International Braz J Urol
Vol. 35 (2): 228-247, March - April, 2009

UROLOGICAL SURVEY

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STONE DISEASE

Combined retrograde flexible ureteroscopic lithotripsy with holmium YAG laser for renal calculi associated with ipsilateral ureteral stones

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J Endourol. 2009; 23: 253-7

Purpose: The purpose of this study was to evaluate the effectiveness of combined ureteroscopic holmium YAG lithotripsy for renal calculi associated with ipsilateral ureteral stones.
Materials and Methods: Between August 2002 and March 2007, retrograde flexible ureteroscopic stone treatment was attempted in 351 cases. Indication for treatment was concurrent symptomatic ureteral stones in 63 patients (group I). Additional operative time and perioperative complication rates were compared to a group of 39 patients submitted to ureteroscopic treatment for ureteral calculi exclusively (group II).
Results: Mean ureteral stone size was 8.0 ± 2.6 mm and 8.1 ± 3.4 mm for groups I and II, respectively. Mean operative time for group I was 67.9 ± 29.5 minutes and for group 2 was 49.3 ± 13.2 minutes ($p < 0.001$). Flexible ureteroscopic therapy for renal calculi increased 18 minutes in the mean operative time. The overall complication rate was 3.1% and 2.5% for groups I and II, respectively ($p = 0.87$). Mean renal stone size was 10.7 ± 6.4 mm, overall stone free rate in group I was 81%. However, considering only patients with renal stones smaller than 15 mm, the stone free rate was 88%. Successful treatment occurred in 81% of patients presenting lower pole stones, but only 76% of patients with multiple renal stones became stone free. As expected, stone free rate showed a significant negative correlation with renal stone size ($p = 0.03$; $r = -0.36$). Logistic regression model indicated an independent association of renal stones smaller than 15 mm and stone free rate (OR = 13.5; $p = 0.01$).
Conclusion: Combined ureteroscopic treatment for ureteral and ipsilateral renal calculi is a safe and attractive option for patients presenting for symptomatic ureteral stone and ipsilateral renal calculi smaller than 15 mm.

Editorial Comment

The authors are to be commended for the high stone-free rate obtained with the stringent criteria based on CT scan imaging. One might consider that it could be difficult to standardize instrumentation and technique across three continents and across a 5-year time period - this may impact the interpretation of results especially if a larger bulk of the flexible ureteroscopies were conducted in the later portion of the study period when the authors had more experience and better instrumentation. It would be helpful for the authors to define their criteria for using a ureteral access sheath - it is our practice to use it routinely during intrarenal stone extraction to improve stone frees rates and minimizes the risk of ureteral injury.

The authors importantly define the upper limit of stone size to tackle ureteroscopically - 15 mm. Beyond this size one must inform patients of the risk of requiring staged ureteroscopies to render stone-free. Another important consideration is that all patients were stented after the surgery. As 60% of these patients had distal ureteral calculi, they could have been offered the alternative of no stent if intrarenal calculi were not treated at the same setting. Often patients who have had significant stent discomfort in the past will elect to leave the intrarenal stone untreated so as to avoid the ureteral stent.

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Percutaneous versus transurethral cystolithotripsy

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Purpose: To compare transurethral cystolithotripsy (TUCL) and percutaneous cystolithotripsy (PCCL) modalities performed during simultaneous transurethral resection of the prostate (TURP) in patients with prostate hyperplasia and large bladder stones.
Patients and Methods: Sixty-three patients with prostate volume > 40 cc and aggregate stone size > 2.5 cm were enrolled in the study between August 2003 and February 2007. TUCL (n = 38) or PCCL (n = 25) procedures were performed during simultaneous TURP. In the TUCL group, the stones were removed after fragmentation through a 23F cystolithotripter with pneumatic lithotripsy. This was followed by TURP, performed with a 26F continuous-flow resectoscope. In the PCCL group, the stones were removed through a suprapubic 30F Amplatz sheath after fragmentation. TURP was then performed with the suprapubic sheath providing continuous drainage.
Results: Mean age and prostate volumes of the groups were similar. Mean aggregate stone sizes were significantly larger in the PCCL group. The operative time for stone removal was significantly less in the PCCL group while time needed for TURP was statistically similar in the two groups. In the TUCL group, three patients had residual stones necessitating repeated TUCL and urethral stricture developed in three patients.
Conclusion: The smaller caliber of the working channel during TUCL, compared with PCCL, necessitates disintegration of the stones into smaller fragments. This elongates the duration of the intervention and results in increased urethral and bladder trauma. Combined TURP and PCCL is a safer, more effective, and much faster alternative to combined TURP and TUCL in patients with large bladder stones and prostate hyperplasia.

Editorial Comment

The study is limited in its retrospective nature, but provides important support for the empiric approach utilized by the authors. It is clear that transurethral approach carries a higher risk of urethral stricture - this may be related to the duration of instrumentation during stone extraction or it may be related to the size and duration of post-operative catheterization. The authors emphasize the importance of stone extraction prior to TURP as bleeding from the prostatic fossa may obscure the identification of residual stone. The authors also emphasize the importance of leaving the Amplatz sheath in place during the TURP as premature removal of this may lead to extraperitoneal extravasation of irrigation fluid. Another advantage of a percutaneous approach not mentioned by the investigators would be the use of an ultrasonic lithotripter through a rigid nephroscope as a more efficient means of stone clearance. Lastly, it is important to note that these recommendations are specific for men - though less common, larger stones in women can be effectively addressed cystoscopically with a rigid nephroscope and ultrasonic lithotripter.

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ENDOUROLOGY & LAPAROSCOPY

Comparison of different extraction sites used during laparoscopic radical nephrectomy

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J Urol. 2009; 181: 1565-70

Purpose: Laparoscopic radical nephrectomy is commonly performed for renal tumors that are not amenable to nephron sparing treatment. A number of techniques for intact specimen extraction are used. The development of incisional hernias from the extraction site is a known but infrequent delayed complication. We analyzed different extraction sites and risk factors for such hernias.
Materials and Methods: We retrospectively analyzed a cohort of patients undergoing laparoscopic radical nephrectomy with intact specimen extraction through 3 sites. Patients and operation specific parameters were included with particular attention to factors predisposing patients to incisional hernia, including chronic obstructive pulmonary disease, diabetes mellitus, chronic steroid use and a high body mass index.
Results: A total of 181 nephrectomies were performed in 175 patients and 175 kidneys (96.7%) had malignancy. Mean tumor size was 4.9 cm. Mean followup was 28.8 months. Extraction was done from a lower quadrant site in 55 patients (31.4%), from the umbilical site in 58 (33.2%) and from a paramedian site in 62 (35.4%). Patients with paramedian and lower quadrant extraction sites were older ($p = 0.016$), and had a higher body mass index ($p = 0.001$) and greater specimen weight ($p = 0.003$). In 4 patients an incisional hernia developed. An incisional hernia was significantly associated with the paramedian extraction site ($p = 0.015$).
Conclusions: Incisional hernias may occur as a delayed complication of laparoscopic radical nephrectomy. This complication most commonly develops at the extraction site. In patients with a high body mass index using a paramedian extraction site is a significant risk factor for incisional hernia formation.

Editorial Comment

Laparoscopic radical nephrectomy has evolved and questions such as intact organ extraction versus morcellation were answered by different investigators recommending intact extraction for different reasons. Unfortunately, larger extraction sites may cause incisional hernia. The authors have demonstrated that when patients are obese the optimal site for extraction is the paramedian site since it may decrease the chance for incisional hernia after extraction.

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Laparoscopic management of endopelvic etiologies of pudendal pain in 134 consecutive patients

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Purpose: The feasibility of the laparoscopic transperitoneal approach to the pelvic somatic nerves was determined for the diagnosis and treatment of anogenital pain caused by pudendal and/or sacral nerve root lesions.

Materials and Methods: The records of 134 consecutive patients who underwent laparoscopy for refractory anogenital pain were retrospectively reviewed. All neurosurgical procedures, such as neurolysis/decompression of the pudendal nerve and the sacral nerve roots or neuroelectrode implantation to the sacral plexus for postoperative neuromodulation, were done via the laparoscopic transperitoneal approach to the pelvic nerves. Results: A total of 18 patients had Alcock's canal syndrome and decompression was successful in 15. Due to failed decompression 3 patients underwent secondary sacral laparoscopic neuroprosthesis implantation with a decrease of at least 50% on the pain visual analog scale. Sacral plexus lesions or radiculopathies, most commonly postoperative lesions and retroperitoneal endometriosis, were found in 109 patients who underwent laparoscopic neurolysis of the sacral plexus. The final outcome depended on the etiology. Of patients with postoperative nerve damage 62% had a decrease in the mean +/- SD preoperative visual analog scale score of from 8.9 +/- 2.9 (range 7 to 10) to 2.4 +/- 2.3 points (range 0 to 4) at the time of article submission at a mean followup of 17 months (range 3 to 39). Because of failed decompression, 8 patients underwent secondary sacral laparoscopic neuroprosthesis implantation and a decrease in the pain visual analog scale score was achieved in 5. Of patients with an endometriosis lesion of the sacral plexus 78% had a decrease in the mean preoperative visual analog scale score of 8.7 +/- 1.9 (range 8 to 10) to 1.1 +/- 0.7 points (range 0 to 2) at the time of article submission at a mean followup of 21 months (range 2 to 42). All 6 patients with vascular entrapment of pelvic nerves achieved complete relief. The last 7 patients underwent primary sacral laparoscopic neuroprosthesis implantation with at least a 50% decrease in the pain visual analog scale score in 4.
Conclusions: Our findings emphasize that in patients with seemingly inexplicable anogenital pain, especially after failed treatment for Alcock's canal syndrome, laparoscopic exploration of the pelvic nerves must be done for further diagnosis and therapy before prematurely labeling the patients as refractory to treatment.

Editorial Comment

Laparoscopic minimally invasive approach has been applied in Urology for benign, oncological diseases, reconstructive surgery; but this novel approach to manage endopelvic etiologies of pudendal pain is a pioneer approach to a complex urogynecological problem.

The author describe a protocol that when followed seemed to successfully deal with the complex pelvic pain disease.

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IMAGING

Renal cell carcinoma: dynamic contrast-enhanced MR imaging for differentiation of tumor subtypes--correlation with pathologic findings

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Purpose: To retrospectively evaluate whether the enhancement patterns of pathologically proved clear cell, papillary, and chromophobe renal cell carcinomas (RCCs) measured on clinical dynamic contrast agent-enhanced magnetic resonance (MR) images permit accurate diagnosis of RCC subtype.

Materials and Methods: This study was Institutional Review Board approved and HIPAA compliant; informed consent was waived. One hundred twelve patients (76 men, 36 women; age range, 25-88 years; mean age, 58.1 years) underwent MR imaging of 113 renal masses (mean diameter, 5.4 cm) with pathologic diagnoses of clear cell (n = 75), papillary (n = 28), or chromophobe (n = 10) RCC. A 1.5-T clinical MR protocol was used before and after (corticomedullary and nephrographic phases) intravenous administration of contrast agent. Region-of-interest measurements within tumor and uninvolved renal cortex were used to calculate percentage signal intensity change and tumor-to-cortex enhancement index. Subtype groups were compared by using linear mixed-effects models. Receiver operating characteristic (ROC) curve analysis was performed for the comparison of clear cell and papillary RCCs.
Results: On both the corticomedullary and nephrographic phase images, clear cell RCCs showed greater signal intensity change (205.6% and 247.1%, respectively) than did papillary RCCs (32.1% and 96.6%, respectively) ($P < .001$). Chromophobe RCCs showed intermediate change (109.9% and 192.5%, respectively). The tumor-to-cortex enhancement indexes at corticomedullary and nephrographic phases were largest for clear cell RCCs (1.4 and 1.2, respectively), smallest for papillary RCCs (0.2 and 0.4, respectively), and intermediate for chromophobe RCCs (0.6 and 0.8, respectively). Signal intensity changes on corticomedullary phase images were the most effective parameter for distinguishing clear cell and papillary RCC (area under ROC curve, 0.99); a threshold value of 84% permitted distinction with 93% sensitivity and 96% specificity.
Conclusion: Clear cell, papillary, and chromophobe RCCs demonstrate different patterns of enhancement on two-time point clinical dynamic contrast-enhanced MR images, allowing their differentiation with high sensitivity and specificity.

Editorial Comment

Each subtype of RCC is associated with a different prognosis and tumor behavior. If possible, preoperative characterization of RCC subtypes would influence the degree of preoperative evaluation and the determination of the appropriate extent of surgery (1-3). For example a patient with a subtype that tends to not metastasize or recur, such as the chromophobe, may not need to undergo a complex metastasis survey and unnecessarily wide resection may be avoided, thereby, decreasing postoperative morbidity and mortality (3). For this reason, adequate preoperative characterization of the RCC subtype has been attempted utilizing contrast enhanced CT studies (2,3). On multiphase contrast enhanced the clear cell (70.3%) and papillary (69.2%) subtypes tended to show heterogeneous or predominantly peripheral enhancement, whereas the chromophobe subtype (75%) usually showed homogeneous enhancement.

The authors of this excellent original study found in a study of 112 patients that clear cell, papillary, and chromophobe renal cell carcinoma demonstrated different enhancement patterns when assessed with 3D T1-weighted spoiled gradient-echo sequences before and after (corticomedullary and nephrographic phases) contrast material administration. It is interesting to note that differently from contrast enhanced CT studies, the best results of this dynamic contrast enhanced MR technique was accomplished using analysis of signal intensity in the corticomedullary phase.

As the author mentioned in the text, if their results are confirmed with a larger prospective study, this method would provide equivalent accuracy to that reported for percutaneous biopsy. Probably both techniques will be used together in the preoperative evaluation of renal mass since percutaneous biopsy is the only technique that provides Fuhrman grade immunohistochemical stain.

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Correlation of MR imaging and MR spectroscopic imaging findings with Ki-67, phospho-Akt, and androgen receptor expression in prostate cancer

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Purpose: To retrospectively assess whether magnetic resonance (MR) imaging and MR spectroscopic imaging and selected molecular markers correlate with each other and with clinically insignificant and significant prostate cancer (PCa), as defined at surgical pathologic analysis.
Materials and Methods: The institutional review board approved this HIPAA-compliant study and waived informed consent. Eighty-nine men (mean age, 63 years; range, 46-79 years) with biopsy-proved PCa underwent combined endorectal MR imaging and MR spectroscopic imaging before radical prostatectomy. Suspicion of clinically insignificant PCa was retrospectively and separately recorded for MR imaging and combined MR imaging and MR spectroscopic imaging by using a scale of 0-3. Clinically insignificant PCa was pathologically defined as organ-confined cancer of 0.5 cm(3) or less without poorly differentiated elements. Prostatectomy specimens underwent immunohistochemical analysis for three molecular markers: Ki-67, phospho-Akt (pAkt), and androgen receptor (AR). To examine differences in marker levels for clinically insignificant and significant cancer, a Wilcoxon rank sum test was used. To examine correlations between marker levels and MR imaging or combined MR imaging and MR spectroscopic imaging scores, the Spearman correlation was used.
Results: Twenty-one (24%) patients had clinically insignificant and 68 (76%) had clinically significant PCa at surgical pathologic review. All markers were significantly correlated with MR imaging and combined MR imaging and MR spectroscopic imaging findings (all correlation coefficients > 0.5). In differentiating clinically insignificant from clinically significant PCa, areas under the receiver operating characteristic curves for Ki-67, AR, pAkt, MR imaging, and combined MR imaging and MR spectroscopic imaging were 0.75, 0.78, 0.80, 0.85, and 0.91, respectively.
Conclusion: The use of pretreatment MR imaging or combined MR imaging and MR spectroscopic imaging and molecular marker analyses of biopsy samples could facilitate better treatment selection. Supplemental material: http://radiology.rsnajnls.org/cgi/content/full/250/3/803/DC1.

Editorial Comment

Insignificant prostate cancer is defined as cancer found on biopsy (T1c), with PSAD < 0.15 ng/mL, Gleason score 6 or lower, or no more than 2 cores with cancer or greater than 50% involvement of any core. As we know insignificant prostate cancer is better defined as low-volume, low-grade tumor since around 10 % of this lesions may present with extra-prostatic extension on radical prostatectomy (1). In this very interesting

manuscript, the authors reported a frequency of 24% of patients with clinically insignificant prostate cancer at radical prostatectomy. Although with some controversy (2), the same group of authors has been shown recently that a nomogram that incorporates MRI and MRSI was more accurate than clinical nomograms (clinical stage, PSA level, biopsy data) in order to predict clinically insignificant prostate cancer (3).

In a study of 89 men with biopsy-proven prostate cancer, the authors demonstrated that combined MRI and MRSI findings and three specific biologic markers that are important in proliferation, apoptosis, and cell survival (Ki-67, phospho-Akt, and androgen receptor AR values) correlated with each other and with clinically insignificant and significant prostate cancer defined at pathologic examination of prostatectomy specimens.

We agree with the authors that if a prospective study confirms their results it may represent the beginning of a new era. An era of integration of pretreatment conventional and functional MR imaging of the prostate with histopathological and specific biologic markers analyses of biopsy specimens. In the near future, this integration probably will allow better treatment selection and thus better outcome for patients with prostate cancer.

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PATHOLOGY

TMPRSS2-ERG gene fusions in "minimal" prostatic adenocarcinoma

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Background: Minimal or "insignificant" prostatic adenocarcinoma (MinPCa) is defined as tumors with insufficient virulence to threaten survival. Given recent suggestion of TMPRSS2-ERG gene fusion association with aggressive PCa phenotype, we aimed to evaluate incidence of TMPRSS2-ERG fusion in MinPCa in comparison with grade matched "non-minimal" size PCa.
Design: All 33 prostatectomies classified as containing MinPCa (2002-2003) were retrieved. Diagnois of MinPCa (Gleason Score 6 PCa with total tumor volume < 0.5 CC, single section) was confirmed by a urologic pathologist. Tissue microarray (TMA) was constructed from the 33 cases where each tumor and paired benign tissue was represented by up to triplicate, 1mm, spots. TMA sections of 59 additional archival PCa were used as controls (26 pT2 non-minimal in size, 31 pT3a and 2 pT3b). FISH analysis was performed using break-apart probes for 5' and 3' regions of ERG. Each spot was scored for presence of TMPRSS2-ERG fusion through

deletion or translocation as well as for polyploidy (≥ 3 copies) at the ERG locus. At least 50 cells were scored per tumor.
Results: MinPCa: TMPRSS2-ERG fusion was identified in 46% (16/35) of MinPCa. In 87% (14/16) of positive tumors, fusion was due to deletion. The remaining 13% (2/16) of fusions were based on the demonstration of a split in the two juxtaposed probe signals. Ch21 polyploidy ± fusion and duplication of ERG deletion were not observed in any MinPCa case. Control group: TMPRSS2-ERG fusion was identified in 59% (35/59) of tumors. In 77% (27/35) of positive tumors, fusion was due to deletion. Ch21 polyploidy with ± fusion was present in 13/59 (22%) while polyploidy with duplicate ERG deletion was found in 6/59 (10%) of control tumors. On statistical analysis, there was no significant difference in TMPRSS2-ERG fusion incidence between the MinPCa and control groups ($p = 0.2$). Statistically significant higher rates of ch 21 polyploidy ± fusion was present in control group ($p = 0.0002$). A trend approaching statistical significance for higher incidence of ch21 polyploidy with duplicate deletion was also present in the control group ($p = 0.052$).
Conclusions: TMPRSS-ERG fusion rate of 46% is present in MinPCa. The latter is not significantly different from rate of fusion in control group of non-minimal pT2 and pT3 PCa. A higher rate of Ch21 polyploidy is detected in the control group compared to MinPCa. Our finding of a comparable rate of TMPRSS2-ERG fusion in MinPCa and non-minimal PCa argues against its value as a marker of aggressive PCa phenotype.

Editorial Comment

With higher number of prostate cancer detected in stage T1c due to screening, a higher number of small adenocarcinomas have been detected on needle biopsies. Many of these small adenocarcinomas may have criteria for minimal or "insignificant" cancer: tumor in no more than 2 cores, absence of Gleason grade 4 or 5, tumor not occupying more than 50% of the core, and favorable PSA density (1). It is important to note that these criteria relate to tumor volume and not biological behavior. It would be of utmost importance to know whether a minimal or "insignificant cancer" would behave as a latent (dormant or indolent) cancer or evolve to a clinical cancer.

A notable discovery related to the molecular aspect of prostate carcinoma was the identification by Tomlins et al. (2) of a recurrent chromosomal arrangement encountered in the majority of prostate carcinomas that they studied. Possible rearrangements are of two general types. In the first, the promoter and/or enhancer elements of one gene are aberrantly juxtaposed to a proto-oncogene, thus causing altered expression of an oncogenic protein. In the second, the rearrangement fuses two genes, resulting in the production of a fusion protein that may have a new or altered activity. Tomlins et al. (2) identified recurrent gene fusions of the region of TMPRSS2 to ERG or ETV1 in prostate cancer tissues. TMPRSS2 (21q22.2) is a prostate-specific gene that is present in normal and neoplastic prostate tissue and is strongly induced by androgen in androgen-sensitive prostate cell lines. ERG (21q22.3) and ETV1 (7p21.2) are genes that encode ETS family transcription factors. TMPRSS2:ERG fusion is more frequent and occurs due to a deletion of a region on chromosome 21. TMPRSS2: ETS fusion prostate cancers comprise 40-50% of the PSA screened hospital based prostate carcinoma examined to date, making it the most common genetic rearrangement in human cancer. Emerging data suggested that TMPRSS2:ERG prostate cancer is associated with higher tumor stage and prostate specific death. Therefore, this fusion may be a marker for aggressive prostate cancer.

The study by Albadine et al. found that TMPRSS-ERG fusion rate of 46% is present in minimal or "insignificant" prostate cancer. This finding is not significantly different from rate of fusion in control group of non-minimal confined cancer (pT2) or with extraprostatic extension cancer (pT3). The comparable rate of TMPRSS2-ERG fusion in minimal prostate cancer and non-minimal prostate cancer argues against its value as a marker of aggressive prostate cancer phenotype.

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Are nephrogenic adenomas renal stem/progenitor cell-derived lesions? An immunohistochemical study

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Background: Nephrogenic adenoma (NA) is a benign tumor-like lesion of the urinary tract that histologically resembles the developing distal nephron. Recent evidence suggests that NA is truly a "nephrogenic" lesion, arising from downstream seeding of shed renal tubular cells with implantation and proliferation in areas of damaged urothelium. This proposed pathogenesis and the rarity of the lesion suggest the possibility that NAs arise from kidney stem/progenitor cells that retain the ability to proliferate and develop into renal tubule-like structures when implanted at a distant site. Renal stem/progenitor cells have recently been identified in adult kidney tubules with several markers, including CD133 and PAX2. In our study, we investigate the expression of stem cell surface markers CD133 and CD44 as well as renal-specific transcription factors PAX2 and PAX8 by immunohistochemistry.
Design: Twenty-nine cases of NA from 2000 to 2004 were retrieved from the tissue archives, 18 of which were from urinary bladder and 19 from prostatic urethra. CD133, CD44, PAX2, and PAX8 immunohistochemical staining was performed using the avidin-biotin peroxidase method following antigen retrieval. Complete circumferential membranous staining was considered positive for CD133 and CD44. Distinct nuclear staining was required for PAX2 and PAX8 positivity.
Results: All NAs were positive for renal-specific transcription factors PAX2 and PAX8, consistent with previous studies. CD133 staining was detected focally in eight of 29 (28%) cases. The CD133 positive cells were seen in papillary surfaces, small tubules, and occasionally in the stroma. CD44 staining was detected in seven of ten cases, including five CD133 positive lesions. In the CD44 positive/CD133 positive cases, CD44 was present in the corresponding CD133 areas. CD44 expression, however, was also seen in other areas and in two CD133 negative cases. No staining for these for markers was identified in the epithelium or stroma in prostatic glands, prostatic urethra, or urinary bladder.
Conclusions: Stem cell markers CD44 (70%) and CD133 (28%) were identified in a subpopulation of cells in nephrogenic adenomas, all of which were also positive for renal-specific transcription factors PAX2 and PAX8. Therefore, we suggest that nephrogenic adenomas may arise from transplantation and proliferation of primitive renal cells into an extrarenal stem cell niche. The expression of additional stem cell markers in this regard is currently under investigation.

Editorial Comment

Nephrogenic adenomas usually arise in the setting of prior urothelial injury, such as past surgery, calculi, or trauma. An intriguing and elegant study was able to demonstrate a derivation from renal tubular cells occurring in renal transplant patients.

Mazal et al. (1) reported that the sex-chromosome pattern in examples of bladder nephrogenic metaplastic lesions in the recipient reflected the pattern of the donor patient, and was different from the chromosome pattern of adjacent urothelium in the recipient patient. An additional support for nephrogenic adenomas arising from shed renal tubular cells is positivity for PAX2. Tong et al. (2) reported that 100% of a series of 39 examples of nephrogenic adenomas stained with PAX2, a renal transcription factor which is specific for tubular epithelium. Urothelium and prostate epithelium do not stain with this antibody. These studies support that nephrogenic adenoma is not of urothelial origin and most probably originates from implanted cells shed from renal tubules.

Devaraj et al. considered the possibility that nephrogenic adenomas arise from kidney stem/progenitor cells that retain the ability to proliferate and develop into renal tubule-like structures when implanted at a distant site. They investigated the expression of stem cell surface markers CD133 and CD44 as well as renal-specific transcription factors PAX2 and PAX8 by immunohistochemistry. Renal stem/progenitor cells have recently been identified in adult kidney tubules with several markers, including CD133 and PAX2. Stem cell markers CD44 (70%) and CD133 (28%) were identified in a subpopulation of cells in nephrogenic adenomas, all of which were also positive for renal-specific transcription factors PAX2 and PAX8. These findings suggest that nephrogenic adenomas may arise from transplantation and proliferation of primitive renal cells into an extrarenal stem cell niche.

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BASIC AND TRANSLATIONAL UROLOGY

Oestrogen receptor expression and neuronal nitric oxide synthase in the clitoris and preputial gland structures of mice

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BJU Int. 2008; 102: 1719-23

Objective: To study the presence of oestrogen receptors (ER) and neuronal nitric oxide synthase (nNOS) in the mouse clitoris.
Materials and Methods: A series of sections of the pelvic area, including the preputial glands and clitoris, of 10 mice were assessed by immunocytochemical studies specific for ER-alpha and -beta, and nNOS; selected sections were also stained with Masson's trichrome.
Results: ER alpha was detected in the epithelium of the gland of the clitoris, and in the glandular tissue, preputial and apocrine gland. ER alpha was detected in the nuclei of stromal cells around the cavernous tissue and near the epithelium of the clitoris. Cytoplasm ER alpha was detected in a few cells in an area ventral to the clitoral

gland. There was also nuclear staining in the connective tissue cells surrounding the clitoris. Very light ER beta immunostaining was detected in the clitoris and in the tissue related to it. There were some cells with nuclear staining in the vessels of the cavernous tissue of the clitoris. nNOS immunostaining was detected in the clitoris, the preputial gland and the connective tissue.
Conclusion: ER alpha and beta isoforms, and nNOS, are present in the clitoris and preputial glands of female mice in different cellular locations and with differing levels of receptivity. Functional studies would further elucidate the role of receptor functions and their relationship to the neuronal expression of NO.

Editorial Comment

The authors are to be commended for this interesting study, which provided additional knowledge on the presence of estrogen receptors alpha (ERα) and beta (β), as well as on neuronal nitric oxide synthase (nNOS) and their relationships, in the mouse clitoris.

It was found a diffuse and deep immunostaining for ERα in the epithelium of the gland of the clitoris, and in the glandular tissue and prepuce. Also, ERα was detected in the nuclei of stromal cells around the cavernous tissue and near the epithelium of the clitoris. On the other hand, the authors found very few ERβ immunostaining in the clitoris and in the tissue related to it. However, there were some cells with nuclear staining in the vessels of the cavernous tissue of the clitoris.
In a similar pattern of ERα, although not too strong, nNOS immunostaining was detected in the clitoris, the preputial gland and connective tissue.

Concerning the epithelium of the vaginal wall, it was negative for the immunostaining for ERα and β. Membrane-based nNOS was found in the vaginal wall, and not along the upper vaginal wall, but only in one part, closest to the vaginal opening.

The authors proposed that the nuclear immunostaining for ERα in the stroma of the clitoris suggests a higher receptivity to this hormone. All receptors identified in the clitoris tended to be more intensely expressed in stromal than epithelial cells, suggesting that there is a stromal - epithelial interaction induced by the different sex steroids. ERβ immunostaining was only detected in a few cells in the vascular lumen of the cavernous tissue of the clitoris.

By contrast, with ERα, the study showed that there was no staining in the glandular tissue, epithelium or stroma of the clitoris. The authors speculate that these results suggest that ERβ is not essential for the normal functions that take place in the clitoris of the mouse.

nNOS was immunodetected with a similar pattern of distribution to that of ERα. Therefore, the authors proposed that NO might play a role in controlling blood flow and capillary permeability, the mechanisms of sexual lubrication due to cGMP action, induced by NO. The homeostasis of this system needs cGMP breakdown. It is possible that the physiological response to sexual arousal in the female follows the same biochemical pathway as in the male.

The new knowledge presented in this work, concerning the relationship of estrogen receptivity in the genital sensory field and clitoral vasculogenic processes, represent and important advance in the understanding of the presence and anatomical location of nNOS and ER isoforms.

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Natural orifice translumenal endoscopic surgery (NOTES) renal cryoablation in a porcine model

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BJU Int. 2008; 102: 1715-8

Objective: To present our laboratory experience with natural orifice translumenal endoscopic surgery (NOTES) renal cryoablation.
Materials and Methods: In two female farm pigs, we performed four procedures of NOTES renal cryoablation. In each pig, NOTES was performed through a transgastric approach and a transvaginal approach for each kidney, respectively. The pig was placed in the flank position and pneumoperitoneum obtained using a transabdominal Veress needle. In the first pig, we started with the left kidney with a transgastric approach: a dual-channel video gastroscope (Olympus, Tokyo, Japan) was used, the stomach wall was punctured using a needle-knife, a guidewire was passed into the abdominal cavity and the access dilated using a controlled radial expansion balloon. The bowel was mobilized medially and the Gerota's fascia overlying the upper pole was dissected. Under direct endoscopic vision, a cryoablation probe was introduced percutaneously into the anterior upper pole of the kidney. The pig was then flipped to the right flank position and a transvaginal approach was used: the gastroscope was introduced through the posterior fornix of the vagina. For the second pig, we performed initially a transgastric right-side cryoablation then a transvaginal left-side cryoablation as described for the first pig.
Results: All four procedures were performed successfully, with no intraoperative complications. No additional laparoscopic ports or open conversions were necessary. The vision of the kidney and the ice-ball was adequate for all cases. The mean operative duration was 83 min. Stomach closure was tested watertight, and there were no abdominal or pelvic injuries found at autopsy.
Conclusions: NOTES can provide adequate minimal surgical dissection for safe and effective percutaneous renal cryoablation under direct videoscopic monitoring at kidney locations otherwise not accessible percutaneously. Both transgastric and transvaginal approaches can be used effectively for renal cryoablation providing a minimally invasive scar-less surgery.

Editorial Comment

This is an interesting bench to bedside research, demonstrating the usefulness of the pig model for research in endourology and videoendoscopy. It has been shown that the pig is the best animal model for translational research in urology, due to its renal similarities with humans, concerning intra-renal anatomy of collecting system, arteries and veins (1-3). Also, abdominal and pelvic cavities in pigs are similar to humans, both in volume and in organ position. So, it is possible to transpose the laboratory research to clinical setting very fast.

The present paper clearly demonstrated the feasibility of NOTES for videoendoscopic monitoring of percutaneous renal cryoablation both by transgastric and transvaginal approaches.

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UROLOGICAL ONCOLOGY

Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate

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Background: In addition to other treatments, patients with prostate cancer (pCA) and bone metastasis receive bisphosphonates. Since 2003, a previously unknown side-effect of bisphosphonates-bisphosphonate-associated osteonecrosis of the jaws (BP-ONJ)-has been described, and frequency has since increased. An exact incidence is still unknown.
Objectives: The aim of this study was to assess the incidence and additional factors in the development of BP-ONJ.
Design, Setting, and Participants: From July 2006 to October 2007, patients with advanced pCA and osseous metastasis receiving bisphosphonate therapy in the Department of Urology or Haematology and Oncology at the Johannes-Gutenberg-University Mainz, Germany, received a dental examination. In all, 43 patients were included.
Measurements: Patients were checked for exposed bone, osteonecrosis, mucosal defects, inflammation, and oral hygiene. Further points were the applied bisphosphonate, co-medication, the duration of application, and possible trigger factors for BP-ONJ.
Results and Limitations: Eight of 43 patients developed BP-ONJ (18.6%). All patients had received zoledronate at least 14 times. Two patients had received bondronate, and one patient had received pamidronate before switching to zoledronate. All patients had had a previous tooth extraction or a denture pressure sore, and all patients had received additional chemotherapy and corticosteroids.
Conclusions: The reason for this relatively high incidence compared to other studies might be the prospective study design and thorough dental examination. In studies with such small numbers as have been published to date, nondetection or nonreported cases of BP-ONJ have an influence on the outcome. The incidence of BP-ONJ in patients with pCA might be an underestimated problem.

Editorial Comment

Bisphosphonates are widely given in patients with a high risk for, or manifest, bone metastases. In most patients with advanced prostate cancer, this drug is considered standard therapy. Recently, the risk for developing dental complications became evident but neither the true incidence nor risk factors are known. This paper helps to clarify the situation.

Nearly 19% of patients from this uncontrolled series suffered from some sort of osteonecrosis. Most were highly pretreated with biphosphonates and steroid and/or docetaxel therapy. Urologists should be aware

of this possible complication and should work closely together with experienced dentists. Special attention should be given to multimodally treated patients.

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Long-term survival after gemcitabine and cisplatin in patients with locally advanced transitional cell carcinoma of the bladder: focus on supplementary treatment strategies

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Objective: The objective was to evaluate response and survival, as well as efficacy of subsequent supplementary treatment and follow-up strategy in patients with locally advanced transitional cell carcinoma of the bladder following combination chemotherapy with gemcitabine and cisplatin (GC).
Methods: A total of 84 patients with locally advanced (T4b, Nx, M0 or Tx, N2-3, M0) received GC. After chemotherapy, the strategy was close surveillance in patients with complete response, and supplementary radical cystectomy or radiotherapy whenever possible in patients with partial response.
Results: A total of 25 patients (29.8%) with complete response to chemotherapy were followed by close surveillance. This group achieved a median overall survival of 47.6 mo. Another 25 patients had partial response to chemotherapy. Of these patients, 16 had supplementary treatment, with 10 achieving "no evidence of disease" (NED). Thus, a total of 35 patients achieved NED with a median overall survival of 48.7 mo versus 10.2 mo in patients not achieving NED (hazard ratio=0.10; 95%CI, 0.05-0.20; $p<0.0001$). The rate of NED was higher in the group of patients who had a cystectomy compared with the group who received radiotherapy as supplementary treatment.
Conclusions: In patients with locally advanced bladder cancer, NED following chemotherapy alone or chemotherapy plus supplementary cystectomy or radiotherapy is essential to achieve long-term survival. Patients with a partial response should be offered radical cystectomy whenever possible, which seems to be superior to radiotherapy. Close surveillance may be an alternative to immediate cystectomy in patients with complete response following chemotherapy.

Editorial Comment

Patients with locally advanced bladder cancer cannot be cured by surgery or radiotherapy alone. Systemic cytotoxic chemotherapy is the only option here. In contrast to patients with visceral metastases, patients without distant metastases and locoregional disease form a group with rather favorable prognosis. A group of 84 patients with this disease was analyzed for long-term survival after Gemcitabine-Cisplatinum (GC) – based chemotherapy.

Median overall survival of the group was 16.3 months. There was a significant difference between patients who had no evidence of disease (NED) after GC or after GC and supplementary treatment (e.g. cystectomy) in comparison to those who had a partial response and underwent supplementary treatment. Median survival in the first and second groups was nearly 48 months whereas the third group had less than 12 months median survival. Patients who underwent cystectomy as treatment after GC significantly fared better than patients who received

radiotherapy. In conclusion, relative long-term survival is possible in this cohort of patients and multimodal treatment should aim at eradicating all disease possible.

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NEUROUROLOGY & FEMALE UROLOGY

Nonsurgical transurethral collagen denaturation for stress urinary incontinence in women: 12-month results from a prospective long-term study

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J Minim Invasive Gynecol. 2009; 16: 56-62

Study Objective: To assess efficacy of nonsurgical transurethral collagen denaturation (Renessa) in women with stress urinary incontinence (SUI) caused by bladder outlet hypermobility.
Design: Continuing, prospective, 36-month, open-label, single-arm clinical trial. Twelve-month results from intent-to-treat (ITT) analysis are reported. Canadian Task Force classification II-2.
Setting: Thirteen physician offices or ambulatory treatment centers.
Patients: Women with SUI secondary to bladder outlet hypermobility for 12 months or longer who failed earlier conservative treatment and had not received earlier surgical or bulking agent therapy.
Interventions: Women were treated as outpatients and received an oral antibiotic and local periurethral anesthesia before undergoing treatment with transurethral radiofrequency collagen denaturation.
Measurements and Main results: Voiding diaries and in-office stress pad weight tests yield objective assessments. Subjective measures include the Incontinence Quality of Life (I-QOL), Urogenital Distress Inventory (UDI-6), and Patient Global Impression of Improvement (PGI-I) instruments. In total, 136 women received treatment (ITT population). Patients experienced significant reductions versus baseline in median number of leaks caused by activity/day and activity/week ($p < .0026$ for both), with 50% of patients reporting 50% or more reduction. Pad weight tests revealed that 69% of women had 50% or more reduction in leakage (median reduction 15.2 g; $p < .0001$); 45% were dry (29% no leaks; 16% < 1-g leakage). Significant improvements occurred in median scores on the I-QOL (+9.5 [range -66.0 to 91.0]; $p < .0001$) and mean scores on the UDI-6 (-14.1 +/- 24.7; $p < .0001$). Furthermore, 71.2% showed I-QOL score improvement, including 50.3% with 10-point or greater improvement, and 49.6% reported on the PGI-I that they were “a little,” “much,” or “very much” better. Conclusion: At 12 months, treatment of SUI with nonsurgical transurethral collagen denaturation resulted in significant improvements in activity-related leaks and quality of life.

Editorial Comment

Authors report on the therapy of female stress urinary incontinence using transurethral radiofrequency (RF) collagen denaturation. This report entails the 12-month results from an ongoing 36-month intent to treat study. The authors identified the following: no significant adverse events; that the procedure was very well tolerated; and using this minimally invasive technique, results similar to transurethral bulking agents were obtained.

This review revisits a new technology which has been previously surveyed in this journal (1). In that study, the authors noted the safety of the therapy as well as its clinical efficacy when reported in comparison to a sham treatment. Though the study did report a significant number of patients who were lost to follow-up, withdrew consent, or opted for surgery, this is not unexpected in view of the large number of study centers (13 centers) which were incorporated into the study. Of note is that the procedure appears to be very safe, very fast and highly competitive with bulking therapy in the patient with urethral hypermobility. This refined application of the radiofrequency energy to alter collagen is distinctly different from the ablative therapy used for neoplastic conditions or benign gynecological diagnoses. Though the therapy does not appear to preclude further surgery, it should be avoided in patients who already have injectable therapy secondary to potentially variable application of the energy to the periurethral implant. That this technology may be applied in the office with the use of a local periurethral anesthetic and has a very short post-procedure convalescence period renders it a therapeutic option that warrants a close review by treating physicians.

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Urethral diverticula in 90 female patients: a study with emphasis on neoplastic alterations

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Purpose: Urethral diverticula are uncommon and occur predominantly in women. We examined a large series of female urethral diverticula to determine associated neoplastic alterations and subsequent clinical outcomes.
Materials and Methods: All pathological evaluations of female urethral diverticulectomies performed at our institution between 1981 and 2007 were retrospectively reviewed and the clinicopathological features were correlated.
Results: During this period 90 women underwent urethral diverticulectomy at our institution. Patient age was 24 to 78 years (mean 45). The most common clinical finding was urinary incontinence (29 of 78 women or 37%). Diverticular size was 0.3 to 5.0 cm (mean 1.7). Neoplastic alterations identified in 5 patients (6%) were glandular in nature, including 1 clear cell and 4 invasive adenocarcinomas. Superficial changes associated with invasive carcinoma included villous adenoma in 1 case, intestinal metaplasia in 2 and high grade dysplasia in 3. An additional 3 patients had extensive intestinal metaplasia. Of the 90 patients the remaining 82 demonstrated benign findings, including nephrogenic adenoma in 10 (11%). All 5 patients with invasive carcinoma underwent anterior pelvic exenteration with urinary diversion. In 2 patients with invasive adenocarcinoma metastatic disease subsequently developed, of which they died.
Conclusions: Although most cases of surgically resected diverticula demonstrate benign features, approximately 10% show atypical glandular findings, including invasive adenocarcinoma. Due to the risk of malignancy in a

subset of patients careful clinical examination and followup are warranted in all patients to exclude neoplastic disease.

Editorial Comment

The authors report on an impressive numerical series of 90 patients who underwent urethral diverticulectomy. The most common associated clinical finding with the urethral diverticulum was urinary incontinence. Pathologic evaluation of the resected tissue revealed 10% with atypical glandular findings; consequently, the authors urged the readership to have careful follow-up in those patients secondary to the association with invasive adenocarcinoma.

This large series on urethral diverticula warrants reading and review by those actively involved in female urology. Though the most common clinical finding associated with urethral diverticulum was urinary incontinence, 4 out of the 5 patients who had a carcinoma of the involved urethral diverticulum presented with urinary retention. In addition, the authors noted that a review of the position of nephrogenic adenomas throughout the urothelial tract identified a higher prevalence in the urethral diverticulum. This would be something to keep in mind on evaluating a urethral diverticulum that is associated with a submucosal mass. The high mortality rate quoted in this series for patients with invasive adenocarcinoma involving a urethral diverticulum highlights the importance of close follow-up in those patients that have atypical glandular findings on pathologic analysis of the resected diverticulum.

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PEDIATRIC UROLOGY

Updated experience with the Monti catheterizable channel

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Urology. 2008; 72: 782-5

Objectives: The Monti catheterizable channel is used as an integral part of continent bladder reconstruction in children. We have updated our ongoing experience at Riley Children's Hospital with 199 patients.
Methods: We identified 199 patients for retrospective review, including all patients for whom a Monti ileovesicostomy was created from January 1997 to August 2004. We assessed the complications, surgical procedures, and stomal continence.
Results: At mean follow-up of 28 months, we found that 194 of 199 patients (97.5%) continued to use their Monti catheterizable channel for bladder drainage. Early surgical complications occurred in 7 patients (3.5%), usually in those who had undergone simultaneous bladder augmentation (5 of 7). Revision was required in 16 patients (8%) for stomal stenosis (n = 11), prolapse (n = 2), or superficial stomal problems (n = 3). Of the 199 patients, 17 (8.5%) required 19 bladder or channel revisions. The primary indications were related to elongation and angulation of the channel in 7 and deficient tunnel length in 8. Minor difficulty with catheterization was noted in 16 patients (8%), and endoscopy with minor procedures was required in 4 patients (2%). Leakage from the channel was uncommon, occurring in only 4 of 115 patients (3.5%).

Conclusions: With increasing demand for simultaneous appendicocecostomy for stool continence at bladder reconstruction, we continue to use the Monti ileovesicostomy for bladder drainage. Our experience with nearly 200 patients has demonstrated the durability and success of this technique.

Editorial Comment

During a seven-year period, 199 patients underwent a Monti catheterizable stoma procedure, 90 male and 109 females. Eighty-eight percent of the patients had a neuropathic bladder and over 97% of the patients underwent an additional simultaneous procedure. Seventy percent of them had bladder augmentations at the same time. Seven patients (3.5%) had early surgical complications. Sixteen (8.0%) had stomal revisions and 19 patients (9.5%) underwent channel revisions. Sixteen (8.0%) of the patients had difficulty catheterizing and 4 (3.5%) had incontinence after the channel was made.

The authors conclude that this is a favorable outcome to a catheterizable stoma. This is their procedure of choice when the appendix is used for appendicocecostomy bowel irrigation regimen. They preferred a spiral Monti technique whenever a longer channel is required, rather than a double Monti technique.

The authors have a mean follow up of 28 months and their results are favorable compared to their own and another study in the literature. Even though the complication rate seems high, these patients benefit greatly from a continent catheterizable stoma. Most of the complications and revisions are on the stoma and channel itself and the channel can be made functional and the patients and caregivers will be highly satisfied.

It should be noted that one or two other complications were in non-compliant patients and particularly when a continent catheterizable stoma is considered, careful attention to patient compliance before the surgery is performed will minimize these unfortunate complications afterwards. If the catheterizable stoma is not used for a brief period of time, often it closes and cannot be recovered.

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Corporeal grafting for severe hypospadias: a single institution experience with 3 techniques

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J Urol. 2008; 180 (4 Suppl): 1749-52; discussion 1752

Purpose: Correction of severe chordee by corporeal body grafting has been successfully performed using various grafts and biomaterials. We report a single institution comparison of our experience using small intestinal submucosa, tunica vaginalis and dermal grafts at stage 1 hypospadias repair.
Materials and Methods: A retrospective chart review was performed of the records of all patients who underwent staged hypospadias repair from 1985 to 2006 with corporeal body grafting at stage 1 with small intestinal submucosa, tunica vaginalis or dermal grafts. Age at grafting, time between stages, residual chordee at stage 2 repair and the need for additional plication or chordee correction at stage 2 were recorded.
Results: A total of 71 patients were identified with a median age of 10 months at stage 1 repair and a median of 7.6 months between stages 1 and 2 repair. Dermal grafts, tunica vaginalis and small intestinal submucosa grafts were used in 29, 21 and 20 patients, respectively. One patient received a combination of small intestinal submucosa and tunica vaginalis. None of the patients receiving tunica vaginalis graft required any further correction of chordee. One patient with a dermal graft and 1 receiving small intestinal submucosa required Nesbit

plication at stage 2 repair for minor ventral chordee. One patients receiving small intestinal submucosa showed severe fibrosis at the graft site, requiring excision and repeat grafting with tunica vaginalis. This patient has been previously described. The 2 patients with small intestinal submucosa related complications had 4-ply grafts. We have seen no complications associated with 1-ply small intestinal submucosa. At limited followup we have not seen residual chordee after stage 2 repair.
Conclusions: In a large group of children requiring corporeal grafting for severe chordee we observed successful chordee correction with 1-ply small intestinal submucosa, tunica vaginalis or dermal grafts.

Editorial Comment

A 20-year experience of corporeal grafting in a staged hypospadias procedure is reported. Grafts were either small intestine submucosa, tunica vaginalis or dermal grafts. All of the patients have completed a second stage hypospadias repair. The urethral plate was divided when routine maneuvers to correct chordee still left 45° of ventral curvature. Tunica vaginalis was used as a graft in all the cases rather than a flap and each of the grafts were approximately 25% larger than the corporeal defect that was created to correct the chordee. Graft placement and success were verified after suturing the graft in place by an artificial erection.

Initially for the SIS graft, 4-ply SIS was used in 12 patients and subsequently 1-ply has been used. Of the 71 patients in this study, the median age was 10 months. 29 dermal grafts, 21 tunica vaginalis grafts and 20 SIS grafts were used. One of the dermal graft patients and one of the 4-ply SIS patients required a subsequent repair. The authors concluded that each of the grafting materials were successful. They note that they have not used 4-ply SIS for several years and that long-term and post-pubertal outcome is not available.

This manuscript shows that over two decades, several types of grafting materials have been used and each showing good success. In skilled hands, there is not a reason to choose one graft material over another. The second stage of the repair was not made more difficult by any of the graft procedures and it is heartening to know that the surgeon can make a personal and patient-appropriate choice and expect good outcomes.

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