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UROLOGICAL SURVEY

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STONE DISEASE

Computed tomography—an increasing source of radiation exposure

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No abstract available.

Editorial Comment

The authors reported that 62 million CT scans are performed annually in the United States; including 4 million in children. The radiation dose, a measure of ionizing energy absorbed per unit of mass, is 10 milligrays compared to 0.01 for a PA chest x-ray. The radiation dose from a CT scan depends on the number of scans (for example with and without contrast), the tube current, the scanning time in milliamp-seconds, the size of the patient, the axial scan range, the scan pitch (or degree of overlap between adjacent CT slices), the tube voltage in kilovolt peaks and the scanner design.

The theoretical risk of ionizing radiation is that it can stimulate the generation of hydroxyl radicals which can then lead to DNA fragmentation or base damage. The authors extrapolate these risks from increased risks of cancer in atomic-bomb survivors (with a mean radiation dose of 40 milligrays) and nuclear industry workers (with a mean radiation dose of 20 milligrays), though in these situations the individuals were exposed to a uniform total body dose, while with CT imaging there is non-uniform exposure with efforts to limit exposure to the focused region of interest. The authors then go on to extrapolate the estimated attributable risk of death from cancer to a single CT scan, and report that the bulk of the risk occurs if the CT imaging is performed prior to the age of 15 years old, and the highest risk is related to digestive system malignancy after abdominal imaging.

Though this article received dramatic coverage by the press and led to heated discussions in our clinics, it is clear that the article is weak on science and strong on editorial opinion. The authors state that the evidence for an increased risk of cancer after a common CT scan is "reasonably convincing" though in the next sentence state that "no large-scale epidemiologic studies of cancer risk associated with CT scans have been reported."

The author's statement that 2% of cancers in the United States are attributable to CT scan imaging is unsubstantiated. They fail to acknowledge that while CT imaging exposes patients only to x-rays, atomic-blast survivors were exposed to particulate radiation, neutrons and other radioactive materials, the biological significance of which are unknown, and as such it is inaccurate to extrapolate from cancer risk in this cohort.

The authors acknowledge that though the individual risk estimates for attributable risk of death from cancer is very low, they believe it important from a public health standpoint. What is not calculated is the attributable risk of death by not imaging or by ordering a substandard imaging modality for fear of radiation.

As CT-scanners and CT-scan imaging becomes assimilated into ambulatory urology clinics, it is imperative for the supervising urologist to become educated on the techniques of adjusting image parameters to minimize radiation dose while maintaining adequate resolution of the image. Though this article emphasizes the importance of evaluating the need for a test before ordering it, it crosses the border of raising awareness into the realm of raising hysteria.

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Prestenting improves ureteroscopic stone-free rates

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J Endourol. 2007; 21: 1277-80

Purpose: Although the use of stents after ureteroscopy has been studied extensively, relatively little has been published about stent placement before complicated ureteroscopic procedures. In this study, we examined our experience with stent placement before ureteroscopic management of renal and ureteral stone disease.
Patients and Methods: A total of 90 patients underwent ureteroscopic surgery on 115 renal units by a single surgeon from 2001 to 2006. All patients had documented follow-up with imaging either by CT or intravenous urography (IVU) with tomography. Patients were classified into two groups depending on whether they had a stent placed before ureteroscopy. Baseline characteristics, operative indications for stent placement, stone-free rates, and complications were compared between groups.
Results: Baseline characteristics were similar between the groups. The majority of patients received stents before stone management because of technical considerations during surgery (17/36, 47%) or infection (13/36, 37%). Strict stone-free rates after ureteroscopic treatment were 47% in the 79 procedures without previous stents, compared with 67% in the 36 procedures with prestenting ($P < 0.05$). Including small fragments (2 mm or smaller), stone-free rates improved to 54% v 78%, respectively ($P < 0.02$). Complications were not significantly different in the two groups ($P = 0.70$).
Conclusion: Although routine stent placement is not necessary before all ureteroscopic procedures, we demonstrate that it is associated with good stone-free rates and few complications. In this retrospective cohort, prestenting was associated with significantly higher stone-free rates. Prestenting should be considered in challenging cases.

Editorial Comment

The authors state that when possible a larger and longer ureteral stent used for prestenting, however further details regarding the specific stent size are not provided. Similarly the authors do not comment on the duration of prestenting. The authors do not comment on their practice of fragmenting versus basketing the treated stone. The authors do not comment on the percentage of patients imaged with CT scan in each group – if a greater proportion of unstented patients underwent postoperative CT scan imaging, the higher sensitivity of the test may explain the noted differences in stone-free rates.

Infection is known to result in decreased ureteral peristalsis, which theoretically could facilitate stone passage. Though 22% of the presented patients had calculi smaller than 5 mm, it is not reported what proportion of patients spontaneously passed stones prior to ureteroscopy. The authors utilized small ureteral access sheaths (10 mm internal diameter) in 20% of patients who were not prestented, and larger ureteral access sheaths (14 mm internal diameter) in 40% of patients who were prestented. One would anticipate that this would impact stone free rates, and may be the most important observation of this study. However, stone-free rates were not stratified based on sheath size. Similarly we are not told whether the decision to use a smaller sheath vs. larger sheath was empiric based on the presence of a stent or the result of difficulty passing a larger sheath.

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ENDOUROLOGY & LAPAROSCOPY

A comparison of the incidence and location of positive surgical margins in robotic assisted laparoscopic radical prostatectomy and open retropubic radical prostatectomy

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Purpose: Surgical technique, patient characteristics and method of pathological review may influence surgical margin status. We evaluated the incidence and location of positive surgical margins in 200 sequential robotic assisted laparoscopic radical prostatectomy and 200 sequential open radical retropubic prostatectomy cases.
Materials and Methods: From July 2002 until December 2006 a total of 1,747 patients underwent radical prostatectomy at our institution (robotic assisted laparoscopic radical prostatectomy in 1,238, radical retropubic prostatectomy in 509). From these we selected the last 200 consecutive radical retropubic prostatectomies and 200 robotic assisted laparoscopic radical prostatectomies performed before August 2006. Preoperative clinical characteristics including age, clinical stage, prostate specific antigen and Gleason score were evaluated. Postoperatively pathological specimens were assessed for specimen weight, Gleason score, tumor volume, pathological stage and margin status. The incidence and location of positive surgical margins were compared between robotic assisted laparoscopic radical prostatectomy and radical retropubic prostatectomy.
Results: Patients undergoing robotic assisted laparoscopic radical prostatectomy compared to radical retropubic prostatectomy had more favorable tumor characteristics including lower prostate specific antigen, clinical stage and Gleason score. No statistically significant differences were found between groups for prostate volume or tumor volume. However, tumor volume as a percentage of prostate volume was higher among radical retropubic prostatectomy compared to robotic assisted laparoscopic radical prostatectomy cases (17.7% vs 13%, $p = 0.001$). The overall incidence of positive surgical margins was significantly lower among the robotic assisted laparoscopic radical prostatectomy compared to radical retropubic prostatectomy cases (15% vs 35%, $p < 0.001$). The incidence of positive surgical margins according to pathological stage for robotic assisted laparoscopic radical prostatectomy vs radical retropubic prostatectomy cases was 16 of 171 (9.4%) vs 33 of 137 (24.1%) for pT2 ($p < 0.001$) and 14 of 28 (50%) vs 36 of 60 (60%) for pT3. In both groups the apex was the most common site of positive surgical margins with 52% in the robotic assisted laparoscopic radical prostatectomy group vs 37% in the radical retropubic prostatectomy group ($p > 0.05$).
Conclusions: In the hands of surgeons experienced in robotic assisted laparoscopic radical prostatectomy and radical retropubic prostatectomy, there was a statistically significant lower positive margin rate for patients undergoing robotic assisted laparoscopic radical prostatectomy. The most common location of a positive surgical margin in robotic assisted laparoscopic radical prostatectomy and radical retropubic prostatectomy cases was at the apex. Patients treated with radical retropubic prostatectomy had higher risk features which may have independently influenced these results. The method of pathological specimen analysis and reporting may account for the higher positive margin rates in both groups compared to some reports.

Editorial Comment

The authors report an intra-institutional comparison of positive margin rates between open and robotic assisted laparoscopic radical prostatectomy (RALP). A total of 1,747 (1,238-robotic and 509 open) patients were studied during 4-year period. In both groups, the apex was the most common site of a positive surgical margin (52% in the RALP group vs. 37% in the open group). Although stratification methods were applied to the study, the open group had higher tumor volume while the robotic group had significant lower PSA levels and higher Gleason score 4/5 (27.5% of the open vs. 14% of the robotic group). This study reports the skills of fellowship

trained surgeons and in particular one surgeon that had vast experience in RALP and open radical prostatectomy; reducing the bias of the learning curve among different surgeons. Thus far, similar functional and oncological outcomes have been reported despite the surgical technique (open, laparoscopic or robot assisted laparoscopic prostatectomy) when the procedure is performed by experienced surgeons.

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Incidence of local recurrence and port site metastasis after laparoscopic radical nephroureterectomy

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Objectives: To address the incidence of local recurrence and port site metastasis in patients who underwent laparoscopic radical nephroureterectomy (RNU) for upper tract transitional cell carcinoma (TCC).
Methods: Between August 1993 and February 2006 116 laparoscopic RNU were performed in 115 patients at our institution. A traditional open excision, a laparoscopic stapler resection or a different approach was used for the management of the distal ureter in 76, 27, and 11 cases, respectively. Clinical follow-up as well as perioperative and pathologic data were retrospectively collected.
Results: Perioperative and pathologic data were available in all 116 cases. Clinical outcomes were available in 107 patients with a mean follow-up of 30.5 months (range 1 to 148). Six patients (5.6%) had a local recurrence develop, including 1 patient with port site metastasis (0.9%) at an average of 5.7 months. In 2 of these patients, violation of the ipsilateral urinary tract was noted perioperatively.
Conclusions: We report, in this large single-center series of laparoscopic RNU, a low incidence of local recurrence. Our results confirm that a laparoscopic approach to upper tract TCC does not result in a clinically significant increased risk of tumor spillage provided that principles of oncologic surgery are followed.

Editorial Comment

Laparoscopy radical nephroureterectomy (LRNU) has been challenged and questioned as treatment of upper tract transitional cell carcinoma (TCC) due to the possible port or bladder cuff resection sites recurrence. Different authors demonstrated diverse methods to manage the bladder cuff during LRNU and similar recurrence rates and outcomes to the open technique have been reported. This single-center retrospective study (107 patients) demonstrated that the laparoscopic approach did not increase the risk of tumor spillage when principles of oncologic surgery are followed.

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IMAGING

Detection of prostate cancer with MR spectroscopic imaging: an expanded paradigm incorporating polyamines

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Purpose: To characterize benign and malignant prostate peripheral zone (PZ) tissue retrospectively by using a commercial magnetic resonance (MR) spectroscopic imaging package and incorporating the choline plus creatine-to-citrate ratio ([Cho + Cr]/Cit) and polyamine (PA) information into a statistically based voxel classification procedure.
Materials and Methods: The institutional review board approved this HIPAA-compliant study and waived the requirement for informed consent. Fifty men (median age, 60 years; range, 44-69 years) with untreated biopsy-proved prostate cancer underwent combined endorectal MR imaging and MR spectroscopic imaging. Commercial software was used to acquire and process MR spectroscopic imaging data. The (Cho + Cr)/Cit and the PA level were tabulated for each voxel. The PA level was scored on a scale of 0 (PA undetectable) to 2 (PA peak as high as or higher than Cho peak). Whole-mount step-section histopathologic analysis constituted the reference standard. Classification and regression tree analysis in a training set generated a decision-making tree (rule) for classifying voxels as malignant or benign, which was validated in a test set. Receiver operating characteristic and generalized estimating equation regression analyses were used to assess accuracy and sensitivity, respectively.
Results: The median (Cho + Cr)/Cit was 0.55 (mean +/- standard deviation, 0.59 +/- 0.03) in benign and 0.77 (mean, 1.08 +/- 0.20) in malignant PZ voxels (P = .027). A significantly higher percentage of benign (compared with malignant) voxels had higher PA than choline peaks (P < .001). In the 24-patient training set (584 voxels), the rule yielded 54% sensitivity and 91% specificity for cancer detection; in the 26-patient test set (667 voxels), it yielded 42% sensitivity and 85% specificity. The percentage of cancer in the voxel at histopathologic analysis correlated positively (P < .001) with the sensitivity of the classification and regression tree rule, which was 75% in voxels with more than 90% malignancy.
Conclusion: The statistically based classification rule developed indicated that PAs have an important role in the detection of PZ prostate cancer. With commercial software, this method can be applied in clinical settings.

Editorial Comment

The ratio of choline and creatine to citrate (Cho+Cr/Cit), is the parameter for the detection of prostate cancer on MR spectroscopic imaging (MRSI). As we know this ratio is increased in prostate cancer due to the elevation of choline (high turnover of phospho-lipid in cell membranes of the proliferating tissue) and reduction in the level of citrate (converted to a citrate-oxidating metabolism).Although there is no consensus, voxels are considered very suggestive of cancer if the ratio of choline and creatine to citrate is more than 3 standard deviations above the average ratio (1). However, using these criteria false positive results occurs due to prostatitis and prostatic atrophy. The authors of this meticulous and well-performed prospective study offers additional data regarding the possible role of another metabolite (polyamine) which may help increase the accuracy for the detection of prostate cancer by MRSI. When the polyamine peak is higher or at the same level of the peak of choline and the ratio of Cho+Cr / Cit is above 1.1, the voxel should be considered malignant. However if the ratio is below 1.1 the voxel should be considered benign. As suggested by the authors we already started to apply this method in clinical settings particularly for the detection of prostate cancer in patients with negative biopsies (at least 2) and elevated PSA. In the near future, we will present our preliminary results of this prospective study. It

would be interesting to see if this expanded paradigm will be useful to avoid false positive results with MRSI of the prostate. Other prospective studies from different institutions in similar or distinct clinical settings are warranted.

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The incidental indeterminate adrenal mass on CT (> 10 H) in patients without cancer: is further imaging necessary? Follow-up of 321 consecutive indeterminate adrenal masses

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Objective: The objective of our study was to determine whether follow-up imaging evaluation is necessary for incidentally discovered indeterminate adrenal lesions (> 10 H) on CT in patients with no known malignancy.
Materials and Methods: A computer search of CT reports from January 2000 to December 2003 identified patients with incidentally detected, indeterminate, but benign-appearing adrenal lesions who had no known malignancy and no clinical suspicion of hyperfunctioning adrenal mass. Patients with adrenal masses diagnostic on the initial CT or heterogeneous masses were excluded. Two hundred ninety patients with 321 lesions met the study criteria. Each lesion was determined to be benign or malignant based on histopathology, characterization with diagnostic imaging studies, or a minimum of 1 year of stability on imaging follow-up or 2 years of stability on clinical follow-up.
Results: Of the 321 lesions, 318 masses (99.1%) were confirmed to be benign and clinically insignificant. These included three (0.9%) histologically confirmed adenomas, 198 (61.7%) adenomas by imaging characterization, five (1.6%) other benign lesions, 71 (22.1%) masses stable on imaging follow-up, and 41 (12.8%) masses with clinical stability. There were three (0.9%) clinically unsuspected functioning masses: one cortisol-producing adenoma and two pheochromocytomas. There were no metastatic adrenal lesions, even among the 13 patients who subsequently developed malignancy elsewhere.
Conclusion: All of the incidentally detected adrenal masses with a CT attenuation of > 10 H were benign in patients with no known malignancy. Follow-up imaging to characterize an incidental adrenal mass appears to have a limited role in this patient cohort.

Editorial Comment

Adrenal incidentalomas are found in up to 5% of abdominal CT examination and most of these adrenal lesions observed in patients with no known malignancy are presumed to be benign adenomas as long as they appears as homogeneous, well-defined lesion, round or oval, less than 3 cm, and with attenuation equal or below 10UH. Nowadays imaging plays an essential role for the accurate characterization of the nature of these

incidentalomas. The imaging armamentarium used for this evaluation includes unenhanced CT, chemical shift MRI, CT histogram and CT contrast washout analysis. More recently, promising results of MR spectroscopic imaging have been reported, adding to the armamentarium of adrenal imaging (1).There is still controversies regarding how to follow these patients presenting with radiologic diagnosis of adrenal adenoma; some radiologists do not suggest any follow-up, others recommends repeat dedicated imaging studies at 6, 12, and 24 months. As pointed out by the authors of this manuscript the American College of Radiology states that extensive and costly workup is usually not justified for small (< 3 cm) adrenal masses. The authors of this interesting retrospective study state that none of the adrenal masses (with CT attenuation of > 10UH) incidentally detected in patients without cancer were malignant. Similar findings have been reported in other series in the literature. The authors also did not find any case of a primary adrenal cortical carcinoma or found any enlargement of the lesion in the follow-up study, although enlargement of 1 cm over 1 year can be found in 5% of benign adenomas. Although this study has important limitation already highlighted by the authors (lack of routine biochemical screening in all patients, absence of follow-up in 32 patients, and short follow-up in 66 patients), their results are challenging and calls for further prospective studies to confirm that all small adrenal lesions incidentally found in patients with not known cancer need no follow-up imaging or at least need a less rigid scheme of imaging follow-up.

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UROGENITAL TRAUMA

Renal injury mechanisms of motor vehicle collisions: analysis of the crash injury research and engineering network data set

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Purpose: Injury prevention requires efficient diagnosis and management, and knowledge of collision kinematics may allow first responders to triage victims earlier based on crash scene assessment. We identified possible collision patterns and vehicle interior components that may have a role in kidney injury following motor vehicle collision.

Materials and Methods: A total of 115 cases (131 renal injuries) were identified in the multicenter Crash Injury Research and Engineering Network database. For each case a crash investigation was performed, identifying vehicle kinematic characteristics, vehicle damage profile and an assessment of the interior compartment to determine points of occupant contact and restraint system use. A multidisciplinary team reviewed each case to establish a probable mechanism for all injuries sustained. Review of the medical record was performed to identify subject demographics and injury characteristics. Cases were analyzed based on frontal vs side impact.

Results: Of the subjects 52% were male. Mean age was 36.1 years and median injury severity score was 33. Overall injuries were low grade in 72.5% of patients, 30% were unrestrained and 47.6% of collisions were side impact. No difference was observed between frontal and lateral collisions with respect to renal injury severity. For frontal impact the seat belt was the source in 26 of 29 renal injuries (90%) and 12 of 15 unrestrained cases (80%) were due to direct impact with the steering column. Of 131 side impact injuries 62 were attributable to impact with lateral compartment elements. Side impact injuries were associated with lateral door panel impact (41 of 61) with the armrest accounting for 22. The mean lateral compartment intrusion was 29.6 cm. No grade V injuries occurred when vehicle intrusion was less than 30 cm. The mean change in velocity for frontal and lateral collisions was 24.0 and 31.5 mph, respectively ($p < 0.05$). In frontal collisions the change in velocity for kidney injuries sourced to the steering wheel vs seat belt injuries was statistically greater (41.5 vs 28.4 mph, $p = 0.05$).
Conclusions: Renal injury in frontal and side impact collisions appears to occur after direct impact from objects in the vehicle compartment. For frontal crashes occupant acceleration into the seat belt or steering wheel seems to result in renal injuries. Side impact injuries occur when the vehicle side panel intrudes into the compartment, striking the occupant. Further collision evaluation in larger data sets is required to substantiate our findings.

Editorial Comment

When evaluating a trauma patient in the emergency department one of the important aspects to elicit is the mechanism of injury. If the mechanism is blunt, the typical questions to be answered are the speed of the vehicle, location of the victim (passenger or diver, front or back seat), restrained / unrestrained, and if the victim was ejected from the vehicle. The above study by Kuan et al., is the first study on blunt kidney injuries to analyze the injury pattern by the direction of the collision, lateral or frontal, and if the victim was restrained or unrestrained. With frontal collisions, kidney injuries are due to deceleration and sheering either from collision with the steering column or instrument panel or the seat belt. For lateral collisions, renal injury appears to be from compartment intrusion striking the flank. The overall injury severity increases in relation to the degree of intrusion, with the majority occurring with intrusions > 30 cm. Perhaps mandatory side air bags would minimize the injuries from such lateral intrusions.

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Role of magnetic resonance imaging in assessment of posterior urethral distraction defects

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Objectives: To determine the clinical usefulness of magnetic resonance imaging (MRI) in the assessment of posterior urethral distraction defects.
Methods: A total of 21 male patients, 6 to 35 years old, with posterior urethral distraction defects underwent MRI of the pelvis and combined antegrade retrograde urethrography before surgical repair. Repair was performed with a bulboprostatic urethral anastomosis through the perineum in 13 patients and transpubically in 8. The MRI and urethrographic findings were compared and correlated with the operative findings. The MRI findings were also correlated with the incidence of posttraumatic impotence.

Results: On MRI, the length of urethral defect and type of prostatic displacement could be correctly determined in 86% and 89% of the patients, respectively. Also, MRI precisely delineated the extent of scar tissue, which varied according to the type and magnitude of the original trauma. Furthermore, MRI revealed the presence of paraurethral false tracks in 3 patients. In addition, MRI demonstrated avulsion of the corpus cavernosum, as well as lateral prostatic displacement in all 6 patients with posttraumatic impotence.
Conclusions: Preoperative MRI can provide useful information that might help determine the appropriate surgical repair. It correctly estimates the length of the urethral defect, clearly demonstrates the type and degree of prostatic displacement, precisely delineates the site and density of scar tissue, and reveals the presence of paraurethral false tracks. Also, MRI can identify the cause of posttraumatic impotence such as avulsion of the corpus cavernosum and thus might predict the potency outcome in these cases.

Editorial Comment

Posterior urethral distraction defects were classically described as prostato-membranous disruption injuries by Turner-Warwick. In other words, posterior urethral injuries from pelvic fracture are not urethral strictures but scar tissues that fill the gap from the displacement of the prostate or the bulbar urethra. While many of the urethral injuries from pelvic fracture are at the prostato-membranous junction, roughly as many are at the bulbo-membranous junction. When preparing for a posterior urethroplasty, a well performed and simultaneous VCUG and RUG are needed. The keys here a properly performed study is to first perform a static cystogram to test the competence of the bladder neck, and then have the patient void, in order to fill the prostatic urethra. In this day and age with an aggressive initial management of primary realignment with flexible cystoscopes, the final distraction defect distance is typically < 2 cm and only occasionally > 2 to 3 cm. For such short distances, there is rarely the need for an abdominal perineal approach. The progressive perineal approach, as detailed by Webster, will typically bridge all gaps. In my personal experience with posterior urethroplasty, I have only needed to perform a pubectomy 2 times in over the last 10 years. In conclusion, while having a MR imaging of the urethra preop is nice, it is more of a luxury then a true necessity. The area that I have found the pelvic MR to be a value is when the prostate is displaced laterally and it is those circumstances that the prostatic urethra can be difficult to find. The other interesting finding from pelvic MR study, is that impotence after pelvic fracture may be due to avulsion of the corpus cavernosum from the ischium, and not necessarily a vascular injury at Alcock's canal.

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PATHOLOGY

Different types of atrophy in the prostate with and without adenocarcinoma

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Objectives: The purpose of this study was to evaluate, according to a classification proposed by a working group, the extent and type of atrophy lesions in radical prostatectomy specimens obtained from patients with prostatic

carcinoma and benign prostatic hyperplasia (BPH), and to compare the prevalence and types of atrophy between two investigated groups.
Methods: Histologic analysis of 1096 slides from 50 patients with carcinoma and 277 slides from 31 patients with BPH was performed to evaluate, according to the new prostatic atrophy classification, the number of foci and type of atrophic lesions.
Results: Age, Gleason grade, and TNM showed no significant correlation with the number of proliferative atrophy (PA) and proliferative inflammatory atrophy (PIA) foci ($p > 0.05$). PIA was significantly more frequent in prostates with carcinoma (1.63 vs 1.27 atrophic lesions per slide) ($p < 0.001$), whereas PA displayed an increased frequency in BPH (2.28 vs 0.76 atrophic lesions per slide) ($p < 0.001$).
Conclusions: We confirmed that PA and PIA are common findings in prostates with and without carcinoma, but the question of whether inflammation produces tissue damage and PA or whether some other insult induces the tissue damage and atrophy directly, with inflammation occurring secondarily, is still unresolved.

Editorial Comment

In this study, the authors found that patients with benign prostatic hyperplasia (BPH) had a significantly higher number of prostatic atrophy foci compared with patients with carcinoma. On the other hand, in patients with carcinoma, inflammatory prostatic atrophy was more prevalent compared with prostatic atrophy without inflammation, and slides from these patients contained a significantly higher number of inflammatory prostatic atrophy foci compared with slides from BPH patients. The authors recognize that slides with carcinoma contained peripheral and transitional zones, whereas slides with BPH were mainly composed of transitional zones. Thus, the obtained different prevalence of atrophy in malignant and benign cases could partially reflect the difference in distribution between various anatomic compartments of the prostate.

In a study on autopsies, we found inflammatory atrophy in 66% and atrophy without inflammation in 22% of analyzed cases (1). We did not find any association between the presence of inflammatory atrophy and the likelihood of cancer, and no topographic association between atrophy and prostate cancer foci as well as high-grade prostatic intraepithelial neoplasia (PIN).

The link between atrophy and /or inflammatory atrophy and prostate cancer is theoretically attractive but controversial (1-8). It has been difficult to verify a clinical connection between the lesions. A recent report associating extension of prostatic atrophy to serum PSA elevation added a novel interest to this intriguing lesion (9,10).

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Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience

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Purpose: We updated our experience with a strategy of expectant treatment for men with stage T1c prostate cancer and evaluated predictors of disease intervention.
Materials and Methods: A total of 407 men with a median age of 65.7 years (range 45.8 to 81.5) with stage T1c (99.8%) or T2a (0.2%) prostate cancer suspected of harboring small volume prostate cancer based on needle biopsy findings and prostate specific antigen density have been followed in a prospective, longitudinal surveillance program with a median followup of 2.8 years (range 0.4 to 12.5). A recommendation for treatment was made if disease progression was suggested by unfavorable followup needle biopsy findings (Gleason pattern 4 or 5, greater than 2 biopsy cores with cancer or greater than 50% involvement of any core with cancer). Cox proportional hazards regression was used to evaluate the affect of multiple covariates on the outcome of curative intervention.
Results: Of 407 men 239 (59%) men remained on active surveillance at a median followup of 3.4 years (range 0.43 to 12.5), 103 (25%) underwent curative intervention at a median of 2.2 years after diagnosis (range 0.96 to 7.39) and 65 (16%) were either lost to followup (12), withdrew from the program (45), or died of causes other than prostate cancer (8). Older age at diagnosis ($p = 0.011$) and an earlier date of diagnosis ($p = 0.001$) were significantly associated with curative intervention.
Conclusions: Recognizing that over treatment of prostate cancer is prevalent, especially among elderly patients, a program of careful selection and monitoring of older men who are likely to harbor small volume, low grade disease may be a rational alternative to the active treatment of all.

Editorial Comment

The preliminary results of this study were published in 2002 (1). In the conclusion of this update, the authors, considering that over treatment of prostate cancer is prevalent, especially among elderly patients, a program of careful selection and monitoring of older men who are likely to harbor small volume, low grade disease may be a rational alternative to the active treatment of all. Of 407 men, 239 (59%) men remained on active surveillance at a median follow-up of 3.4 years (range 0.43 to 12.5) and less than half 103 (25%) underwent curative intervention at a median of 2.2 years after diagnosis. The recommendation for treatment was made if

disease progression was suggested by unfavorable follow-up needle biopsy findings based on extension of the tumor and Gleason grading.

The pathology report has a decisive importance for the selection of patients for expectant management. In patients with stage T1c prostate cancer and prostate-specific antigen (PSA) < 0.15 ng/mL, the biopsy should not show Gleason pattern 4 or 5, greater than 2 biopsy cores with cancer or greater than 50% involvement of any core. Patients that fulfill these criteria have a 79.9% probability for harboring insignificant tumors (less than 0.5 cm^3) (2). Insignificant, however, does not mean latent (dorment or indolent) tumor. It means a small volume tumor with favorable pathological findings: low-grade Gleason score, confined to the prostate and no positive surgical margins. Unfortunately, so far there is no marker for the biological behavior of prostate cancer.

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INVESTIGATIVE UROLOGY

Protective effects of cranberries on infection-induced oxidative renal damage in a rabbit model of vesico-ureteric reflux

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Objective: To evaluate the protective effects of cranberry fruit, which have known antioxidant effects, on infection-induced oxidative renal damage in a rabbit model of vesico-ureteric reflux (VUR).
Materials and Methods: In all, 36 New Zealand male rabbits were divided into five groups, with a sham operation in four rabbits serving as the control (group 1). To create unilateral VUR the roof of the left intravesical ureter was incised, and VUR confirmed 2 weeks after surgery. In all, 32 rabbits with VUR were divided into four groups; 2, VUR alone (with sterile urine); 3, a group infected with Escherichia coli; 4, with intravesical E. coli instillation but fed cranberries; and 5, intravesical E. coli instillation plus an intraperitoneal injection with melatonin group. At 3 weeks after surgery the rabbits were killed, the kidneys obtained and examined histopathologically to evaluate inflammation, fibrosis and tubular changes. Oxidative renal damage was evaluated by measuring malondialdehyde in the renal tissue.
Results: Grossly, the refluxing kidney was larger than the contralateral normal kidney, and the refluxing ureter was dilated and tortuous. Microscopy of tissues from the kidneys in group 3 showed apparent periglomerular mononuclear cell infiltration, tubular dilatation and atrophy, and interstitial fibrosis. The kidneys from groups 2, 4 and 5 showed mild mononuclear cell infiltration with no interstitial fibrosis. The level of malondialdehyde in the

kidneys of group 3 was significantly higher than that in group 2, 4 and 5 ($P < 0.05$); the level in groups 4 and 5 did not differ significantly from that in group 2.
Conclusions: This study shows that cranberries have an anti-inflammatory effect through their antioxidant function and might prevent infection-induced oxidative renal damage. Thus, clinically cranberries might be used as a beneficial adjuvant treatment to prevent damage due to pyelonephritis in children with VUR.

Editorial Comment

The cranberry, a fruit with antioxidant properties, has been used for preventing urinary tract infections. Cranberry juice is also known to have activity against oxygen free radicals, which are produced during infection and are important for promoting renal damage. The authors evaluated the protective effects of cranberries on infection-induced oxidative renal damage in rabbits with experimental vesico-ureteral reflux.

It was demonstrated that melatonin and cranberry powder decreased inflammation and the accumulation of malondialdehyde in the kidney, which suggests that cranberry compounds act as an antioxidant as well as an anti-adherent in preventing infection-induced renal damage.

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Proportional analysis of pig kidney arterial segments: differences from the human kidney

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Purpose: To present a systematic study and a proportional analysis of the arterial segments of the pig kidney.
Materials and Methods: Sixty-one three-dimensional endocasts of the arterial segments of pig kidneys were studied. Each segment was injected with a resin of a different color. Cavalieri's principle was used to calculate the volume of each renal segment, and these results were compared with the results from the point-counting planimetry method used on photographs of pig-kidney surfaces.
Results: Two to five renal segments were observed. Division into two segments, a cranial and a caudal, was the most common (42.62%). The renal volume ranged from 101 to 173 cm(3) (mean 130.85 cm(3)). The cranial segment was present in 39 of the 57 casts (68.42%). It presented the greatest median value of proportional area (50.00%) and also the greatest maximum value of proportional area, accounting for as much as 74.04% of the total kidney area. The ventral segment, which was found in 20 of the 57 casts (35.09%), presented the lowest median value of proportional area (13.87%) and showed the most variation in area (coefficient of variation 72.89%). There was no significant statistical difference between the segmental areas as evaluated by Cavalieri's principle and by the point-counting planimetry method.
Conclusions: The distribution and size of the renal-arterial segments in pigs are not similar to those of the human kidneys. Therefore, this information must be taken into account by practitioners of urologic training or ablation using pigs as the animal model, as the structure of the porcine arterial segments cannot be transposed to humans.

Editorial Comment

The pig has been used as the favorite animal model for training and experimental research in urology, including many studies on laparoscopic total and partial nephrectomy, hemostasis techniques and more recently,

ablative technologies, including radio frequency ablation and cryoablation. Therefore, a comprehensive knowledge on the proportional areas of the arterial segments would be important for evaluating the extension of experimental lesions in pigs. The aim of this study was to provide an analysis of the pig kidney segmentation and an analysis of the proportional area of each segment as measured on polyester resin endocasts of the kidney arterial vasculature.

The results demonstrated that the arterial segmental pattern in pigs are not similar to those of the human kidneys, and therefore, the experimental findings concerning renal ablative techniques using the pig must not be completely translated to clinical setting in humans.

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Does benign prostatic hyperplasia originate from the peripheral zone of the prostate? A preliminary study

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Objective: To compare the histological characteristics, cell proliferation, apoptosis and biological features in benign prostatic hyperplasia (BPH) in the peripheral (PZ) and transition zone (TZ) of the prostate.
Patients and Methods: Tissue from BPH in TZ and PZ was obtained from 68 patients undergoing transrectal ultrasonography-guided biopsy and used for both morphometric analysis and immunohistochemical studies. The epithelial, stromal and luminal composition of the tissue was determined using a computer-assisted method for quantitative morphometric analysis. Apoptosis was detected as the apoptotic index (AI) using the TdT dUTP nick-end labelling assay. Cell proliferation was determined as the proliferation index (PI) using Ki-67 immunostaining. The expression of epidermal growth factor receptor (EGFR), transforming growth factor beta1 (TGFbeta1), androgen receptor (AR) and bcl-2 were assessed immunohistochemically.
Results: There was no difference in the stroma/epithelium ratio between PZ and TZ hyperplastic nodules ($P > 0.05$). The mean AI in epithelium was almost identical to the corresponding PI. In stroma, no apoptotic cells were detectable. There was a significantly higher PI and AI in the glandular epithelial cells in PZ hyperplastic than in TZ hyperplastic nodules, but no difference in PI of the stromal cells between PZ and TZ hyperplastic nodules. There was significantly higher expression of TGFbeta1 and lower expression of EGFR and bcl-2 in PZ than TZ hyperplastic nodules ($P < 0.05$). There was no difference in AR expression between PZ and TZ hyperplastic nodules ($P > 0.05$).
Conclusions: These results indicate that some hyperplastic nodules in PZ might originate from the PZ, and the formation of these nodules might be modulated in a different way from that in the TZ.

Editorial Comment

It is well accepted that benign prostatic hyperplasia (BPH) develops from the transition zone (TZ) and from the periurethral glans, while carcinoma originates from the peripheral zone (PZ). Nevertheless, previous studies, including studies by that same group, reported that hypoechoic lesions in the PZ can be found as BPH

histologically. Some authors suggested that the hyperplastic nodules in the PZ might be exophytic BPH in the TZ or the migration of ectopic TZ tissue into the PZ. The authors of the present study speculate that it is more likely that the hyperplastic nodules might originate from the PZ.

In the present study, the epithelial, stromal and luminal composition of the tissue was determined using a computer-assisted quantitative morphometric analysis method in biopsy specimens obtained from patients with PZ or TZ hypoechoic nodules on transrectal ultrasound, and that were histologically confirmed as BPH. The incidence of apoptosis and cell proliferation was analyzed comparatively in these hypoechoic nodules according to the zonal location. The authors also examined the relative expression of proteins involved in the regulation of prostate proliferation and apoptosis: (i) epidermal growth factor receptor (EGFR), which is in the signal transduction pathway that participates in the mediation of cell growth and has been implicated in prostatic epithelia cell proliferation in vitro; (ii) TGFβ1, the most extensively studied negative growth factor. The predominant effect of TGFβ1 on growth in vivo and in vitro is inhibition of cell proliferation; (iii) bcl-2, a potent apoptosis suppressor; and (iv) androgen receptor (AR); steroid binding to AR could stimulate proliferation and differentiation of epithelial cells and inhibit prostate cell apoptosis.

The results of the present study showed that no apoptotic cells were detectable in stroma, which indicated stromal growth due to cell proliferation, in the absence of cell death. The authors discussed that recent studies reported that the cell apoptotic rate in different regions of the ductal system is different, apoptosis being much less in the proximal ends. The proximal and distal regions of the ductal system correspond to the TZ and PZ of the human prostate. The present results showed that the cell apoptotic rate in the epithelium was much higher in PZ than in TZ hyperplastic nodules, which was in concordance with the higher TGF 1 and lower bcl-2 expression in the epithelium of PZ than TZ hyperplastic nodules. In the present study, TGFβ1 staining was intense in the epithelial cells, and bcl-2 expression was consistently restricted to the basal cell layer. This might explain why no apoptotic cells were detectable in the stroma of PZ and TZ hyperplastic nodules.

So, the authors concluded that the present results indicate that some hyperplastic nodules in the PZ might originate from the PZ, and the formation of these nodules might be modulated in a different way to that in the TZ.

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RECONSTRUCTIVE UROLOGY

Terminal urothelium differentiation of engineered neoureter after in vivo maturation in the "omental bioreactor"

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Eur Urol. 2007; 52: 1492-8

Objective: Long ureteric defects may theoretically be repaired with the use of tissue-engineered neoureter. However, attempts to construct such a neoureter in animal models have failed because of major inflammatory response. Avoidance of such inflammation requires a well-differentiated urothelium. We investigated whether omental maturation of a seeded construct in a pig model could achieve terminal differentiation of the urothelium to allow construction of a stricture-free neoureter.

Material and Method: Bladder biopsies were taken to allow urothelial and smooth muscle cell cultures. These cultured cells were used to seed small intestinal submucosa (SIS) matrix. After 2 wk of cell growth, the in vitro SIS-seeded construct was shaped around a silicone drain and wrapped by the omentum to obtain neoureters. These neoureters were left in the omentum without any contact with urine, and then harvested 3 wk later for histologic and immunohistochemical studies.
Results: Before implantation, the in vitro constructs were composed of a mono- or bilayer of undifferentiated urothelium overlying a monolayer of smooth muscle cells. After 3 wk of omental maturation, these constructs were vascularized and comprised a terminally differentiated multilayered urothelium with umbrella cells over connective tissue and smooth muscle cells, with no evidence of fibrosis or inflammation.
Conclusion: We obtained, for the first time, with this model of in vivo maturation in the omentum, a mature neoureter composed of a well-differentiated multilayered urothelium.

Editorial Comment

The anatomy and structure of the ureter is still not completely understood. Because of its embryonic development the blood supply restricts the reconstructive possibilities. Over a decade researchers look into the option to find a better substitute of a ureter than the common used ilium interpronat (1). With the improvement of Mitrofanoff the diameter of the segment was adjusted but still complications are seen although the needed length of ileum was significantly reduced and the resorption reduced (2).

Baumert et al. (3) present impressively a “sandwich model” with differentiated urothelium and a single layer of smooth muscle cells on SIS® different to others (4).

During the recent years researchers presented remarkable results demonstrating the progress tissue engineering (5). One important lesson, even known in the reconstructive surgery prior, was the need of the optimized nutrition of the in vitro created tissue. Atala et al. reported an optimized outcome of the clinical used in vitro pre-seeded scaffold for bladder reconstruction with an omental flap wrapping (6).

On the one hand the presented indication of a neo-ureter using an omentum flap makes the created ureter even more maneuverable compared to the possible “short” mesenterium of the ileum interpronat. On the other hand, Dahms et al. (7) published 10 years ago the ureter replacement by an acellular matrix, which was regenerated by urothelium and smooth muscle cells and functional, but in the following study in the rodent as well in the large animal model the created ureter shrunk after the stent removal although the prior seen urothelium lining was present (data not published). Some might argue that the presented approach will prevent the shrinking but as the author state it needs to be proven. Because others have made similar experiences - probably only a minority is published - it should be considered to report the outcome of an extended follow-up after the stent removal and as a replacement for a ureter.

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A quantitative method for evaluating the degradation of biologic scaffold materials

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Scaffolds derived from naturally occurring extracellular matrix (ECM) have found extensive use in the fields of tissue engineering and regenerative medicine. Many of these scaffolds are designed to degrade rapidly as they are replaced by new host tissue. Other scaffolds are chemically crosslinked to slow the rate of degradation or add strength to the scaffold. Commercially available ECM scaffolds have considerable variability with regards to tissue origin and methods of processing, and little is known about their rate of degradation and the fate of their degradation products. A novel method is described herein to integrally label ECM with a radioactive isotope ((14)C). It was found that a number of tissues are efficiently labeled, including heart, liver, trachea, pancreas, small intestine, and urinary bladder tissue. Of the tissues analyzed, only spleen was not found to contain detectable levels of (14)C. The technique is extremely sensitive, accurate, and safe, but requires access to accelerator mass spectrometry, and is expensive and time consuming. This model represents the first described quantitative method to determine the rate of degradation for an ECM scaffold and to track the fate of the degradation products.

Immune response to biologic scaffold materials

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Biologic scaffold materials composed of mammalian extracellular matrix are commonly used in regenerative medicine and in surgical procedures for the reconstruction of numerous tissue and organs. These biologic materials are typically allogeneic or xenogeneic in origin and are derived from tissues such as small intestine, urinary bladder, dermis, and pericardium. The innate and acquired host immune response to these biologic materials and the effect of the immune response upon downstream remodeling events has been largely unexplored. Variables that affect the host response include manufacturing processes, the rate of scaffold degradation, and the presence of cross species antigens. This manuscript provides an overview of studies that have evaluated the immune response to biologic scaffold materials and variables that affect this response.

Editorial Comment

Biologic scaffold materials in the currently available form are unsatisfactory for reconstruction of the lower urinary tract. They are to some extend an obstacle to vascularization and re-innervation of the reconstructed

segment, but they also lead to a reaction of intact surrounding tissue due to a normal immune and inflammatory response. In the two papers selected here, the authors have tried to develop a model for a quantitative determination of the degradation process and the tracking of extracellular matrix used as scaffold for urinary bladder reconstruction, for example. Furthermore the host response which is or maybe responsible for scaffold degradation has been worked up. These data are very important and very timely because due to the problems with artificial matrix acellular derived from human or animal sources are currently the most commonly used materials in tissue engineering for clinical purposes.

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NEUROUROLOGY & FEMALE UROLOGY

State of the art of where we are at using stem cells for stress urinary incontinence

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Neurourol Urodyn. 2007; 26: 966-71

Aims: This review aims to discuss: 1) the neurophysiology, highlighting the importance of the middle urethra, and treatment of stress urinary incontinence (SUI); 2) current injectable cell sources for minimally-invasive treatment; and 3) the potential of muscle-derived stem cells (MDSCs) for the delivery of neurotrophic factors.
Methods: A PUB-MED search was conducted using combinations of heading terms: urinary incontinence, urethral sphincter, stem cells, muscle, adipose, neurotrophins. In addition, we will update the recent work from our laboratory.
Results: In anatomical and functional studies of human and animal urethra, the middle urethra containing rhabdosphincter, is critical for maintaining continence. Cell-based therapies are most often associated with the use of autologous multipotent stem cells, such as the bone marrow stromal cells. However, harvesting bone marrow stromal stem cells is difficult, painful, and may yield low numbers of stem cells upon processing. In contrast, alternative autologous adult stem cells such as MDSCs and adipose-derived stem cells can be easily obtained in large quantities and with minimal discomfort. Not all cellular therapies are the same, as demonstrated by the differences in safety and efficacy from muscle-sourced MDSCs versus myoblasts versus fibroblasts.
Conclusions: Transplanted stem cells may have the ability to undergo self-renewal and multipotent differentiation, leading to sphincter regeneration. In addition, such cells may release, or be engineered to release, neurotrophins with subsequent paracrine recruitment of endogenous host cells to concomitantly promote a regenerative response of nerve-integrated muscle. The dawn of a new paradigm in the treatment of SUI may be near.

Editorial Comment

The authors describe the current status of research into using stem cell therapy for stress urinary incontinence. This is an excellent read for those who wish to gaze through the looking glass into the future of urology. The last paragraph of the Introduction section alone is worth reading and looking back upon in one or

two decades to see if the predictions are fulfilled. Clearly, patient interest will continue to drive us away from surgery and into minimally invasive therapies to restore functionality to diseased areas of the urologic system. One does not have to wait a decade to already notice this desire (1). The section on neurophysiology is clear and distinct as is the discussion on stem cell therapy and the reasoning of using muscle-derived stem cells.

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Does the tension-free vaginal tape procedure (TVT) affect the voiding function over time? Pressure-flow studies 1 year and 3(1/2) years after TVT

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Neurourol Urodyn. 2007; 26: 995-7

Aim: The aim was to evaluate the voiding function over time after the TVT procedure for stress incontinence.
Materials and Methods: Thirty-eight women with urodynamic stress urinary incontinence were included in the study. For voiding function assessment the patients were asked if voiding had changed postoperatively, and objectively uroflowmetry, residual urine measurement and pressure-flow were performed preoperatively, 1 year and 3(1/2) years postoperatively.
Results: At 1/3(1/2) years follow-up 87%/69% were subjectively cured and 13%/26% improved, respectively. The objective cure rate was 89%/74%. Subjectively 77%/63% of the patients felt an altered voiding function towards more difficult voiding one and 3(1/2) years after surgery, respectively. Objectively all the uroflowmetry variables deteriorated and residual urine volume increased over time although the changes were not statistically significant between the 1 and 3(1/2) years follow-up. Pressure-flow variables were essentially unchanged.
Conclusion: The changes in voiding function after a TVT do not reverse over time. This may imply a potential risk of development of clinically important impaired emptying function.

Editorial Comment

The authors of this paper reviewed both subjective as well as objective data in evaluating voiding habits and bladder function 1 year and 3(1/2) years after placement of a TVT. The researchers found that there was a steady deterioration in uroflow measures as well as an increase in residual urine between the initial and long-term follow-up. Urodynamic criteria were essentially unchanged.

This study is quite interesting in that it explores the question of what happens long-term to voiding function after a no-tension technique anti-incontinence operation. Those patients will often view a successful operation as imperfect based on voiding habits has previously been reported (1) and is well evidenced here by comparing the patient perceptions with the pad and leakage episodes reported in the manuscript table. The noted worsening of uroflow measures and the increase in post void residuals from the 1 year mark to 3(1/2) years mark

raises the concern of what happens to the younger patient who has an anti-incontinence procedure at the time of her pelvic prolapse surgery in her forties: is she doomed to a life of voiding dysfunction and possible pharmacological therapy from age 60 onwards? This should be food for thought for the clinician who adds a sling as a prophylactic step to the prolapse surgery planned.

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PEDIATRIC UROLOGY

Phimotic ring topical corticoid cream (0.1% mometasone furoate) treatment in children

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J Pediatr Surg. 2007; 42: 1749-52

Background/Purpose: Phimosis, owing to the presence of a preputial fibrotic ring, is surgically treated in 1% of children. During the last decade, however, topical steroid treatment has been proposed for phimosis.
Methods: We present a double-blind study comparing 0.1% mometasone furoate topical cream vs moisturizing cream (placebo) for the treatment of phimosis. Children aged from 2 to 13 years (n = 110) presenting with phimosis (Kikiro's classification grade 5) and scheduled for circumcision were included in this trial. The patients were evaluated after 8 weeks of topical treatment with moisturizing cream (n = 54) or steroid cream (n = 56). Nonresponders from both groups received an additional 8 weeks of steroid cream treatment.
Results: In the steroid group, the ring disappeared and glans exposure was obtained in 49 (88%) of 56 patients vs 28 (52%) of 54 patients in the placebo group ($P < .05$). After a second treatment, in the steroid group, 5 of the 7 patients were finally cured vs 22 of the 26 in the placebo group ($P < .05$). Two children with persisting phimosis (Kikiro's retractability grade 5 and appearance grade 3) in the steroid group (4%) vs 4 children in the placebo group (7%) ended up receiving postectomy.
Conclusions: The present investigation adds up and supports the effectiveness of phimosis topical corticoid treatment. Nevertheless, hygiene and preputial traction, when appropriately performed, seem to play an important role in the disappearance of the phimotic ring as well. New studies are necessary to confirm if this is true or not.

Editorial Comment

These authors did a double-blind placebo controlled study on boys 2-13 years-of-age with a mean of 4.6 years, with symptomatic phimosis with degree 5 phimosis according to the classification of Kikiros (1). An eight

week trial was undertaken with either mometasone or a placebo moisturizing cream, being lightly applied to the preputial ring and during the first four weeks, parents were instructed to add “just a light preputial retraction maneuver” and during the second four weeks, the preputial retraction was “increased to a moderate degree”. After eight weeks, boys showing total absence of preputial ring, Kikiros grade 1 or 2 were considered cured and degrees 3, 4, and 5 were considered non-responders and entered a second eight-week-long treatment session, all with mometasone. Four groups were then examined. The placebo group that were cured in the first eight weeks, the placebo group that were non-responders in the first eight weeks and treated with mometasone for another eight weeks. Group 3, the mometasone cured group in the first eight weeks and then Group 4 was mometasone treatment for an additional eight weeks.

Results - Of the initial 130 patients, 110 were available at the end of the study. 88% of the steroid cream patients were considered successes, while 52% of the placebo group patients were considered successes. 19 of the 26 placebo failures responded during the second treatment period to the corticosteroid and 5 of 7 of the mometasone failures were cured with a second eight weeks of treatment.

Comments - The mometasone is a moderate-strength topical corticosteroid and this study shows that it may be a good alternative to the betamethasone that has been reported in the literature and with less side effects. None of these patients had any side effects. It is interesting to note that 52% of the placebo group had success with gentle to more moderate retraction of the foreskin without the benefit of any steroids. It is likely that this is an important adjunct to the treatment regimen, regardless of the medication chosen. I believe that one of the important aspects of this study is that the patients who were chosen for the study were severely phimotic and are often thought not to be good candidates for medical treatment, and yet the success rates were excellent. It is refreshing to see physician scientists doing high quality double-blind placebo studies and they should be applauded for their efforts.

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Do holding exercises or antimuscarinics increase maximum voided volume in monosymptomatic nocturnal enuresis? A randomized controlled trial in children

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Purpose: We assessed prospectively the efficacy of holding exercises and/or antimuscarinics (oxybutynin chloride and placebo) for increasing maximum voided volume in prepubertal children with monosymptomatic nocturnal enuresis.
Materials and Methods: We randomly allocated 149 children to 5 groups, namely holding exercises with placebo (group A), holding exercises with oxybutynin (group B), placebo alone (group C), oxybutynin alone (group D)

and alarm treatment (controls, group E). Maximum voided volume was the greatest voided volume from a 48-hour bladder diary, and holding exercise volume was the greatest volume produced with postponement of voiding after a fluid load, once daily for 4 days. Study medication, holding exercise procedures and alarm treatment were administered for 12 weeks.
Results: Holding exercises combined with placebo or oxybutynin significantly increased holding exercise volume and maximum voided volume, by 25% ($p < 0.001$) and 21% ($p < 0.01$), respectively, in group A, and by 43% ($p < 0.001$) and 41% ($p < 0.001$), respectively, in group B. Medication without holding exercises (groups C and D) did not increase holding exercise volume or maximum voided volume, and in these groups oxybutynin was not significantly superior to placebo. A borderline increase in holding exercise volume did not affect maximum voided volume in group E. Monosymptomatic nocturnal enuresis response was significantly lower with all 4 holding exercise volume modulating treatments (7%) compared to alarm therapy (73%).
Conclusions: In the treatment of children with monosymptomatic nocturnal enuresis maximum voided volume can be increased significantly through holding exercises, but not with oxybutynin chloride alone. Compared to controls, increasing maximum voided volume had a minimal effect on monosymptomatic nocturnal enuresis.

Editorial Comment

The authors performed a randomized prospective controlled study selecting patients who had at least 14 wet nights out of 28 nights. Patients were excluded if they had previously been treated with an alarm, desmopressin or anticholinergics within three months of the start of the study. If the patients were younger than age 5 or greater than Tanner stage I. They were randomized into a 12 week trial with group A having holding exercises with a placebo, group B holding exercises with oxybutinin, group C placebo alone, group D oxybutinin alone, and group E 12 weeks of alarm therapy. End points of the study were a maximum voiding volume compared to a cystographic bladder capacity and compared to holding exercise volume. The holding exercise was done and baseline maximum bladder volume was obtained from a 48 hour frequency-volume chart including voided volumes while asleep. Holding exercises were done with a 20m L/kg body weight oral loading during 30 minutes, with voiding being postponed as long as possible and then voided volume noted. During the 12 week study, patients had normal fluid intakes and voiding regimens and were to note wet and dry nights in a diary for 12 weeks. Holding exercises were to be done 4 days per week during the 12 week treatment span. Oxybutinin was to be administered twice daily at 4 pm and immediately before bedtime, with the placebo medication being administered on the same schedule. 149 children were randomly allocated to treatment groups, ages ranging from 5.9-12.7 years, with 108 boys and 41 girls.

Results - The holding exercise volume at the end of the study increased significantly in the two groups that did the holding exercises and had either placebo or oxybutinin. In the two groups without the holding exercise studies during the 12 week, there was no statistical change. Maximum voided volumes increased by 21% in the holding exercise with placebo group and 41% in the holding exercise with oxybutinin group. In the two groups without holding exercises the changes were insignificant. In the 5th group with wetting alarms alone, a full response was found in 73% and the holding exercise volume was significantly increased, but there was no change in the maximum voided volume. Multi-factorial logistic regressions showed that the holding exercises had no significant influence on the rate of response of monosymptomatic nocturnal enuresis with success being only about 7%, with or without holding exercises.

Comments - Many years in the past, holding exercises for nocturnal enuretic patients were encouraged in hopes that the bladder capacity would increase and the patients would be able to go all night without wetting. The treatment was abandoned because of lack of success and this randomized controlled trial suggests that this was good judgment by former urologists. It is no surprise that oxybutinin was not effective in reducing nighttime wetting, as other studies have shown, and for monosymptomatic nocturnal enuresis that it is not effective. It also suggests that antimuscarinic effects are greatest on abnormal bladders and that in patients with normal daytime

bladder function oxybutinin does not make a significant difference. There may be a slight advantage of encouraging holding exercises in conjunction with other nocturnal enuresis treatments but this study does not lend a strong support to this. I believe this study may be a significant foundation for further studies but it shows in a controlled randomized fashion that treatments that have been given up in the past are not effective in the combinations that were used.

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