urethra.

crosis. After the suture passing, a cystoscopy is performed in order to confirm that there was no bladder perforation. First, the 4 sutures are tied over the pubis on one side, making sure that the sling is well stretched over the urethra. We remove the urethral catheter and, through the cystostomy, connect a bag containing physiological saline solution at 60 cm from the pubis level. We produce tension over the sling tying up the 4 sutures on the opposite side, until the moment when the leakage of saline solution through the urethra stops. The bladder is compressed to assure that the pressure was not excessive and the patient can void. During the surgery, the surgical field is irrigated with a saline solution containing rifampicin and gentamicin. Perineal and abdominal incisions are closed in 2 planes. No drainage is performed. Cystostomy is kept until the patient is able to void and has residual urine lower than 100 mL, which usually occurs within 2 to 4 days.

Patient is discharged from hospital on the day that follows surgery with the cystostomy closed. He is instructed to measure postvoiding residual urine, and the cystostomy is removed when the patient voids spontaneously, for more than 24 hours, with a residue lower than 100 mL.

RESULTS

In 2 cases (6.6%) there was infection in the perineal incision (both patients were diabetic) requiring the sling removal. In 1 case (3.3%), the patient could not void after 4 weeks. We verified that the urethral leak pressure was 55 cm of water, and the sutures were loosened to a leak pressure of 45 cm, but even then, the patient did not void. Bethanecol use was started with a dose of 20 mg 3 times a day,

Figure 3 – Schematic drawing of a schematic sagital section showing how the sutures are passed and fixed anteriorly and posteriorly to the pubis.
with the patient starting to void satisfactorily afterwards, with residual urine of 80 mL, when the cystostomy was removed.

Twenty-five patients (66.6%) are continent, with no need for pads. Four patients (14.5%) had a significant improvement, however, with persistency of some degree of SUI, passing from use of geriatric pads to smaller absorbent pads, in the amount of 1 to 3 units daily. Six patients (20%), including the 2 who had the slings removed, had minimal or no improvement. In 3 cases (10%), that are currently continent, reoperation was required aiming to apply more tension to the sling after a period of 30 to 90 days, due to progressive incontinence, with all becoming continent. Four patients had previously undergone (6 months or more) placing of Marlex sling with fixation in the ischiopubic rami, unsuccessfully. The difficulty to dissect the urethra in these cases was slightly higher. Previous perineal radical prostatectomy did not impair the dissection of bulbar urethra.

COMMENTS

Male urinary incontinence, due to sphincteric insufficiency, which occurs after prostatic endoscopic resection or radical surgery, is a highly feared complication, for its consequences over the patient’s quality of life. Surgical attempts to correct this picture are not recent, and in the 70's, along with the development of the artificial sphincter, Kaufman proposed several techniques, with discouraging long-term results (13,14). Periurethral injections of several expansive materials showed to be effective in cases of mild or moderate SUI only (2-4). The authors’ personal experience with collagen (Contigem®) was also disappointing. Artificial sphincters became the “gold standard” for treating moderate or severe incontinence, with optimal results in 75% to 87% of cases (3,15). However, its high cost prevents its use in great part of our population. With the improvement in sling techniques, we started their use.

We ended up developing this technique because we understand that, with slings fixed on the ischiopubic rami, the required compression on the bulbar urethra often was not achieved. Cespedes & Jacoby (8) recommend its use in cases of slight to moderate incontinence. The lack of familiarity with bone screws, as well as the fact that such material is not covered by the Brazilian Single Health System (SUS) prompted the use of fixation with sutures on the pubis.

We understand that, since the sling is an obstructive process, the detrusor muscle must be normal, and if the patient has any co-morbidity that could cause a hypocontractile bladder, a scrupulous urodynamic study must be performed pre-operatively.

Stenosis of urethra or bladder neck is a relative contra-indication, because if the patient requires internal urethrotomy, the sling would not allow the procedure to be performed, though in no case there was impossibility to catheterize the patient with a Foley catheter. Bladders with low capacity and/or low compliance are a relative contra-indication (2,8,15).

Though it is not described in other techniques, in our opinion, the use of suprapubic cystostomy is quite advantageous, since it prevents the appearance of a potential ureteral lesion at the sling site due to the urethral catheter, enables the easy assessment of residual urine, and assures that the patient can empty the bladder if urinary retention occurs within the first postoperative days.

In relation to the sling material, the use of non-absorbable material is always recommended, since this surgery requires that the tension on the urethra be permanently maintained (2,8,9). We believe that synthetic materials - polypropylene, Dacron, PTTE mesh, etc - are easy to handle and, since the pressure over the urethra is low and largely extended, the risk of urethral erosion is minimal. The use of aponeurosis of rectus abdominis muscle or fascia lata can be a good option as well.

In our first cases, we used polypropylene mesh and subsequently started to use segments of Dacron arterial graft, due to the higher availability of this material at our institution. The follow-up in this series is still very short, however, since results have been encouraging, in relation to other techniques previously employed by the authors (except for the artificial sphincter), we consider it a very good option for patients who have no conditions to acquire the artificial sphincter. Patients have been followed with ultrasonography of the urinary tract, urodynamic study
and questionnaire about quality of life (16), and those will be the object of a new study when they reach a minimum of 6 months follow-up.

CONCLUSION

The technique proposed by the authors is feasible to be performed by any urologist at any hospital in any country, with low cost. The early results are similar to other techniques described. However, urethral tolerance to the sling, detrusor function and maintenance of urinary continence need still to be assessed in the medium- and long-term.

REFERENCES


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EDITORIAL COMMENT

This work has several merits. Among them, we can include the authors’ objective and concern in developing a procedure for surgical correction of postprostatectomy urinary incontinence that is feasible in our setting, according to the cost of existing alternatives, whether artificial urinary sphincter or perineal sling with bone fixation. This need becomes evident upon the performance of 30 surgeries for this purpose in a 12-month period, evidencing the repressed demand of this problem. These patients probably would not have other therapeutic alternative with the exception of this proposal.

However, before the changes described here become indiscriminately used, some data deserve to be better evaluated. There is no current agreement on the efficacy of male slings for treating postprostatectomy incontinence, basically because there is no data for interpretation (International Consultation on Incontinence, 2004). Early works did not present comparable surgical procedures, and pre-operative assessment and cure or improvement criteria were dubious. Technical modifications of procedures that are not absolutely established lack, from the beginning, a comparative term. It is evident in this series of cases that improvement occurred in a significant group of patients (20 “continents” patients in 30 procedures). However, this improvement criterion must be seen with restrictions such as: postoperative follow-up of 2 to 12 months, with median of 4 months; the lack of reference to objective characteristics of pre-and postoperative urinary leakage; the requirement of preventive cystostomy in all cases, with an unreported number needing to maintain it for up to 14 days due to residual urine superior to 100 mL.

Other case series of slings with bone fixation recently presented at the International Consultation on Incontinence, Paris, 2004 (Abstracts # 445, 447 and 453), and also subjected to all interpretation restrictions mentioned above, with similar results, but with longer postoperative follow-up, even if considered insufficient, show absence of urinary obstruction and postvoiding residual urine as a common feature. If the main merit of the proposed procedure is the feasibility for its performance due to lower cost, this latter feature is, currently and beforehand, its Achilles’ heel. The authors owe us results for minimal periods of 1 and 2 years, when we will be able to effectively conclude about its applicability.

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ADENOMATOID TUMOR OF SUPRA-RENAL GLAND

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ABSTRACT

Adenomatoid tumors of adrenal gland are rare, asymptomatic neoplasias, with benign behavior, and usually are diagnosed incidentally.

We report a case of a voluminous adenomatoid tumor of left adrenal gland in a 42-year old man who sought evaluation because of renal colic due to left nephrolithiasis. During the investigation, a tumor localized in left adrenal gland was identified by ultrasonography (14.3 x 10.5 x 19.0).

The patient underwent adrenalectomy and pyelolithotomy with histopathological and immunohistochemical diagnosis of adenomatoid tumor of adrenal gland, being the largest one described in the literature to the moment. The patient does not present any signs of recurring lesion after a 3-year follow-up.

Key words: adrenal glands; neoplasms; adenomatoid tumors; nephrolithiasis


INTRODUCTION

Adenomatoid tumors of adrenal gland are rare, asymptomatic neoplasias, with benign behavior, and usually are diagnosed incidentally (1). Adenomatoid tumors appear more frequently in the genital system both in males and in females (2). The literature reports only 16 cases of adrenal adenomatoid tumors (3). In this work, we report one case of voluminous adenomatoid tumor affecting the left adrenal gland.

CASE REPORT

Caucasian, 42-year old man was referred due to presenting, during investigation of renal colic, a mass measuring 14.3 x 10.5 x 19.0 cm localized on left adrenal gland in ultrasonographic imaging. The patient had a previous history of systemic arterial hypertension with moderate tension levels since he was 28 years old, and elimination of urinary stones at the ages 32 and 39. On the physical examination, he presented blood pressure of 150 x 100 mmHg (using captopril) and a mass with firm consistency and indefinite limits on left hypochondrium. Abdominal computerized tomography demonstrate a tumor measuring 10.5 x 9.9 cm localized on left adrenal gland, caudally displacing the ipsilateral kidney, showing peripheral impregnation by the contrast agent, presenting heterogeneous texture, with hypodense areas in its interior, possibly corresponding to necrotic areas, and a stone measuring 3.2 x 2.7 cm in left renal pelvis corresponding to renal lithiasis. Dosing for urinary vanillylmandelic acid, cortisoluria, 17-hydroxyprogesterone, hydro-epiandrosterone sulfate, androstenedione, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, total and free testosterone, thyrotrophin, thyroxine and cortisol (following 1 mg of dexamethasone) were within the normal range.
Adrenalec-tomy and pylolithotomy were performed by open approach, with no intercurrences trans- or post-operatively. The adrenal gland weighed 535 g and upon sectioning it showed predominance of multicystic, yellowish and opaque tissue, with the tumor being predominantly solid. Histological examination with hematoxylin-eosin demonstrated mesothelial cells similar to epithelial lineage cells arranged as small tubules, cysts or string-shaped, with histological pattern compatible with adenomatoid tumor of adrenal gland (Figure-1). Immunohistochemical study by the immunoperoxidase technique using the markers AE1, AE3, vimentin, CEA and CD31, demonstrate that neoplastic cells were positive to AE1, AE3 and vimentin (Figure-1), and negative to the other markers, confirming the diagnosis.

The patient has not shown signs of recurrent lesion after a 3-year follow-up.

COMMENTS

Adenomatoid tumors are benign neoplasias with mesothelial origin, with cases rarely reported in extra-genital sites (2). There are 8 cases describing adenomatoid tumor of adrenal gland, occurring mostly in males, involving more frequently the left adrenal gland (1). With the increasing use of imaging examinations for diagnostic of other pathologies, adrenal

**Figure 1** – Histological and immunohistochemical studies of the adenomatoid tumor of adrenal gland. A) Proliferation of mesothelial cells similar to epithelial lineage cells, arranged as small tubules, cysts, or string-shaped (HE, X80). B) Positivity for cytokeratins in epithelial-like cells. CEA negative. Positive to AE1 and AE3 (Imunolabeling, X200). C) Positivity for vimentin expressed in mesothelial cells (Imunolabeling, X200).
ADENOMATOID TUMOR OF SUPRA-RENAL GLAND

tumors have been more diagnosed, usually in an incidental way. Apparently, there are no specific characteristics that enable us to radiologically distinguish adenomatoid tumors from other adrenal lesions (4). The differential diagnosis of an adrenal mass includes adrenal adenoma or carcinoma, myelolipoma, pheochromocytoma, cysts and metastatic neoplasias (1). There are no reports in the literature of lesion recurrence following complete surgical removal, and this treatment is definitive.

REFERENCES


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SPONTANEOUS NEPHROCUTANEOUS FISTULA

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ABSTRACT

Spontaneous renal fistula to the skin is rare. The majority of cases develop in patients with antecedents of previous renal surgery, renal trauma, renal tumors, and chronic urinary tract infection with abscess formation.

We report the case of a 62-year old woman, who complained of urine leakage through the skin in the lumbar region for 2 years. She underwent a fistulography that revealed drainage of contrast agent to the collecting system and images suggesting renal lithiasis on this side. The patient underwent simple nephrectomy on this side and evolved without intercurrences in the post-operative period.

Currently, the occurrence of spontaneous renal and perirenal abscesses is extremely rare, except in patients with diabetes, neoplasias and immunodepression in general.

Key words: kidney; lithiasis; fistula; lumbar region; nephrectomy

INTRODUCTION

Spontaneous renal fistula to adjacent organs is not an uncommon phenomenon, however the spontaneous communication between kidney and skin is rare and few cases are described in the literature (1-3). The occurrence of spontaneous fistulas in patients without surgical history is rare (3). All cases reported in the literature are associated with chronic urinary tract infection and nephrolithiasis.

The authors report one more case of this rare complication of lithiasis-induced chronic pyelonephritis.

CASE REPORT

A 62-year old woman was admitted to the urology service reporting urine leakage from the skin in the lumbar region for 2 years. She referred local inflammatory process with drainage of purulent secretion at the onset of the clinical picture. There was no report of previous pyelonephritis. The physical examination evidenced a fistulous orifice in skin on left lumbar region (Figure-1). Urine culture was negative. The patient denied diabetes or past history of local trauma.

Figure 1 – Fistulous orifice in skin on left lumbar region (arrow).
A fistulography was performed, revealing drainage of the contrast agent to the collecting system, and images suggesting renal lithiasis on this side (Figure-2). Renal scintigraphy with DMSA revealed relative renal function of only 5% on the left side. The contralateral kidney was normal.

Patient underwent left lumbotomy, where an atrophic kidney was found, with adhesions to adjacent structures. Then a simple left nephrectomy was performed.

The pathological examination of the surgical specimen revealed chronic pyelonephritis associated with multiple renal calcifications. Testing for tuberculosis in the renal tissue was negative. Patient evolved without intercurrences and was discharged from the hospital on the seventh postoperative day.

**COMMENTS**

Renal fistulas usually are complications of surgical procedures on the kidney, renal trauma, tumors, and chronic urinary tract infections with formation of perirenal abscess (1). Such abscesses can derive from organs that are adjacent to the kidney, as well as from the kidney itself, by extension of urinary infection to the adjacent tissues, either by contiguity or by lymphatic route. In other occasions, abscesses can originate from an urinoma or urinary pseudocyst, that arise as result of external or surgical trauma on the kidney, promoting loss of continuity between it and the surrounding tissues (2).

Currently, the occurrence of renal and perirenal abscesses is rare, except patients with diabetes, with neoplasias or immunodepression in general. The outcome of these abscesses, when left untreated, is unforeseeable (2).

Fistulas can develop between the kidney and the pleural cavity, lungs and bronchia, bowel, and skin. However, the latter are rare, and whenever they occur, they typically involve patients with a past history of renal surgery (1).

The majority of fistulas presents spontaneous drainage through the lumbar region following those points with lowest resistance, such as the lumbar triangle (Petit) and the lumbar quadrilateral (Grynfeld), establishing a fistulous pathway that communicates the perirenal tissues and collecting system with the external environment (2). The association with infectious renal stones is frequent and has occurred in all cases described in the literature (1-3). The patient in this case had a staghorn stone in the involved kidney.

Therapeutic approaches must be based on the renal function and on the patient’s ability to tolerate the surgical procedure, and can include total nephrectomy, partial nephrectomy or isolated antibiotic therapy (3). In the present case, the patient evolved without postoperative intercurrences and was free of symptoms.

**REFERENCES**


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NEOPLASIA IN HORSESHOE KIDNEY WITH PYELIC FUSION AND CROSSED SINGLE URETER

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ABSTRACT

Horseshoe kidney with pyelic fusion and crossed single ureter is a rare anomaly, with only 3 cases described in the literature. Such anomaly can be accompanied by other abnormalities, such as congenital scoliosis and situs inversus totalis. We present one case of this malformation associated with malignant neoplasia, treated with partial nephrectomy.

Key words: kidney; anomalies; kidney neoplasms

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INTRODUCTION

Horseshoe kidney with pyelic fusion and crossed single ureter is a rare anomaly, with only 3 cases found in a research of literature through Medline. We present one case of this malformation associated with malignant neoplasia, treated with partial nephrectomy.

CASE REPORT

Female, 26-year old patient, complaining of colic on right lumbar region, underwent investigation by plain x-ray of abdomen that revealed no abnormality. An ultrasound of urinary tract was performed, showing a solid expansive lesion measuring 8 x 4 cm in upper pole and middle portion of the right kidney, associated with horseshoe kidney. Abdominal computerized tomography (CT) (Figure-1) confirmed sonographic findings, demonstrating pyelic fusion associated with crossed single ureter as well.

No distant lesions were observed during staging. A cystoscopy was performed evidencing single ureteral meatus on the right side. Considering this condition, radical nephrectomy was indicated through bilateral subcostal incision, with partial nephrectomy being feasible, with cold ischemia during 30 minutes (Figure-2). No macroscopically involved lymph node was observed intraoperatively.

The pathological examination of the surgical specimen revealed clear cell carcinoma, Furhman nuclear grade I, measuring 8.3 x 5.5 x 4.5 cm, weighing 200 g, infiltrating the renal capsule, but with margins free of neoplasia. The pelvis and renal vein were not involved.

Patient has been followed for 8 months without any signs of recurrence.

COMMENTS

Horseshoe kidney with pyelic fusion and crossed single ureter is a rare anomaly, and to the moment we have not found reports in the literature concerning malignant neoplasia in association with such anomaly. The etiology of the malformation is unknown; however, some authors postulate that the ureter crosses the midline and divides itself in 2 halves, providing bilateral renal development (2). Associated extra-urinary anomalies have been described, such as situs inversus totalis and congenital
scoliosis (2,3), however they were not observed in this case.

Even though the development of neoplasia in this malformation is rare, we believe that the outcome is probably similar to other malignant renal tumors. Surgical planning is fundamental for a successful treatment.

REFERENCES


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CAKE KIDNEY DRAINED BY SINGLE URETER

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ABSTRACT

Cake kidney is a rare congenital anomaly of the urogenital tract, with a few more than 20 cases described in the literature. It can be diagnosed at any age range. Normally, drainage is achieved by 2 ureters, and there are only 5 reports in the literature of cake kidney drained by a single ureter. The authors describe one more case of this rare malformation of the urinary tract.

Key words: kidney; abnormalities; ureter; hydronephrosis

INTRODUCTION

Cake kidney is a rare congenital anomaly of the urogenital tract, and it is normally drained by 2 ureters. There are only 5 reports in the literature of cake kidney drained by single ureter (1). The early diagnosis of potential complications that can accompany this anomaly must be always made in order to prevent permanent renal damage (2). The authors report one case of cake kidney manifested as hydronephrosis associated with urinary infection, and discuss the therapeutic approach.

CASE REPORT

Male, 5-months old child, presented a history of recurrent urinary tract infections. There was already a previous history of 2 hospitalizations due to acute pyelonephritis. At the moment, he was under antimicrobial prophylaxis with nitrofurantoin.

The patient underwent renal ultrasonography that revealed bilateral hydronephrosis, more pronounced on the right side. Voiding urethrocystography was normal. Renal scintigraphy (Figure-1) revealed the presence of a cystic renal mass with pelvic localization, with an obstructive pattern for clearance of radiopharmaceutical ($T_{1/2} = 39 \text{ min.}$).

The child was operated due to suspicion of ureteropelvic junction (UPJ) stenosis in a single kid-

Figure 1 – Renal scintigraphy (DTPA) showing a single renal mass with radiopharmaceutical retention.
CAKE KIDNEY DRAINED BY SINGLE URETER

ney. The surgical finding was cake kidney with pelvic location, presenting extra-renal calices. The ureter was single and presented moderate dilation (Figure-2). Due to the child’s young age, a decompressive pyelotomy was performed. The child had a good outcome postoperatively, being discharged from the hospital on the fourth postoperative day. Currently he is under prophylaxis without new episodes of urinary infection.

COMMENTS

Cake kidney is a rare congenital malformation of the urogenital tract, which can be diagnosed at any age group, from childhood to the eightieth decade of life (3).

This anomaly occurs at an early phase in the embryological development (2). Under normal conditions, the 2 masses of metanephrogenic tissue arise in the pelvis and ascend to their definitive position in the lumbar region, bilaterally. During such migration, they undergo a lateral deviation, with axial deflection and internal rotation.

During the formation of a cake kidney, the nephrogenic blastemas would be compressed between the umbilical arteries at the beginning of the cranial migration of the ureteral buds, and this would lead to their fusion (2). Fused kidneys, such as the cake kidney, are prevented from ascending and remain in an ectopic pelvic position. The rare occurrence of a single ureter draining the fused renal mass can be caused by the regression of the second ureteral bud following the fusion of the metanephric blastemas (3).

The majority of diagnosed cases have been reported to present malformations in other organs or in their blood supply, such as abnormal testicular migration, Fallot’s tetralogy, vaginal or sacral agenesis, anal abnormalities, among others (3).

The diagnosis of cake kidney is not necessarily associated with a poor prognosis. However, complications that can be associated with anatomic malformations such as urinary stasis, infection, formation of stones, and vascular involvement, can cause serious clinical problems (2). Therefore, cases of cake kidney must be investigated in order to exclude concomitant anomalies and to prevent complication.

REFERENCES


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VESICOURETHRAL ANASTOMOSIS FACILITATED BY A NEW DISPOSABLE INSTRUMENT

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ABSTRACT

The author presents a prototype of a disposable device that enables, in one single movement, the passing of all suture stitches in the urethral stump that will be anastomosed to the bladder or to a neobladder, with the advantage of a regular distribution of these stitches around the urethral circumference. In tests with animals, the device showed to be easily applicable, effective and safe.

Key words: prostatectomy; cystectomy; vesicourethral anastomosis; device; pigs


INTRODUCTION

Since the pioneer studies by Walsh et al. (1), radical prostatectomy has become popular throughout the world. However, the vesicourethral anastomosis is still regarded as the critical part in this surgery. The difficulty is due to the retraction and collapse of the urethral stump, to the restricted access, and restricted space at this pelvic site (2). Overcoming such obstacles would make the procedure less extensive, with a more adequate anastomosis, reducing the index of complications such as urine extravasation, prolonged catheterization, stenosis of the anastomosis and urinary incontinence (3).

Some techniques have been reported aiming to aid in the reconstruction of the urinary tract, including simultaneous urethroscopy, maneuvers that push or pull the urogenital diaphragm towards the bladder neck, special catheters that reveal the urethral lumen and guide suture needles, specific intrapelvic retractors, modified suture techniques, special forceps and even organic adhesives (4).

None of these alternative techniques has been universally established and direct vesicourethral anastomosis is still the standard method for reconstruction following radical prostatectomy (3,5).

SURGICAL TECHNIQUE

The new instrument for passing the stitches on the urethral stump is composed by a silicone piston with one of the extremities tapered. This piston has 6 almost straight surgical needles inserted by the extremity that is connected to the suture around its circumference, in a 45-degree angle. This silicone is tightly inserted into a cylinder (Figure-1) so that the 6 needles close next to the silicone and inside the cylinder (Figure-2). The device is ready to be inserted in the urethral stump (Figure-3) until the cylinder’s margin (Figure-4). At this moment the lock (pin) is removed, keeping the cylinder fixed and pushing the silicone piston until the surgeon can feel the needles opening in the urethral lumen. The cylinder is completely removed (Figure-5) and the piston is pulled until the 6 needles are exteriorized through the urethral wall (Figure-6). Each needle is pulled (Figure-7), trespassing the corresponding suture through the urethra (Figure-8). The procedure...
Figure 1 – Device showing the needle-piston as it is inserted in the cylinder.

Figure 2 – Device showing the needles closed inside the cylinder.

Figure 3 – Device being introduced into the animal’s urethral stump.

Figure 4 – Device correctly inserted.

Figure 5 – Piston with open needles inside the urethral lumen.

Figure 6 – Exteriorization of all needles after piston traction.
is repeated with the other needles until the 6 stitches are completed (Figure-9), when the urethral stump is then ready to be anastomosed to the bladder or to a neobladder.

This instrument can be useful in laparoscopic radical prostatectomy as well, since the vesicourethral anastomosis is performed with great difficulty during this surgery.

In our experiment, the device location in the urethral stump was easily performed in 10 procedures in pigs, and in all of them, the mechanism of opening and passing of needles through the urethra worked as devised by the author.

The prototype used in the animals was manufactured in a quite simple way. A 4-0 polyglactin needle-suture was used with a 2-cm curve needle, which was manually rectified and inserted in the piston. In the other extremity of the suture, the use of a separate curve needle was required for passing the stitch on the bladder neck.

COMMENTS

This device serves only as a vehicle for the 6 surgical needles, using the urethral lumen as access route and enabling the simultaneous passing of all stitches with a regular distribution around the urethral circumference. In animal experiments, this new disposable instrument showed to be easily handled, efficient and safe. With the prototype’s technological improvement, it is expected that those results can be reproduced in humans.

REFERENCES

3. Novicki DE, Larson TR, Andrews PE, Swanson SK, Ferrigni RG: Comparison of the modified vest and the
VESICOURETHRAL ANASTOMOSIS WITH NEW INSTRUMENT


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EDITORIAL COMMENT

The author presents an ingenious alternative, which at first site seems useful and feasible. However, it is important to point that in more delicate and retracted urethras, the needles could transfix improper sites, and may include little urethral tissue, eventually even rupturing it, without an adequate coaptation with the bladder. On the other hand, it may include excessive urethral tissue, which could involve the sphincteric complex.

The author must be commended and the urologic community anxiously waits for clinical results.

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USE OF SMALL INTESTINE SUBMUCOSA AS URETERAL ALLOGRAFT IN PIGS

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ABSTRACT

Purpose: The aim of the present study was to evaluate the biocompatibility of small intestine submucosa (SIS) in the reconstruction of the ureter in swine.

Materials and Methods: An experimental study was performed in 10 half-breed pigs weighing between 20 and 30 K, in which a previously prepared segment of SIS measuring approximately 2.0 cm was implanted in the upper third part of the right ureter.

Results: Of the 10 operated animals, one died 14 days after the surgery due to a dehiscence on the suture line of the implanted graft. The remaining 9 animals were submitted to ultrasound examination of the urinary tract and were sacrificed on the 40th postoperative day. The macroscopic evaluation showed no calculus, incrustation, fistula, abscesses or adhesions in the ureters with the graft. Microscopic evaluation with hematoxylin-eosin and Sirius red showed in the experimental area (graft) the presence of urothelium in 100% of the cases, collagen in 100% of the cases, and smooth muscle layer in 87.5% of the animals. In the area adjacent to the graft (proximal and distal), we observed 92.86% of urothelium, 42.86% of collagen and 71.43% of smooth muscle. In the contralateral ureter, it was found 100% of urothelium and smooth muscle and just 11.11% of collagen. The microscopic analysis of the kidneys whose ureters received the graft of SIS evidenced congestion in 55.55%, pelvic edema in 66.66% and interstitial nephritis in 77.78%. Hydronephrosis was present in 33.33% and chronic pyelonephritis in 44%. Only 1 animal presented total absence of glomerulus in the renal parenchyma.

Conclusion: The SIS graft behaved as a biological tissue support, allowing the regeneration of the urothelium and smooth muscle grow, despite of chronic inflammatory process.

Key words: small intestine; submucosa; ureter; graft; swine


INTRODUCTION

Ureteral reconstruction represents a great challenge to the urologist, especially if a long segment of ureter is involved. Per decades, surgeons look for alternative ways to repair and to reconstruct the ureter, using different materials and techniques (1-3).

The current options for treatment are ureteroureterostomy, ureteroneocistostomy with the psoas hitch, transureterostomy, Boari flap and renal mobilization. Therefore, when a long ureteral segment is lost, other options are used such as permanent percutaneous nephrostomy, auto transplantation or simple nephrectomy (2,3).

Another procedure that is being widely used at present in ureteral surgeries is the endoscopic treatment. However, this technique is not widely accepted and it is currently limited to patients with moderate strictures (4,5).

Among the structures used for ureteral reconstruction are the appendix, veins (as the umbilical vein), arteries, Fallopian tube, skin grafts,
stomach and peritoneum, even though with limited success. Alloplastic materials, such as cobalt-chromium, polyvinyl chloride, polyethylene, polytetrafluoroethylene, silver, silicon rubber, polyester, collagen and polyglactin have been investigated and the results were disappointing (rejection, stone formation, migration, urinary leak, anastomotic stricture and hydronephrosis with renal loss) (1,2,6-8).

Results from numerous pre-clinical studies have demonstrated that SIS is capable of inducing host tissue proliferation and replacement when implanted in various sites. In the urinary tract, the SIS has been shown as a promising graft (9-19). It induces host tissue proliferation and replacement. Studies on the composition of SIS revealed water content of approximately 90%. The protein content consists primarily of collagens, type I, III and V. The three-dimensional matrix provides a suitable structural environment for the resident cells of a tissue. The glycoproteins, proteoglycans and glycosaminoglycans help the cell to attach and settle within the matrix. This property contributes to the re-population of the matrix and cell migration, proliferation and differentiation (20). Another component of the SIS biomaterial, critical to its mechanism of action is the growth factor content (21). They stimulate cell division, migration and differentiation. Among the growth factor found in the SIS membrane are fibroblasts growth factor-2, transforming growth factor β and vascular endothelial growth factor (22,23). Several studies have demonstrated resistance to bacterial infection and lack of adverse immunological reaction, probably due to the acellular condition and significant collagen composition, which is highly preserved across the species. The immunological response is restricted to the Th2 pathway, which may allow acceptance and remodeling of graft tissue (12).

The aim of the present study is to evaluate the SIS biocompatibility when used as a graft for ureter repair.

**MATERIALS AND METHODS**

An experimental study was accomplished in 10 half-breed pigs weighing between 20 and 30 Kg.

The protocol was approved by Institutional Animal Care and Use Committee of our Institution.

The small intestine was harvested from pigs sacrificed at a slaughterhouse and the SIS was prepared in the laboratory of Experimental Surgery of the Pontifical Catholic University of Parana. The tunica mucosa was mechanically removed from the inner surface and the serosa and tunica muscularis were mechanically removed from the outer surface. This procedure produces a thin translucent graft composed mainly of the submucosa layer of the intestinal wall. The membrane obtained was immediately placed in a solution containing neomycin 10% and normal saline solution, and stored at 5°C for 12 hours. A small segment of the membrane was then wrapped up in a catheter in order to produce a fine straw of the submucosa.

Under general anesthesia, a midline abdominal incision was made in the pig. The retroperitoneum was accessed. A segment of 2 cm length of the upper right ureter, involving two-thirds of its diameter was removed, parallel to the ureteral axis. A 4F pediatric nasogastric tube was inserted into the ureter through the created gap. A submucosa straw wrapped up the catheter and was sutured at the cut edges of the ureter with an uninterrupted 5-0 catgut suture (Figure-1).

No procedures were performed in the left ureter, which was used as a control. On the 30th
postoperative day, all animals were submitted to an ultrasound examination of the urinary tract and on the 40th postoperative day the pigs were sacrificed for removal of both kidneys and both ureters. The presence of adhesions, fistulas and abscesses were analyzed. The diameter of the upper third of the left ureter was measured as well as the diameter of the right ureter, in the site where the submucosa graft was placed and 1 cm proximal and 1 cm distal to it.

The site of the graft was named experimental area. The 2 areas adjacent to the graft were named referential areas. The correspondent areas of the left ureter were named control areas.

Microscopic evaluations - A sample of the experimental areas, the referential areas and the control areas were fixed in a 5% formalin solution. The paraffin embedded tissue blocks were sectioned and stained with hematoxylin-eosin to evaluate the inflammatory reaction, the urothelium, collagen and muscle ingrowth. It was possible to quantify the inflammatory reaction into acute or chronic through a score table (Table-1).

The variables congestion, edema and neutrophils characterize an acute inflammatory process. The presence of granulation tissue, fibrosis and mononuclear cells characterize a chronic inflammatory phase. Thus, the results between $-9$ and $-1$ were considered as acute inflammatory phase, between $-1$ and $+1$ as absence of inflammatory process, and between $+1$ and $+9$, chronic inflammatory phase.

The Sirius red staining was used to evaluate the collagen and muscle densitometry through Image Pro Plus Software. Under optical Zeiss microscope, with a magnification of 100X, 6 areas of the specimen were selected. The images were captured by a digital video camera and processed by a video-board in a personal computer. As the collagen and muscle can be stained in different colors, it was possible to quantify the amount of each component.

Both kidneys were also evaluated microscopically. The specimens were also stained with hematoxylin-eosin to assess the congestion, pelvic edema, interstitial nephritis, hydronephrosis, chronic pyelonephritis and glomerular absence.

Statistical analysis - The data were presented as mean ± standard deviation, median or frequencies, when appropriate. Comparisons of smooth muscle and collagen percentage between groups were performed using the t-test for paired observations. Friedman test and Wilcoxon test were used to determine significant differences among groups for the inflammatory reaction. Comparisons between groups for nominal variables were made with binomial test. The tests were 2-sided and p-values less than 0.05 were considered significant.

RESULTS

Of the 10 animals submitted to SIS graft implantation on the ureter, 1 died 14 days after surgery due to a dehiscence of the anastomosis. The ultrasound evaluation of the urinary tract, performed on the 30th post-operative day, showed a dilatation of the right renal pelvis in 2 pigs (22.22%) in relation to the left renal pelvis. It was not possible to accomplish a reliable ultrasound evaluation of both ureters.

<table>
<thead>
<tr>
<th>Inflammatory process</th>
<th>Variables</th>
<th>Absence</th>
<th>Discreet</th>
<th>Moderate</th>
<th>Accentuated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute -</td>
<td>Neutrophils</td>
<td>0</td>
<td>-1</td>
<td>-2</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
<td>0</td>
<td>-1</td>
<td>-2</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>Congestion</td>
<td>0</td>
<td>-1</td>
<td>-2</td>
<td>-3</td>
</tr>
<tr>
<td>Chronic +</td>
<td>Monocytes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Granulation tissue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Fibrosis</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
The macroscopic evaluation of the ureters showed no fistula, incrustation or abscess. The measurements of diameter showed partial stenosis in one animal and severe stenosis in another one. Table-2 shows the mean diameter of the right ureter in the site of the graft and 1 cm above and bellow this area, as well as the measure of the correspondent area of the left ureter.

All measured diameters of the right proximal ureter were significantly greater than the diameter of the correspondent area of the left ureter. No statistically significant difference was found in the diameter of the right proximal ureter when compared to the graft site.

The histological analysis of the specimens stained with hematoxylin-eosin showed in the experimental area (area where the graft was placed) the presence of urothelium in 100% of the cases, collagen in 100% of the cases and smooth muscle layer in 87.5% of the animals. In the referential areas, that is, the areas adjacent to the site of the graft, urothelium was seen in 92.86%, collagen in 42.86%, and smooth muscle in 71.43% of the cases. In the control ureter (left ureter), urothelium and smooth muscle were seen in 100% of the animals, and collagen in 11.11%. Comparing the 3 studied areas of the right ureter; it was observed that the presence of urothelium and smooth muscle was similar. However, the presence of collagen was higher in the experimental area in relation to the adjacent referential areas and in relation to the control left ureter (Table-3).

### Table 2 – Mean diameter of the studied areas.

<table>
<thead>
<tr>
<th>Ureter</th>
<th>N</th>
<th>Mean diameter</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ureter diameter (control ureter)</td>
<td>9</td>
<td>0.49</td>
<td>0.13</td>
</tr>
<tr>
<td>Right proximal diameter</td>
<td>9</td>
<td>1.48</td>
<td>0.97</td>
</tr>
<tr>
<td>Graft site diameter</td>
<td>9</td>
<td>0.91</td>
<td>0.40</td>
</tr>
<tr>
<td>Right distal diameter</td>
<td>9</td>
<td>0.67</td>
<td>0.23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ureter x proximal right ureter</td>
<td>p = 0.0077*</td>
</tr>
<tr>
<td>Left ureter x graft site in the right ureter</td>
<td>p = 0.0173*</td>
</tr>
<tr>
<td>Left ureter x distal right ureter</td>
<td>p = 0.0519</td>
</tr>
<tr>
<td>Proximal right ureter x graft site</td>
<td>p = 0.1235</td>
</tr>
<tr>
<td>Proximal right ureter x distal right ureter</td>
<td>p = 0.0077*</td>
</tr>
<tr>
<td>Graft site x distal right ureter</td>
<td>p = 0.1282</td>
</tr>
</tbody>
</table>

* statistically significant

### Table 3 – Urothelium, collagen and smooth muscle areas (in percentage) in the studied sites.

<table>
<thead>
<tr>
<th></th>
<th>Control Area</th>
<th>Referential Area</th>
<th>Experimental Area</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelium</td>
<td>100%</td>
<td>92.86%</td>
<td>100%</td>
<td>p ≥ (0.05 )</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>100%</td>
<td>71.43%</td>
<td>87.50%</td>
<td>p ≥ (0.05 )</td>
</tr>
<tr>
<td>Collagen</td>
<td>11.1%</td>
<td>42.86%</td>
<td>100%</td>
<td>Control area x referential area p ≥ 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Referential area x experimental area p = 0.0004*</td>
</tr>
</tbody>
</table>

* statistically significant
Regarding the inflammatory process, we observed that the graft area showed a higher degree of inflammation when compared to the referential area and to the control ureter (left ureter) \((p = 0.0002)\). Table-4 shows the analysis of the inflammatory parameters with their respective scores and the final average score.

The acute inflammatory reaction was not different among the 3 studied areas. Concerning edema, neutrophils and congestion that characterized the acute process, no significant statistical difference was observed.

Concerning chronic inflammatory reaction, the concentration of granulation tissue was significantly higher in the graft area when compared to the control ureter \((p = 0.0078)\). The fibrosis was greater in the experimental area when compared to the referential and control area \((p = 0.0156\) and \(p=0.0039\), respectively). No statistically significant difference was observed in the referential area when compared to the control area. Concerning monocytes, their concentration was significantly higher in the graft area and in the referential area when compared to the control ureter \((p = 0.0039)\), however, no statistically significant difference was noted in the graft area when compared to the referential area.

The morphometric analysis of the specimens stained with the Sirius red was performed in order to assess the percentage of area occupied by smooth muscle and collagen (Table-5). We observed that the

**Table 4** – Analysis of the inflammatory parameters with their respective scores and the final average score \((C = \text{control ureter, } R = \text{referential area, } E = \text{experimental area})\)

<table>
<thead>
<tr>
<th>Pig</th>
<th>Congestion</th>
<th>Edema</th>
<th>Neutrophils</th>
<th>Granulation</th>
<th>Fibrosis</th>
<th>Monocytes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>R</td>
<td>E</td>
<td>C</td>
<td>R</td>
<td>E</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>-1</td>
<td>-3</td>
<td>-1</td>
<td>-1</td>
<td>-2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
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<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
</tr>
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<td>6</td>
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<td>7</td>
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<td>-2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>-1</td>
<td>-2</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-2</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 5** – Percentage of collagen and smooth muscle in the studied areas. (mean ± standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Referential Area</th>
<th>Experimental Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>77.10 ± 7.50</td>
<td>70.94 ± 11.66</td>
<td>50.55 ± 14.78</td>
</tr>
<tr>
<td>Collagen</td>
<td>22.74 ± 7.50</td>
<td>29.05 ± 11.66</td>
<td>49.443 ± 14.79</td>
</tr>
</tbody>
</table>

* statistically significant
presence of smooth muscle was significantly higher in the control area and referential area, when compared to the experimental area. Regarding the amount of collagen in the studied areas, we could demonstrate that the experimental area showed a higher percentage of collagen in relation to the other 2 areas.

The histological study of the right kidneys demonstrates congestion in 55.55%, pelvic edema in 66.66% and interstitial nephritis in 77.78% of the specimens. The hydronephrosis was present in 33.33% and the chronic pyelonephritis in 44% of the right kidneys. In one animal, we could observe the total absence of glomerulus in the renal parenchyma. The left kidney showed interstitial nephritis and congestion in 11.11% of the kidneys and pelvic edema in 33.33% of the specimens.

COMMENTS

The ideal biomaterial for urinary tract reconstruction would allow regeneration of tissue and maintenance of its function (1). Unfortunately, the reconstruction of a long segment of ureter is always a challenge for the surgeon. Tubular and non-tubular organs have been tried with limited success. The small intestine submucosa (SIS) has been used in different organs and structures such as the lower urinary tract, abdominal wall, bone, tendons, bladder, small bowel and skin (1,10,11,24-26), with great success regarding tissue regeneration. When implanted in such structures it becomes indistinguishable from the host tissue. The biomaterial is remodeled by the host into replacement tissue with site-specific structural and functional properties. When implanted in a bladder site with pressurized static flow, SIS was remodeled into a tissue with measurable contractile activity. Jaffe et al. using this material in the reconstruction of the ureter in rabbits, verified that 3 native muscular layers of the ureter appeared in the collagen matrix of the grafted submucosa (11). The mechanisms of tissue remodeling are not yet completely understood. It has been shown that host cells proliferate and differentiate into site-specific tissue structures. Angiogenesis, cell migration, differentiation and deposition of extracellular matrix have been associated with this regenerative process. The proteoglycans and glycoproteins contain specific sites on their protein portion that help cells to attach and settle within the matrix. Another component of the matrix is the growth factors that stimulate growth and cell division, migration and differentiation.

The animal model chosen in this study was the pig, since its ureter presents a suitable diameter for the anastomosis and morphologically has a great similarity to the human ureter.

At the beginning of the study, we tried to implant the SIS in the canine ureter, but we had technical difficulties due to its small diameter and rigidity of its wall.

The urinary tract was evaluated on the 30th post-operative day in all animals, when they were submitted to ultrasound examination. The renal pelvis was dilated in 22.2% of the animals when compared to the left renal pelvis. In this study, the ultrasound did not appear to be a reliable examination. The great amount of gazes in the swine bowels did not allow a good visualization of the ureters.

All animals were sacrificed on the 40th post-operative day in order to assess surgical complications (abscess, fistula, incrustation), to measure the ureters diameter and to get the specimens for histological analysis. One pig died due to urinary fistula and 2 pigs developed hydronephrosis due to stenosis in the area of the SIS implantation.

Liatsikos et al. (9) used a 5F double-J stent to secure patency of the ureter. Probably if we had used the stent, the strictures in 2 animals could be avoided, but we must keep in mind that the stents can cause reflux to the kidney when the bladder contracts.

Concerning the ureters, we could verify that the right ureter showed significantly greater diameters in all the studied areas. It is important to note that when we compared the proximal right ureter and the site of the SIS implantation there was no statistically significant difference. This suggests that apart from the 2 animals mentioned above, SIS implantation did not determine important stenosis. The most important aspect of ureteral replacement is maintaining the normal drainage of the kidney, which requires the recovery of peristaltic activity in the ureter. Naturally, to have this activity smooth muscles are necessary.
On the 40th postoperative day, our histological studies showed that muscular regeneration was present in 50% of the implanted area. In the referential areas, the muscle was present in 70.94% of the studied areas and in 77.1% of the control left ureter. Probably, if we had sacrificed the animals after a 3 months period or longer, we would find a greater percentage of muscles.

The consequences of a lesser concentration of smooth muscle and lack of innervation could explain the right ureteral enlargement comparing to the control left ureter. In the present study, SIS demonstrated to have a special characteristic of differentiation in the experimental area. There was evidence of urothelium regeneration along the ureteral segments implanted with SIS, supported by a collagen and smooth muscle background. Liatsikos et al. (9) observed urothelium regeneration in the 7 cm length of the SIS graft. They believe that this urothelial regeneration was because they maintained one third of the ureteral diameter. In spite of the fact that we maintained the same segment of the ureter, we do not believe that this could induce urothelial regeneration. The urothelium lining depends on the adjacent urothelium, besides the existence of a local neovascularization. Further studies, with total removal of the ureteral segment must be done in order to evaluate this property of the SIS membrane.

Regarding the inflammatory process, we did not observe acute inflammatory reaction. A chronic moderated inflammatory reaction was present in the graft area of the ureter; however, this reaction was not statistically different from the adjacent referential areas. In addition, a foreign body type reaction was not seen in the graft area.

We concluded that SID evolved in the grafted area to a chronic inflammatory tissue and high amount of muscular tissue, acting as a biologic scaffold, allowing the regeneration of the urothelium and the deposition of the collagen necessary for the repair of the ureteral injuries.

REFERENCES


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EDITORIAL COMMENT

This is a very interesting article even though the number of animals studied is small and especially due to the short time frame analyzed. I am sure that if a third or forth group had been studied with 90 or 120 days we would certainly have more relevant information.

The authors have informed that they have used an ureteral catheter, apparently to model, during the surgery but they do not mention if this catheter has been withdrawn or not. In the discussion it is said that they did not used a double J with a fear of vesico-ureteral reflux. This is irrelevant, because we know that the use of these catheters is not harmful for a short period of time, either in animals or human beings. If this experiment was made in female animals it could allow the withdrawing of those catheters in the desired period using a common cystoscope.

Finally, I believe that this material, that is being already used with other objectives could also be used in this field. I believe that further studies are needed with a more appropriate methodology aiming at solidifying the results presented here.

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Nifedipine versus tamsulosin for the management of lower ureteral stones
From the Division of Urology, University of Turin, Orbassano, Turin, Italy
J Urol. 2004; 172: 568-571

Purpose: We evaluate and compare the effectiveness of 2 different medical therapies during watchful waiting in patients with lower ureteral stones.

Materials and Methods: A total of 86 patients with stones less than 1 cm located in the lower ureter (juxtavesical or intramural tract) were enrolled in the study and were randomly divided into 3 groups. Group 1 (30) and 2 (28) patients received daily oral treatment of 30 mg deflazacort, (maximum 10 days). In addition group 1 patients received 30 mg nifedipine slow-release (maximum 28 days) and group 2 received 1 daily oral therapy of 0.4 mg tamsulosin (maximum 28 days), Group 3 patients (28) were used as controls. Statistical analyses were performed using Student’s test, ANOVA test, chi-square test and Fisher’s exact test.

Results: The average stone size for groups 1 to 3 was 4.7, 5.42 and 5.35 mm, respectively, which was not statistically significant. Expulsion was observed in 24 of 30 patients in group 1 (80%), 24 of 28 in group 2 (85%) and 12 of 28 in group 3 (43%). The difference in groups 1 and 2 with respect to group 3 was significant. Average expulsion time for groups 1 to 3 was 9.3, 7.7 and 12 days, respectively. A statistically significant difference was noted between groups 2 and 3. Mean sodium diclofenac dosage per patient in groups 1 to 3 was 19.5, 26, and 105 mg, respectively. A statistical significant difference was observed between groups 1 and 2 with respect to group 3.

Conclusions: Medical treatments with nifedipine and tamsulosin proved to be safe and effective as demonstrated by the increased stone expulsion rate and reduced need for analgesic therapy. Moreover medical therapy, particularly in regard to tamsulosin, reduced expulsion time.

Editorial Comment
A number of trials have demonstrated the utility of pharmacologic therapy in promoting spontaneous ureteral stone passage and in reducing the time for and pain associated with stone expulsion. The efficacy of calcium channel blockers (nifedipine) in conjunction with corticosteroids has now been proven in several prospective, randomized clinical trials, and recently the combination of an alpha-1 receptor antagonist (tamsulosin) and a corticosteroid has likewise demonstrated benefit in the medical management of distal ureteral calculi. Propiglia and colleagues performed a head-to-head comparison of the 2 medical regimens (nifedipine/deflazacort versus tamsulosin/deflazacort) compared with a control, no-treatment arm and found that both treatment groups demonstrated a significantly higher rate of stone expulsion, a shorter time to spontaneous passage (only the tamsulosin arm was statistically significant compared with control) and a reduced need for analgesics.

Although adverse effects associated with the use of nifedipine and tamsulosin are low, all trials involving these drugs have reported a small number of patient drop-outs as a result of perceived side effects from the medication. Given the perhaps greater potential for problems due to nifedipine compared with tamsulosin, as well the proven benefit of the tamsulosin regimen in reducing time to stone passage, the combination of tamsulosin/corticosteroid may provide the best chance of spontaneous passage for distal ureteral stones. It remains to be seen if pharmacological therapy will prove to be as effective in promoting the spontaneous passage of stones located in the middle and proximal ureter as well as stones in the distal ureter. Furthermore, these studies have not separated the effect of the corticosteroid from that of the calcium channel blocker or alpha-1 blocker. Hopefully, future study will define the role of each agent in reducing symptoms and promoting
stone passage. However, for now, there is ample evidence supporting the use of these agents in appropriate patients with < 1 cm distal ureteral stones.

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Metabolic risk factors and the impact of medical therapy on the management of nephrothiasis in obese patients
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J Urol. 2004; 172: 159-163

Purpose: Previous studies have demonstrated that obesity can increase the risk of stone formation as well as recurrence rates of stone disease. Yet appropriate medical management can significantly decrease the risk of recurrent stone disease. Therefore, we analyzed our obese patient population, assessing the risk factors for stone formation and the impact of selective medical therapy on recurrent stone formation.

Materials and Methods: A retrospective chart review was performed to identify obese patients with stone disease from our Stone Center. Metabolic risk factors for stones were identified as well as patient response to medical therapy. A similar analysis was performed on a group of age and sex matched nonobese stone formers.

Results: Of 1,021 patients 140 (14%) were identified as obese (body mass index greater than 30). Of these patients complete metabolic evaluations were available in 83 with an average follow-up of 2.3 years. The most common presenting metabolic abnormalities among these obese patients included gouty diathesis (54%), hypocitraturia (54%) and hyperuricosuria (43%), which presented at levels that were significantly higher than those of the nonobese stone formers (p <0.05). Stone analysis was available in 32 obese patients with 63% having uric acid calculi. After initiating treatment with selective medical therapy obese and nonobese patients’ demonstrated normalization of metabolic abnormalities, resulting in an average decrease in new stone formation from 1.75 to 0.15 new stones formed per patient per year in both groups.

Conclusions: Obesity, as a result of dietary indiscretion, probable purine gluttony and possible type II diabetes, appears to have a significant role in recurrent stone formation. Appropriate metabolic evaluation, institution of medical therapy and dietary recommendations to decrease animal protein intake can significantly improve the risk of recurrent stone formation in these often difficult to treat patients.

Editorial Comment
With an increase in the proportion of obese individuals, interest in medical evaluation and treatment of problems unique to or overrepresented in this patient population has expanded. Stone disease is no exception, and the unique challenges posed by the surgical treatment of morbidly obese individuals have encouraged efforts to reduce the risk of stone occurrence. Ekeruo and colleagues reviewed the outcomes of medical evaluation and treatment of 83 obese stone formers at an average follow-up of 2.3 years, and found that gouty diathesis, hypocitraturia and hyperuricosuria were the most common metabolic abnormalities identified, and that these abnormalities were more pronounced than those identified in a group of matched non-obese stone formers. Moreover, uric acid stone composition was overrepresented in this patient group (63%) compared with the non-
obese group in whom uric acid stones comprised only 11% of stones. Some of these finding are expected based solely on overindulgent eating patterns (elevated urinary calcium, uric acid and oxalate). However, the finding of low urine pH is particularly interesting given the recent report showing that insulin resistance (commonly seen in obese patients) is associated with a defect in ammoniagenesis, thereby leading to an acid urine and subsequent promotion of uric acid stones (1). Although a high acid ash diet (from overindulgence in animal protein) can itself cause a decrease in urinary pH, the findings seen above persisted even when patients were maintained on a controlled metabolic diet, suggesting that the effect is, at least in part, diet-independent.

Of note, the initiation of directed medical and dietary therapy aimed at correcting the underlying metabolic abnormalities resulted in normalization of urinary parameters and a reduction in the rate of stone formation. As such, metabolic evaluation and medical and dietary therapy should be encouraged in these patients, with a good expectation of reduced stone recurrence and consequently less frequent need for surgical intervention.

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ENDOUROLOGY & LAPAROSCOPY

Nifedipine versus tamsulosin for the management of lower ureteral stones
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J Urol. 2004; 172: 568-571

Purpose: We evaluate and compare the effectiveness of 2 different medical therapies during watchful waiting in patients with lower ureteral stones.

Materials and Methods: A total of 86 patients with stones less than 1 cm located in the lower ureter (juxtavesical or intramural tract) were enrolled in the study and were randomly divided into 3 groups. Group 1 (30) and 2 (28) patients received daily oral treatment of 30 mg deflazacort, (maximum 10 days). In addition group 1 patients received 30 mg nifedipine slow-release (maximum 28 days) and group 2 received 1 daily oral therapy of 0.4 mg tamsulosin (maximum 28 days), Group 3 patients (28) were used as controls. Statistical analyses were performed using Student’s test, ANOVA test, chi-square test and Fisher’s exact test.

Results: The average stone size for groups 1 to 3 was 4.7, 5.42 and 5.35 mm, respectively, which was not statistically significant. Expulsion was observed in 24 of 30 patients in group 1 (80%), 24 of 28 in group 2 (85%) and 12 of 28 in group 3 (43%). The difference in groups 1 and 2 with respect to group 3 was significant. Average expulsion time for groups 1 to 3 was 9.3, 7.7 and 12 days, respectively. A statistically significant difference was noted between groups 2 and 3. Mean sodium diclofenac dosage per patient in groups 1 to 3 was 19.5, 26, and 105 mg, respectively. A statistical significant difference was observed between groups 1 and 2 with respect to group 3.
Conclusions: Medical treatments with nifedipine and tamsulosin proved to be safe and effective as demonstrated by the increased stone expulsion rate and reduced need for analgesic therapy. Moreover medical therapy, particularly in regard to tamsulosin, reduced expulsion time.

Editorial Comment

This group from Italy has contributed much to the active pharmacologic management of ureteral stones. They and others have demonstrated the effectiveness of nifedipine (calcium-channel blocker) or tamsulosin (alpha-1 blocker) in combination with corticosteroids and non-steroidal anti-inflammatory agents to facilitate stone passage from the ureter. Spontaneous ureteral stones and ureteral fragments after extracorporeal shock wave lithotripsy both have been shown to pass more frequently, sooner, and with less pain compared to controls. Unfortunately, all of the randomized studies have included corticosteroids and non-steroidal anti-inflammatory agents in the treatment arms, and the distinct effects of the calcium-channel blocker or alpha-1 blocker alone cannot be ascertained. Nonetheless, at our institution we have used the combination of calcium-channel blockers and non-steroidal anti-inflammatory agents for the treatment of ureteral colic. We have been unwilling to subject stone patients, with potential upper urinary tract obstruction and risk for infection, to the risks of corticosteroids. Anecdotally we have seen favorable results, but we cannot make any statement as to the comparative effectiveness to a treatment also including corticosteroids. This new study, however, leads us to believe that the alpha-1 blocker tamsulosin may have even greater effectiveness than nifedipine. Although the incidence of adverse effects was low in this study (only one patient in each of the treatment groups had to suspend therapy owing to adverse effects), one would expect tamsulosin to have fewer adverse effects in general. The use of tamsulosin and non-steroidal anti-inflammatory agents (plus corticosteroids if the studied treatment is to be applied exactly) should be considered the current best pharmacologic management of ureteral colic.

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15-Year experience with the management of extrinsic ureteral obstruction with indwelling ureteral stents

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Purpose: We assessed the success of retrograde placement of indwelling ureteral stents in the management of ureteral obstruction due to extrinsic compression.

Materials and Methods: Between July 1987 and December 2002 adequate followup was available for 101 patients who underwent primary retrograde ureteral stenting for extrinsic ureteral obstruction. Mean age at presentation was 61.4 years (range 33 to 90). Chart review was performed on all patients for primary diagnosis, symptomatology, degree of hydronephrosis, creatinine levels (baseline, treatment and post treatment), location of compression, size and number of stents used, progression to percutaneous nephrostomy tube (PNT), stent failure, days to stent failure, post-stent therapy and status at last followup.

Results: Mean length of followup was 11 months (range 1 to 127). In 101 patients 138 ureteral units (UU) were stented. Total stent failure occurred in 41 (40.6%) patients and 58 (42.0%) UU. A total of 40 (29.0%) UU required PNTs at a mean of 40.3 days (range 0 to 330) with 18 PNTs placed in less than 1 week.
Cases of stent failure that did not undergo PNT placement included 18 (13.0%) UU at a mean of 52.4 days (range 3 to 128). A total of 90 (89.1%) patients had metastatic cancer at stenting with 32.2% dead at 5.8 months (range 1 to 32). Univariate and multivariate analyses identified cancer diagnosis, baseline creatinine greater than 1.3 mg/dl and post-stent systemic treatment as predictors of stent failure. Proximal location of compression and treatment creatinine greater than 3.11 mg/dl were marginal predictors of failure on univariate analysis, while proximal location of obstruction was also marginally significant on multivariate analysis. No predictors were identified for early stent failure (less than 1 week).

Conclusions: At almost 1 year followup stent failure due to extrinsic compression occurred in nearly half of treated patients. Analysis of data revealed a diagnosis of cancer, baseline mild renal insufficiency and metastatic disease requiring chemotherapy or radiation as predictors of stent failure. Managing extrinsic compression by retrograde stenting continues to be a practical but guarded decision and should be tailored to each patient.

Editorial Comment

The article reviews a common clinical situation, that being placement of a ureteral stent for extrinsic ureteral obstruction. Almost half of the patients treated with ureteral stents failed within the first year, which is remarkably similar to prior reports. In the later years of this current series the success rate improved to greater than 60%. This might be due to different stent materials, but unfortunately the chart review was such that the authors could not reliably assess this factor. It makes sense that a stiffer and less compressible stent would fare better in this situation. Although one small series suggested that a stiffer stent maintained patency longer (1), this has yet to be confirmed in other series. An internal stent has attractiveness over a percutaneous nephrostomy tube for long-term management, but this approximately 50% failure rate must be acknowledged when counseling patients and when performing follow-up.

REFERENCES

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IMAGING

Baseline staging of newly diagnosed prostate cancer: a summary of the literature
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J Urol. 2004; 171 (6 Pt 1): 2122-7

Purpose: Staging for prostate cancer often includes bone scanning and computerized tomography (CT). We systematically reviewed the published evidence for these tests.
Materials and Methods: We searched MedLine for articles on these investigations in newly diagnosed cases of prostate cancer. Data were pooled based on prostate specific antigen (PSA), grade and tumor stage.

Results: Among 23 studies examining the role of bone scan metastases were detected in 2.3%, 5.3% and 16.2% of patients with PSA levels less than 10, 10.1 to 19.9 and 20 to 49.9 ng/ml, respectively. Scanning detected metastases in 6.4% of men with organ confined cancer and 49.5% with locally advanced disease. Detection rates were 5.6% and 29.9% for Gleason scores 7 or less and 8 or greater, respectively. Among 25 studies CT documented lymphadenopathy in 0 and 1.1% of patients with PSA less than 20 and 20 ng/ml or greater, respectively. CT detection rate was 0.7% and 19.6% in patients with localized and locally advanced disease, respectively. Detection rates in patients with Gleason scores 7 or less and 8 or greater were 1.2% and 12.5%, respectively. These risks were typically much greater on pathological evaluation.

Conclusions: Patients with low risk prostate cancer are unlikely to have metastatic disease documented by bone scan or CT. Therefore, these investigations should not be standard practice. However, patients with PSA 20 ng/ml or greater, locally advanced disease, or Gleason score 8 or greater are at higher risk for bone metastases and should be considered for bone scan. CT may be useful in patients with locally advanced disease or Gleason score 8 or greater but appears not to be of benefit in patients with increased PSA alone.

Editorial Comment

This is a very useful summary of the literature regarding the value of performing CT and bone scan in patients with newly diagnosed prostate cancer. Although these data is not new, this study clearly emphasizes that these tests should be done only in patients with high risk of presenting nodal or bone metastasis (PSA > 15 or Gleason score above 7 or clinical stage T3-4). In this group of patient, bone scan should be the first test to be done. If negative, CT of the abdomen and pelvis should be the next step. Since lymph node size does not correlate with the presence of metastasis, any abnormal lymph node demonstrated by CT should be further biopsied (CT-guided lymph node biopsy). Previous study has shown that in asymptomatic patients with newly diagnosed prostate cancer and serum PSA levels of less than 20 ng/ml, the likelihood of positive findings on abdominal/pelvic CT is extremely low (< 1%). In the USA, elimination of staging abdominal/pelvic CT in these patients would reduce medical expenditures for prostate cancer management by $20-50 million per year (1). In our opinion, it would be more beneficial to perform an endorectal MR imaging in the group of patients with moderate or high risk of harboring extraprostatic disease. This test is the best one available for adequate local staging of the disease. Endorectal MR imaging of the prostate has remarkable strength in the prediction of extra-prostatic extension of the disease and plays an important role in the evaluation of prostate cancer particularly when evaluated by an uroradiologist (2).

REFERENCES

Patient radiation dose at CT urography and conventional urography
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Radiology 2004; 232: 126-32

Purpose: To measure and compare patient radiation dose from computed tomographic (CT) urography and conventional urography and to compare these doses with dose estimates determined from phantom measurements.

Materials and Methods: Patient skin doses were determined by placing a thermoluminescent dosimeter (TLD) strip (six TLD chips) on the abdomen of eight patients examined with CT urography and 11 patients examined with conventional urography. CT urography group consisted of two women and six men (mean age, 55.5 years), and conventional urography group consisted of six women and five men (mean age, 58.9 years). CT urography protocol included three volumetric acquisitions of the abdomen and pelvis. Conventional urography protocol consisted of acquisition of several images involving full nephrotomography and oblique projections. Mean and SD of measured patient doses were compared with corresponding calculated doses and with dose measured on a Lucite pelvic-torso phantom. Correlation coefficient (R(2)) was calculated to compare measured and calculated skin doses for conventional urography examination, and two-tailed P value significance test was used to evaluate variation in effective dose with patient size. Radiation risk was calculated from effective dose estimates.

Results: Mean patient skin doses for CT urography measured with TLD strips and calculated from phantom data (CT dose index) were 56.3 mGy +/- 11.5 and 54.6 mGy +/- 4.1, respectively. Mean patient skin doses for conventional urography measured with TLD strips and calculated as entrance skin dose were 151 mGy +/- 90 and 145 mGy +/- 76, respectively. Correlation coefficient between measured and calculated skin doses for conventional urography examinations was 0.95. Mean effective dose estimates for CT urography and conventional urography were 14.8 mSv +/- 9.0 and 9.7 mSv +/- 3.0, respectively. Mean effective doses estimated for the pelvic-torso phantom were 15.9 mSv (CT urography) and 7.8 mSv (conventional urography).

Conclusion: Standard protocol for CT urography led to higher mean effective dose, approximately 1.5 times the radiation risk for conventional urography. Patient dose estimates should be taken into consideration when imaging protocols are established for CT urography.

Editorial Comment

CT urography is an evolving concept and developing technique, which combine the ultimate diagnostic capabilities of intravenous urography and CT. In many institutions, intravenous urography has already been replaced by CT urography to evaluate patients with hematuria and other genitourinary conditions. This paper emphasizes the most important drawback of this technique, which is related to the radiation exposure. In our institution the miliamper seconds (mAs) settings are chosen depending upon clinical indication and patients’ age and body habitus. Recent studies have shown that low-dose (reduced mAs) unenhanced CT is appropriate for the diagnosis of ureteral stones. Similarly efforts have been made in order to perform a low-dose protocol for CT urography. The standard protocol for multislice CT urography usually include 4 phases of imaging [noncontrast, arterial phase (25-30 seconds after intravenous injection of contrast); nephrographic phase (100 seconds) and excretory phase (180 seconds)]. In order to obtain a significant reduction in patient effective radiation dose without deterioration of imaging quality one should optimize the number of phases to be done and also do not include the kidneys and the pelvis in every phase. This can be done by adequate adjustment of the technical parameters to the patient’s weight and clinical situation. To obtain good results with a low-dose
CT urography protocol is possible. Since CT urography is still an evolving technique we believe that further improvement of an optimized protocol will be developed very soon.

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UROGENITAL TRAUMA

**Traumatic rupture of the urinary bladder: is the suprapubic tube necessary?**

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*J Trauma. 2003; 54: 431-6*

Background: Although surgical principles are well accepted for the treatment of an intraperitoneal or extraperitoneal rupture of the urinary bladder, the type and number of drainage catheters needed to obtain a satisfactory outcome with minimal patient morbidity have yet to be determined.

Methods: This was a retrospective review of data on injured patients with the diagnosis of an intraperitoneal or extraperitoneal rupture of the urinary bladder from penetrating or blunt trauma.

Results: Of the 51 patients identified, 28 were treated with suprapubic and transurethral catheters, whereas 23 received a transurethral catheter only. Complications and catheter duration times were similar regardless of type of bladder injury or drainage catheter used (p > 0.5).

Conclusion: These data suggest that there are similar outcomes and complication rates for patients treated with suprapubic and transurethral catheters versus transurethral catheter only. Transurethral catheters alone seem effective in draining all types of bladder injuries.

Editorial Comment

For many years, by habit, many of us have been placing suprapubic tubes (SPT) at the time of open bladder repair. However, this is only one of many papers that advocate using only a urethral catheter alone in these patients (1-3). It appears that using a urethral Foley catheter alone allows for low complications with minimal morbidity. The rate of urinary tract infection, in this study at least, is identical between both groups. In no cases in this small group of 51 patients did a patient seem to “require” the SPT (either as a “safety valve” or to facilitate irrigation).

Although I agree that most bladder injuries may be treated with urethral catheterization alone, there are some theoretical benefits to using a SPT. Patients with SPTs get their urethral catheters removed 11 days earlier in this series (with continued drainage via SPT), which may be more comfortable for the patient. Also, the suprapubic catheter allows for a theoretic “safety valve” if the urethral catheter becomes clogged or inadvertently dislodged, although this was not necessary in this series.

There are probably some uncommon cases where a suprapubic tube would be prudent. In cases of severe ongoing hematuria which is observed in the operating room, or in cases of truly devastating bladder injuries (such as close range shotgun wounds to the bladder), an SPT might help to maximize bladder drainage, especially in the unrepairable or unreliably repaired bladder. Otherwise, the data is clear: after bladder repair, consider using just a urethral catheter. We tend to use a 2-way catheter, as we feel that continuous bladder
irrigation is improper in a recently repaired bladder, but the authors of this study place a 3 way Foley and do use continuous bladder irrigation when necessary.

REFERENCES

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Straddle injuries to the bulbar urethra: management and outcomes in 78 patients
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Purpose: We describe our experience with blunt straddle injuries to the anterior urethra and identify factors that may affect patient outcome.

Materials and Methods: We reviewed the San Francisco General Hospital Urologic Trauma data base to identify men with blunt straddle injury. We analyzed presentation and initial management, location and length of urethral stricture, surgical options, and long-term outcome after reconstruction.

Results: Of 78 patients, 40% presented to the emergency department acutely and 60% presented 6 months to 10 years after injury complaining of obstructive symptoms, of whom 30% reported at least 1 episode of urinary retention. Initial acute management was suprapubic cystostomy in 81% of cases and primary realignment in 19%. Urethral strictures were predominantly located in the proximal bulb. Mean stricture length was significantly longer in men with delayed presentation (2.7 vs 1.8 cm, p < 0.05). No relationship was found between stricture length and the mechanism of injury or initial management technique. However, patients who had undergone primary realignment required complex flap or graft urethroplasty at a greater rate compared with men who had undergone suprapubic diversion (p = 0.054). Transperineal urethroplasty was required in 92% of patients with the majority undergoing end-to-end anastomosis. The success rate was 95% at a mean followup of 25 months (range 10 to 180). Recurrent stricture occurred in 4 men with prior urethral manipulation and it was managed successfully by direct vision internal urethrotomy alone.

Conclusions: After blunt straddle injury to the perineum the primary morbidity is anterior urethral stricture, for which suprapubic cystostomy is appropriate initial management. The majority of patients require surgery but with careful preoperative planning and adequate resection of fibrotic tissue the long-term success rate can approach 95%. If it arises, recurrent stricture responds well to direct vision internal urethrotomy alone.
Editorial Comment

Acute, blunt posterior urethral injuries, I believe, have ample data in the literature to support early endoscopic realignment over a catheter instead of suprapubic tube placement. I was surprised to see that in this series, acute realignment of significant acute blunt anterior urethral injuries was certain no better and potentially worse than suprapubic urinary diversion.

Seventy-eight patients are reported here, of which roughly half present acutely and half present long after the injury (all of these late cases had urethral stricture). Nine percent of those treated with urinary diversion required urethroplasty and 17% of those treated with primary catheter realignment needed surgery (p = not significant). More importantly, the length of the stricture seemed to be much longer on those managed with a urethral catheter (p < 0.5). The reason for this is unclear, and explanations involving “damage to the corpora spongiosum” are usually invoked in the literature. No matter what the reason, the data appears reasonably robust to suggest that acute catheter realignment of these injuries is not a good idea.

Of note, this article, which deals with blunt injury, should not be confused with previously printed works concerning penetrating anterior urethral trauma. This, too, is controversial with some advocating immediate repair and others advocating suprapubic diversion alone.

Although it will be psychologically difficult for me to avoid early urethral realignment of anterior strictures over a catheter (as I so strongly believe that it helps greatly in posterior urethral stricture) this and other series seem to indicate that suprapubic diversion may be the better option.

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PATHOLOGY

Fat invasion in ten-core prostate needle biopsies: incidence, biopsy and clinical findings
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Background: Presence of prostate cancer in the periprostatic adipose tissue signifies an advanced disease if seen on radical prostatectomy (stage pT3a). The significance of fat invasion on needle-core biopsies has not been well studied. The aim of the study is to investigate the incidence of the fat involvement and the associated clinical and biopsy findings on ten-core needle biopsy.

Design: From 07/00 to 12/01, 1,017 patients demonstrated prostate cancer on ten-core needle biopsy in our centralized Urological Pathology for the Calgary Health Region. The clinical and pathology data for all patients have been collected in our prostate cancer database. Fat involvement on one or more biopsy cores has been reported in 23 patients. Only one patient had undergone a radical prostatectomy in our institution until 09/03. All biopsies reported as positive for fat involvement and the prostatectomy specimen were reviewed.

Results: The incidence of fat involvement on needle biopsy was 2.2%. Most common site of fat involvement was the prostatic base (83%) and in 9/23 (39%) patients’ fat involvement was present in more than one site. The patients mean age was 70.1 years (range 57-83). Digital rectal examination and ultrasound findings were abnormal in 14/24 (58%) and 12/24 (50%) patients, respectively. Mean serum PSA was 52.3 ng/ml (median 15.55) and mean PSA density was 2.1 (median 0.45). Prostatic carcinoma was bilateral in 19/23
(83%) of the patients. Perineural involvement was identified in all biopsies with fat invasion; one biopsy showed also muscle involvement. The number of cores positive for prostate cancer ranged from 4 to 10 (mean 8). Mean biopsy Gleason score was 8 (range 7-10) and in 12/24 (50%) of the patients Gleason score was 8. Focal extraprostatic extension was confirmed in the patient who underwent radical prostatectomy.

Conclusions: Invasion of the fat by prostate cancer is uncommonly seen in ten-core prostatic biopsies. It is associated with adverse clinical and biopsy findings, including extensive and multiple core involvement, high Gleason biopsy score, and perineural invasion. It is most commonly seen in the biopsy cores from the prostatic base. Fat involvement should be always reported when identified on prostatic needle biopsies. The fact that during the follow-up period radical prostatectomy was performed only in one patient with fat involvement on biopsy, suggests that these patients, in addition to the adverse biopsy findings, presented with clinically advanced disease.

Editorial Comment

Invasion of fat is almost always a manifestation of extraprostatic spread by cancer. However, a published observation has indicated that rarely, significant expanses of fat may exist within the prostate, where its invasion by carcinoma would be misleading and might be considered evidence of extraprostatic spread (1).

To address this finding we dissected 150 prostates from consecutive autopsies of men over 40 (mean and median age, 61 years) who died of diseases other than carcinoma of the prostate (2). Fat was found amid preceding the most peripheral acini of the gland in only 1 of 150 (0.66%) prostates examined. This fat, comprising a group of 6 adipose cells was seen in only 1 of 45 sections of this prostate, corresponding to 1 of the total of 5,712 sections (0.01%) examined. This section with fat was located in the anterolateral part of the gland.

The study by Yilmaz and Trpkov supports our findings. There are 3 criteria for extraprostatic extension, depending on the site and composition of the extraprostatic tissue: 1) - cancer in adipose tissue, 2) - cancer in perineural spaces of the neurovascular bundles, and 3) - cancer in anterior muscle (3). Our study demonstrated that intraprostatic fat is extremely rare. Invasion of fat in a needle biopsy specimen of the posterolateral region of the prostate appears to always be a manifestation of extraprostatic spread by cancer.

REFERENCES


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Sarcomatoid renal cell carcinoma: an examination of underlying histologic subtype and an analysis of associations with patient outcome

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A sarcomatoid component can occur in all histologic subtypes of renal cell carcinoma (RCC) and indicates an aggressive tumor. We studied 2381 patients treated with radical nephrectomy for RCC between 1970 and 2000. A urologic pathologist reviewed the microscopic slides from all tumor specimens for the presence of a sarcomatoid component, defined as a RCC with any malignant spindle cell component. All tumors with a sarcomatoid component were classified as nuclear grade 4. A total of 120 (5.0%) patients had RCC with a sarcomatoid component, including 94 who died of RCC at a mean of 1.4 years following nephrectomy (median 8 months; range 44 days to 10 years). Cancer-specific survival rates at 2 and 5 years following nephrectomy were 33.3% and 14.5%, respectively. The presence of distant metastases at the radical nephrectomy and histologic tumor necrosis were significantly associated with death from RCC among patients with sarcomatoid RCC. Patients with clear cell (conventional) RCC and chromophobe RCC were more likely to have tumors with a sarcomatoid component (5.2% and 8.7%, respectively) compared with patients with papillary RCC (1.9%). The presence of a sarcomatoid component was significantly associated with death from RCC for all three subtypes (P < 0.001). Even among patients with grade 4 clear cell RCC, the presence of a sarcomatoid component was significantly associated with outcome, both univariately (risk ratio 1.59; P = 0.010) and after adjusting for TNM stage, tumor size, and histologic tumor necrosis (risk ratio 1.46; P = 0.037).

Editorial Comment
The Heidelberg classification of renal cell tumors is based on genetic alterations and classifies malignant parenchymal neoplasms as: 1) - common or conventional renal cell carcinoma which includes tumors with clear and/or eosinophilic cytoplasm; 2) - papillary renal cell carcinoma; 3) - chromophobe renal cell carcinoma; 4) - collecting duct carcinoma which includes the variant medullary carcinoma associated to sickle cell trait; and, 5) - renal cell carcinoma, unclassified (1). From group 5 was separated a new entity named “low-grade mucinous tubular and spindle cell carcinoma” possibly originated from the loop of Henle (2).

It is recognized that sarcomatoid change has been found to arise in all of these types of renal cell carcinoma in this classification. Sarcomatoid features thus do not constitute a type per se, but rather are an indication of progression in renal cell carcinoma.

In the study by Cheville JC et al., patients with chromophobe renal cell carcinoma had a higher frequency of sarcomatoid transformation (8.7%) comparatively to conventional (clear cell) carcinoma (5.2%) and papillary carcinoma (1.9%). This high frequency was also found by Akhtar M et al. (3) in Saudi Arabia where chromophobe renal cell carcinoma has the highest prevalence.

Sarcomatoid change should always be reported by the pathologist. The presence of a sarcomatoid change has an important impact on prognosis. In the study by Cheville et al. the presence of a sarcomatoid component was significantly associated with death both univariately and after adjusting for TNM stage, tumor size, and histologic tumor necrosis.

REFERENCES
Comparison of gene expression profiles between Peyronie’s disease and Dupuytren’s contracture
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Urology 2004; 64: 399-404

Objectives: To compare the gene expression alterations in human Peyronie’s disease (PD) and Dupuytren’s disease (DD) to determine whether they share a common pathophysiology. Multiple mRNA expression profiles of human PD have previously shown that genes that regulate fibroblast replication, myofibroblast differentiation, collagen metabolism, tissue repair, and ossification are involved. DD, a palmar fascia fibrosis, may be associated with PD.

Methods: Total RNA samples from PD plaques, normal tunica albuginea, Dupuytren’s nodules, and normal palmar fascia (nine samples per group) were subjected to differential gene expression profile analysis (Clontech Atlas DNA microarray) comparing PD with tunica albuginea and DD with normal palmar fascia. Changes of more than 2.0 in PD and DD compared with tunica albuginea and normal palmar fascia, respectively, were recorded. Reverse transcriptase-polymerase chain reactions were performed for some genes whose expression was altered in PD.

Results: Some of the gene families upregulated in both PD and DD were (a) collagen degradation: matrix metalloproteinase (MMP), with MMP2 and MMP9, and thymosins (MMP activators), with TMβ10 and TMβ4; (b) ossification: osteoblast-specific factors (OSFs) OSF-1 and OSF-2 (DD only); and (c) myofibroblast differentiation: RhoGDP dissociation inhibitor 1. The genes upregulated in PD only were decorin (an inhibitor of transforming growth factor-beta1 and a part of fibroblast replication/collagen synthesis) and early growth response protein. Reverse transcriptase-polymerase chain reaction confirmed these changes.

Conclusions: These data demonstrate that the pattern of alterations in the expression of certain gene families in PD and DD is similar, suggesting that they share a common pathophysiology and may be amenable to the same therapeutic regimens.

Editorial Comment
The authors present one more wonderful contribution to the knowledge of Peyronie’s disease.

One of the most accepted etiologies for Peyronie’s disease is that it is caused by trauma to the erect penis, resulting in extravasation of fibrin and other blood proteins into the tunica albuginea that, together with other unknown factors, elicit an inflammatory reaction followed by the production of pro-fibrotic agents, such as transforming growth factor-beta1 and reactive oxygen species. Peyronie’s disease may be associated with Dupuytren’s disease, which occurs in the palmar fascia in 21% of the cases. Dupuytren’s disease is characterized by similar fibrotic alterations, although its relationship to trauma is less established.

Analyzing gene expression, this study provides targets of potential pharmacologic modulation of the levels of genes associated with antifibrotic mechanisms. The authors speculate that stimulation of myofibroblast apoptosis and blockade of its differentiation with Rho inhibitors or cortactin may be beneficial, because accumulation of these cells in an abnormal healing process subsequent to trauma may relate to the fibrosis seen in Peyronie’s disease and Dupuytren’s disease.

Previous studies by the same group (1) demonstrated that treatment with L-arginine and phosphodiesterase inhibitors, both stimulating apoptosis and remodeling by nitric oxide/cyclic guanosine monophosphate or cyclic guanosine monophosphate alone, respectively, has been shown to prevent the fibrotic plaque in the TGF-β animal model of Peyronie’s disease.
References


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Effects of peppermint teas on plasma testosterone, follicle-stimulating hormone, and luteinizing hormone levels and testicular tissue in rats

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Urology 2004; 64: 394-8

Objectives: To justify the effects of Mentha piperita labiatae and Mentha spicata labiatae herbal teas on plasma total testosterone, luteinizing hormone, and follicle-stimulating hormone levels and testicular histologic features. We performed this study because of major complaints in our area from men about the adverse effects of these herbs on male reproductive function.

Methods: The experimental study included 48 male Wistar albino rats (body weight 200 to 250 g). The rats were randomized into four groups of 12 rats each. The control group was given commercial drinking water, and the experimental groups were given 20 g/L M. piperita tea, 20 g/L M. spicata tea, or 40 g/L M. spicata tea.

Results: The follicle-stimulating hormone and luteinizing hormone levels had increased and total testosterone levels had decreased in the experimental groups compared with the control group; the differences were statistically significant. Also, the Johnsen testicular biopsy scores were significantly different statistically between the experimental groups and the control group. Although the mean seminiferous tubular diameter of the experimental groups was relatively greater than in the control group, the difference was not statistically significant. The only effects of M. piperita on testicular tissue was segmental maturation arrest in the seminiferous tubules; however, the effects of M. spicata extended from maturation arrest to diffuse germ cell aplasia in relation to the dose.

Conclusions: Despite the beneficial effects of M. piperita and M. spicata in digestion, we should also be aware of the toxic effects when the herbs are not used in the recommended fashion or at the recommended dose.

Editorial Comment

This is the first report concerning the effects of peppermint tea on plasma total testosterone, LH, and FSH levels and testicular histologic features.

Peppermint tea is generally considered a safe drink for regular consumption. The authors demonstrate that both M. piperita and M. spicata tea intake decreased plasma testosterone and increased plasma LH and FSH levels in rats. Histologic studies revealed extensive degenerative changes in the germinal epithelium and spermatogenesis arrest when compared to controls.

Changes in the pituitary-testicular axis may be responsible for the testicular maturation arrest. The statistically significant decrease in both spermatogenesis and plasma total testosterone levels in the experimen-
tal groups was associated with an increase in the plasma FSH and LH levels. These observations prompted the authors to consider the pituitary-testicular axis. The plasma total testosterone levels had decreased and plasma FSH and LH levels increased, as expected. Therefore, the mechanism of spermatogenic abnormalities was more likely a result of the direct effect on germinal epithelium, and the hormonal deficit appeared to be a result of Leydig cell dysfunction. The pituitary gland or hypothalamus may also be affected, and the maturation arrest could have been the result of hypothalamic-pituitary-testicular axis deficiency. However, this hypothesis should be elucidated by additional studies focused on the hypophysial or hypothalamic tissues.

Consumption of M. piperita and M. spicata teas affected spermatogenetic activity at the 20 g/L and 40 g/L dose, respectively, in rats. The authors remember us that despite M. piperita and M. spicata beneficial effects in digestion, people should be aware of their toxic adverse effects when not used in the recommended fashion or at the recommended dose.

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RECONSTRUCTIVE UROLOGY

Current and future strategies for preventing and managing erectile dysfunction following radical prostatectomy
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Eur Urol. 2004; 45: 123-133

Introduction and Objectives: As radical prostatectomy remains a commonly used procedure in the treatment of clinically localized prostate cancer, we critically analyzed current and future strategies for preventing and managing postoperative erectile dysfunction.

Methods: Systematic literature review using Medline and CancerLit from January 1997 to June 2003. Abstracts published in the journals European Urology, The Journal of Urology and the International Journal of Impotence Research as official proceedings of internationally known scientific societies held in the same time period were also assessed.

Results: Patient selection and surgical technique are the major determinants of postoperative erectile function. Apoptosis of corporeal smooth muscle cells plays a role in the development of cavernous veno-occlusive dysfunction following radical prostatectomy. Pharmacological prophylaxis and treatment of postoperative erectile dysfunction is effective and safe. The concepts of cavernous nerve reconstruction and neuroprotection have been associated to promising results.

Conclusions: In the hands of experienced surgeons, properly selected patients undergoing a nerve sparing radical prostatectomy should achieve unassisted or medically assisted erections postoperatively.

Editorial Comment
This paper written by a team of young experts on the treatment of sexual dysfunction nicely describes how erectile function can currently be treated after oncological pelvic surgery. It is a valuable reference for both the pelvic surgeons performing potency preserving techniques and those who deal with these patients postop-
Nerve preservation is currently the only clinically truly proven method of preserving potency after radical prostatectomy or cystoprostatectomy. Although there are data that have shown the results of autologous nerve interposition if autonomic periprostatic nerves cannot be preserved, the true value and applicability needs to be reproduced in larger patient cohorts. Another interesting future aspect may be the use of neurogenesis inducing drugs or pharmatherapeutically protective substances such as immunophilin ligands, which are currently under clinical investigation.

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Neuroanatomy of the human female lower urogenital tract  
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Purpose: The neuroanatomy of the female lower urogenital tract remains controversial. We defined the topographical anatomy and differential immunohistochemical characteristics of the dorsal nerve of the clitoris, the cavernous nerve and the nerves innervating the female urethral sphincter complex.

Materials and Methods: A total of 16 normal female human pelvic specimens at 14 to 34 weeks of gestation were studied by immunohistochemical techniques. Serial sections were stained with antibodies raised against the neuronal markers S-100 and neuronal nitric oxide synthase (nNOS), vesicular acetylcholine transporter, calcitonin gene-related peptide and substance P. The serial sections were computer reconstructed into 3-dimensional images.

Results: Under the pubic arch at the hilum of the clitoral bodies, the branches of the cavernous nerves joined the clitoral dorsal nerve to transform its immunoreactivity to nNOS positive. The cavernous nerves originated from the vaginal nervous plexus occupying the 2 and 10 o’clock positions on the anterolateral vagina and they traveled at the 5 and 7 o’clock positions along the urethra. The urethral sphincter complex was innervated by nNOS immunoreactive and nonimmunoreactive nerve fibers arising from the vaginal nervous plexus and pudendal nerve, respectively.

Conclusions: The dorsal nerve of the clitoris receives nNOS positive branches from the cavernous nerve as a possible redundant mechanism for clitoral erectile function. The urethral sphincter complex has dual innervation, which pierces into the urethral sphincter complex at different locations. The study of the neuroanatomy of the female lower urogenital tract is germane to the strategic design of female reconstructive surgery.

Editorial Comment

This is the second paper on the neuroanatomy of the human clitoris of this group. They examined female human fetal pelvic specimens with regards to neural immunoreactivity. In an elegant study, they were able to demonstrate findings, which are important for some of the more recently available reconstructive techniques in women undergoing pelvic floor or pelvic surgery.

nNOS immunoreactive nerve fibers were demonstrated in the distal clitoris but not in the proximal clitoris. It might be speculated that NO not only plays an important role in female sexual physiology but also
that these specific nerves derive from the cavernous within the clitoral bodies and therefore are supplied by the pelvic autonomic nerves.

The location of these autonomic pelvic nerves were seen at the level of the urethra at the 5 and 7 o’clock joining more cranially the more nervous complex located at the anterior lateral sides of the vagina at the 2 and 10 o’clock positions. There was also a nNOS non-immunoreactive but otherwise autonomic nerve entering the muscular layer of the urethral sphincter complex at the mid urethra. There were no other autonomic nerves seen in the mid urethra.

The location of a dense network of autonomic nerves at the level of the vagina supplied by the inferior hypogastric plexus occupying the 2 and 10 o’clock positions at the rectum mainly at the lateral and anterior vaginal wall which were thinning out on the anterior wall towards the urethra. From there, fibers traveled either along the pathways described above towards the clitoris or towards the proximal mid urethral sphincter.

We learn from these studies for complex surgical procedures at the level of the pelvic floor and urethra to maintain micturition, continence and sexuality in female patients the preservation of autonomic nerves is mandatory and must put there pathways within the whole pelvis into consideration. Further studies will have to follow to demonstrate the functional value and possible changes in adulthood but definitely these data warned consideration during surgery.

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**UROLOGICAL ONCOLOGY**

**A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials**
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J Urol. 2004; 171: 2186-90

Purpose: We determined if 1 immediate instillation of chemotherapy after transurethral resection (TUR) decreases the risk of recurrence in patients with stage Ta T1 single and multiple bladder cancer overall and separately.

Materials and Methods: A meta-analysis was performed of the published results of randomized clinical trials comparing TUR alone to TUR plus 1 immediate instillation of chemotherapy.

Results: Our study included 7 randomized trials with recurrence information on 1476 patients. Based on a median followup of 3.4 years and a maximum of 14.5 years, 267 of 728 patients (36.7%) receiving 1 postoperative instillation of epirubicin, mitomycin C, thiotepa or (2’R)-4’-O-tetrahydropyranyl-doxorubicin (pirarubicin) had recurrence compared to 362 of 748 patients (48.4%) with TUR alone, a decrease of 39% in the odds of recurrence with chemotherapy (OR 0.61, p < 0.0001). Patients with a single tumor (OR 0.61) and those with multiple tumors (OR 0.44) benefited. However, after 1 instillation 65.2% of patients with multiple tumors had recurrence compared to 35.8% of patients with single tumors, showing that 1 instillation alone is insufficient treatment for patients with multiple tumors.
Conclusions: One immediate intravesical instillation of chemotherapy significantly decreases the risk of recurrence after TUR in patients with stage Ta T1 single and multiple bladder cancer. It is the treatment of choice in patients with a single, low risk papillary tumor and is recommended as the initial treatment after TUR in patients with higher risk tumors.

Editorial Comment

This paper should be read by every urologist dealing with superficial bladder cancer. Briefly, the facts are clear-single-shot instillation is a highly effective treatment with low cost. It should be give after every TUR. High-risk tumors deserve further therapy, to my opinion with BCG.

Intravesical cytotoxic drug instillations have their clear role in urology now: as single shot therapy.

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FEMALE UROLOGY

Urinary urgency and frequency, and chronic urethral and/or pelvic pain in females. Can doxycycline help?

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Purpose: Persistent urinary urgency and frequency, and chronic urethral and/or pelvic pain in women are often a diagnostic and therapeutic challenge. This can be frustrating for patients and physicians. The search for an infectious agent often proves futile and after multiple ineffective treatment regimens patients may be classified as having interstitial cystitis or referred to a psychiatrist as the last option. We evaluated whether treatment with doxycycline of the patient and her sexual partner would be beneficial.

Materials and Methods: Women presenting with a history of urinary urgency and frequency, and chronic urethral and/or pelvic pain often associated with dyspareunia and/or a history of recurrent urinary tract infection were evaluated. Initial examinations included urethral and cervical/vaginal swabs, serum analysis, urine examination and culture, and bladder barbitage. A total of 103 women with a median age of 46 years (range 21 to 84) and with a median symptoms history of 60 months (range 3 to 480) were included. All patients had trigonal leukoplakia at cystoscopy, in 15% an infectious organism was identified and 30% had leukocyturia. All were treated with doxycyclines, and a vaginal antimicrobic and/or antimycotic agent following the same regimen, including treatment of the sexual partner.

Results: After treatment with doxycycline 71% of the women were symptom-free or had a subjective decrease in symptoms.

Conclusions: Treatment with doxycycline is effective in more than two-thirds of patients complaining of persistent frequency and urgency, chronic urethral and/or pelvic pain, and dyspareunia as well as a history of recurrent urinary tract infections. In women with negative urinary cultures but a history of urgency/frequency provative treatment with doxycycline is justified and endoscopic findings may support the hypothesis of chronic infection. This should be done especially before contemplating psychiatric treatment or diagnosing the patient.
with interstitial cystitis. We attribute this high success rate to simultaneous treatment of the sexual partner, who may be an asymptomatic carrier, although this remains to be proved.

**Editorial Comment**

The authors review the efficacy of doxycycline therapy for one month on female patients with urinary urgency, frequency, chronic urethral and/or pelvic pain. Of note is that only 15% of the patients had an identified infectious organism. All patients have trigonal leukoplakia at cystoscopy. At the time of treatment with doxycycline the patient also underwent therapy with a vaginal antimicrobial and/or antymycotic agent. In addition, all sexual partners underwent synchronous therapy.

The use of antibiotics in the absence of a true positive culture is a therapy that many of us have tried, in both males and female. Who can say that he has never treated a man with prostatitis with long-term antibiotics in the absence of a positive culture and then experienced a positive clinical result. The subselection of patients to receive therapy with leukoplakia is interesting. Leukoplakia has been described and discussed previously in the literature (1). In addition, it was noted that the patients had synchronous therapy with a vaginal antimicrobial or antymycotic agent and had the sexual partners treated as well. It would be interesting to subdivide the success rates between those patients who had a sexual partner that was treated and those patients who did not have a sexual partner thus obviating the need for therapy for same. Potential difference in success rate would have perhaps shed light on the ping-pong reinoculation effect with a sexual partner versus a difficult primary problem of a non-infectious nature. In addition, that patients had a synchronous therapy with a vaginal antimicrobial and/or antymycotic agent does confuse the issue to a degree. Perhaps vaginal pathology was as much to blame for the troublesome symptoms as was a primary bladder difficulty. The efficacy of doxycycline may be multifactorial including that it is the only medication in its class that is renally excreted thus potentially achieving excellent bladder urine levels. If increased serum antibiotic levels do lend themselves to an increased therapeutic effect, then direction instillation of antimicrobial solutions in the bladder should not be discounted or forgotten in this challenging patient population (2).

**REFERENCES**


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**Does Valsalva leak point pressure predict outcome after the distal urethral polypropylene sling? Role of urodynamics in the sling era**

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*J Urol. 2004; 172: 210-4*
Purpose: Recently sling procedures have been shown to be effective in the treatment of all types of incontinence. In this study we evaluated the role of preoperative Valsalva leak point pressure (VLPP) in predicting the outcome of sling surgery.

Materials and Methods: We prospectively evaluated 174 consecutive patients who underwent a distal polypropylene sling procedure for the treatment of stress urinary incontinence (SUI). Using SEAPI scores patients were divided by VLPP into group 1-60 patients who did not leak on urodynamics, group 2-27 patients with VLPP greater than 80 cm H$_2$O, group 3-71 patients with VLPP 30 to 80 cm H$_2$O and group 4-16 patients with VLPP less than 30 cm H$_2$O. Surgical outcomes were determined by symptom, bother and quality of life questionnaires filled out by patients. The physicians were blinded to patient response.

Results: Mean followup was 14.7 months (range 12 to 30) and mean patient age was 62 years (range 32 to 88). The groups were well matched before surgery with respect to age, number of previous surgeries, and severity of SUI symptoms and urge incontinence. The percentage of patients who were cured or improved was similar among groups. After surgery there was no statistical difference among patient mean self-reported symptoms of or bother from SUI or urge incontinence.

Conclusions: The distal urethral polypropylene sling provides similar symptom improvement in all patients regardless of preoperative VLPP. VLPP is helpful in the diagnosis of SUI but appears to be of minimal benefit in predicting the outcome of the distal urethral polypropylene sling procedure.

Editorial Comment

The authors review the Valsalva leak point pressures obtained preoperatively before the placement of a distal urethral polypropylene sling and then correlate those values with the outcome of sling surgery. This paper is well written and is of great value. It was noted that the valsalva leak point pressure was helpful in evaluating stress urinary incontinence but could not accurately predict which patients would be a surgical success or not. This further highlights the utility of the minimally invasive sling procedure as a therapeutic option for all degrees of stress urinary incontinence. The authors found that patients with lower valsalva leak point pressures were likely to have significantly more severe stress urinary incontinence symptoms. This finding has been noted before (1). The value and role of urodynamic testing in stress urinary incontinence has been a long time subject of discussion in the field of urology (2). This academic contribution continues that intellectual discourse.

REFERENCES

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Abnormal dimercapto-succinic acid scans predict an increased risk of breakthrough infection in children with vesicoureteral reflux

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J Urol. 2004; 172: 1075-7

Purpose: The management of high grade vesicoureteral reflux remains controversial, with breakthrough infections being an indication for surgical repair. We sought to determine if technetium dimercapto-succinic acid (DMSA) scan could help predict which children are at risk for breakthrough urinary tract infection.

Materials and Methods: A retrospective review was performed on children presenting with a febrile urinary tract infection and prenatal hydronephrosis who were found to have vesicoureteral reflux and underwent a DMSA scan. Reflux was tabulated according to the highest grade. DMSA results were graded as 0-normal, no parenchymal or size defects, grade 1-focal parenchymal defects or less than a quarter of a renal unit involved, or grade 2-severe defects to include at least half of a renal unit, bilateral defects or unilateral atrophy.

Results: A total of 120 consecutive patients were evaluated. An abnormal DMSA scan was documented in 57 (33 females and 24 males), and 35 with grade 1 and 2 with grade 2 defects. Of the patients 53 females and 10 males had a normal scan. Of the 57 children with an abnormal DMSA scan 6% presented with grades 1 and 2 vesicoureteral reflux, 24% with grade 3, 38% with grade 4 and 26% with grade 5. Of the children with grades 3 to 5 reflux 60% had a subsequent breakthrough infection. Of the children with grades 3 to 5 reflux 60% had a subsequent breakthrough infection. Of the 63 children with a normal DMSA scan 11% presented with grade 1 reflux, 28% with grade 2, 48% with grade 3, 11% with grade 4 and 2% with grade 5. Of these children 5 had a subsequent breakthrough infection.

Conclusions: An abnormality on DMSA scan in the presence of grade 3 to 5 reflux correlates with a greater chance of having a breakthrough infection (60%). We conclude that children with grade 3 to 5 vesicoureteral reflux and an abnormal DMSA scan are at increased risk for breakthrough urinary tract infection.

Editorial Comment

It has been clearly demonstrated that DMSA scanning is a highly sensitive modality for detecting renal scarring. In particular, it has many advantages over renal ultrasound for this purpose. On the other hand, it is expensive and in terms of cost-effectiveness, the utility of DMSA scanning for determining renal injury in children with reflux has been questioned. In particular, it is important to determine whether the results of DMSA scanning alter management or outcome.

This study looks at differences in outcome of children with reflux based on the results of DMSA scanning. Of 120 children evaluated, 57 had abnormal scans, including 33 girls and 24 boys. In contrast, of the 63 normal scans, only 10 were boys. Furthermore, in follow-up, 60% of those with an abnormal DMSA scan had a breakthrough UTI whereas only 8% of those with a normal DMSA had a breakthrough infection.

The implications of these data are significant. First, as anticipated, boys with reflux have more renal injury, perhaps related to more abnormal neonatal voiding patterns with high intravesical pressures that are passed to the kidney. Second, those who already demonstrated a tendency to renal injury (because of either more abnormal voiding or a host resistance problem that results in a greater rate or more severe UTIs) are more likely to get further UTIs. Not only is this important in the pathophysiology of reflux and reflux nephropathy,
but it suggests that more aggressive management of reflux in this population may be warranted. This in turn suggests value in obtaining a DMSA scan in children with grades 3-5 reflux.

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Vaginal construction using sigmoid colon in children and young adults  
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BJU Int. 2004; 94: 115-9

Objective: To evaluate the age at which patients who required vaginal replacement (an uncommon procedure in children) were diagnosed, and the cause of their anomaly, and to relate these variables to the surgical outcome.

Patients and Methods: Patients who had vaginal replacement at the author’s institution between 1990 and 2002 were reviewed retrospectively. Depending on the age at reconstructive surgery, patients were divided into pre- and post-pubertal groups. Results: A neovagina was constructed in 23 patients during the study period; sigmoid colon was used in 20 but not in two patients with cloacal exstrophy and in one with Mayer-Rokitansky-Kuster-Hauser syndrome (MRKHS). These cases were excluded from the analysis of outcomes and complications. Group 1 comprised patients diagnosed and treated before puberty and group 2 those diagnosed and/or treated afterward. In group 1 the presenting diagnoses included androgen insensitivity syndrome (AIS) in six patients, MRKHS in two, cloacal exstrophy in two, vaginal tumour in one, Mullerian duct renal aplasia cervicothoracic somite dysplasia, vertebral abnormalities, anal atresia, cardiac anomalies, tracheo-oesophageal fistula, and/or oesophageal atresia, renal abnormalities and limb defects syndromes in one each. In group 2 the presenting diagnoses included MRKHS in seven, AIS in two, and congenital adrenal hyperplasia in one. Complications included superficial wound infection (two patients), recurrent introital stenosis, and blind loop mucocele, complete stenosis of perineal neovaginal opening (one each) and dyspareunia in three. Neither age nor pelvic habitus (android vs gynaecoid) influenced the outcome, and the cosmetic results were excellent in all the patients.

Conclusion: Isolated sigmoid neovaginal construction appears to be applicable to many diagnoses and in patients at any age. Although an android pelvis can present technical challenges, in this experience it was not associated with a greater complication rate. The long-term satisfaction with the sigmoid neovagina for intercourse, especially in those constructed before puberty, still requires long-term evaluation.

Editorial Comment

Vaginal reconstruction is an uncommon procedure, but carries special significance when done. It is, of course, most common in patients with some form of intersex and involves the genitalia, both of which raise the anxiety level of parents considerably. Moreover, the type of reconstruction varies considerably by specialty, with plastic surgeons and gynecologists generally recommending skin graft/dilation procedures and pediatric urologists recommending bowel vaginoplasty. Furthermore, the timing of the reconstruction remains highly controversial.

This is an interesting review that helps the reader in several ways. First, I believe that it provides the reader with a realistic estimate of the potential complications of bowel vaginoplasty. Three patients out of 20
had introital stenosis (of course these were quite fixable) and all three who are sexually active suffered from dyspareunia. Fortunately this was not severe enough to prevent sexual activity, but nonetheless, this would be important to mention in preoperative counseling. Interestingly, in the authors hands, bowel vaginoplasty was no more risky in children who were pre-pubertal (mean age 4) than in those who were post-pubertal. This is likely because these patients did not require dilation postoperatively. When using techniques that require dilation postoperatively, the procedure should surely be postponed until after puberty.

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