2008 Research Abstracts

A compilation of investigations made by Cleveland Clinic Glickman Urological and Kidney Institute physicians, research scientists and distinguished colleagues.

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Section 1

Prostate Disease
Surgeon Experience Independently Predicts Biochemical Recurrence following Radical Retropubic Prostatectomy for Organ Confined Disease

Kefer JC, Reuther AM, Klein EA

Introduction: Biochemical recurrence (BR) following open radical retropubic prostatectomy (RP) offers an excellent target outcome, as it relates to cancer cure without influence from other postoperative factors. We hypothesized that surgeon experience predicts BR following RP in patients with and without organ confined disease at a single institution.

Methods: Patients with clinically localized prostate cancer undergoing open RP between 1987-2005 at our institution were analyzed. Exclusion criteria include missing data, or neoadjuvant/adjuvant therapy, leaving 2,123 patients for analysis. Minimum PSA followup was 12 months (median 61 months). Surgeon experience was defined as total number of RP performed prior to each case. Low and high experience was defined as \(<250\) and \(>250\) cases, respectively. BR was defined as rising PSA >0.2 ng/ml. Surgeon experience was correlated with BR using uni- and multivariate Cox proportional hazard models. Analysis was repeated in 1,310 patients with organ confined disease.

Results: High experience predicted decreased BR rate (HR 2.04, p<0.0001), and was unaffected by case-mix or stage migration. Patients with organ-confined disease showed similar results (low vs high experience HR 1.52, p=0.0238), and also demonstrate a significant survival benefit from high experience surgeons on 10-year KM analysis (89% vs. 81%, p=0.0227).

Conclusions: Surgical experience predicts BR following RP, and describes a learning curve for RP with differences in oncologic outcomes and cure rates. These findings suggest that high experience surgeons could use different surgical techniques during RP. A critical area of research involves defining specific techniques associated with the highest oncologic cure rates.
Prostate Disease

Limited Pelvic Lymph Node Dissection Does Not Improve Biochemical Relapse Free Survival at 10 Years after Radical Prostatectomy in Patients with Low Risk Prostate Cancer

Christopher J. Weight, Alwyn M. Reuther, Paul W. Gunn, Craig R. Zippe, Nivedita B. Dhar, Eric A. Klein

Objectives: To compare long term differences in actuarial biochemical relapse-free survival rates from a contemporary series of patients who underwent radical prostatectomy with and without pelvic lymph node dissection (PLND).

Methods: The records of 806 consecutive radical prostatectomy cases performed between January 1995 and June 1999 were reviewed. The entire subset of patients (N = 336) with low risk disease defined by PSA \( \leq 10 \) ng/mL, biopsy Gleason score \( \leq 6 \), and clinical Stage T1 or T2a who did not receive adjuvant or neoadjuvant therapy were divided into two groups according to whether PLND was performed (PLND group, n=140) or omitted (no PLND group, n=196). A Cox proportional hazards model was used to analyze the effect of demographic, pretreatment, surgical and pathologic factors on the likelihood of biochemical failure. Biochemical relapse-free survival for each group was estimated by Kaplan-Meier analysis. The median PSA follow-up time for the entire group was 89.0 months, with a similar follow-up for both cohorts (PLND 94.5 months and no-PLND 88.0 months, Mann-Whitney p=0.14).

Results: The long-term biochemical relapse-free survival rate for the entire cohort was 86.1% at 10 years. The 10-year actuarial biochemical relapse-free rates for the PLND versus no PLND groups were 83.8% and 87.9% respectively (log-rank p=0.33). On univariate analysis, PLND was not an independent predictor of outcome (Wald p=0.33).

Conclusions: The omission of limited PLND in patients with favorable tumor characteristics does not adversely affect biochemical relapse-free survival at 10 years. Such patients can be spared the morbidity and cost of PLND without affecting the chance for cure.

Androgen Deprivation Falls as Orchiectomy Rates Rise after Changes in Reimbursement in the U.S. Medicare Population

Christopher J. Weight MD, Eric A. Klein MD, J. Stephen Jones MD

Background: Expenditures related to use of medical androgen deprivation led in part to the Medicare Modernization Act (MMA) in 2003. This mandated a decline in reimbursement to 80-85% of the average wholesale price starting in 2004, followed by a more significant reduction in 2005 to 106% of the average sales price, which effectively reduced the reimbursement by approximately 50% of 2003 values. We hypothesize that these changes in reimbursement may affect the way practitioners administer these treatments.

Methods: We examined the publicly available dataset, Medicare Part B Extract Summary System (BESS), from years 2001 to 2005 for trends in number of allowed services and dollar amount of allowed charges and payments. The reimbursable Medicare codes of J9217 (leuprolide acetate, Lupron®, Eligard®), J9202 (goserelin acetate, Zoladex®), J9219 (leuprolide acetate implant, Viafurd®) J3315 (triptorelin pamoate, Trelstar™) were examined for medical castration. The code of 54520, simple orchiectomy, was used for surgical castration.

Results: Use of medical castration increased from 2001-2003, while over this same time-period, surgical castration decreased. Total allowed charges for medical castration in 2005 dropped 65% from the 2003 peak.

Conclusion: The use of medical androgen ablation decreased significantly with the decrease in reimbursement. The administration of either surgical or medical castration in the US Medicare population appears closely tied to reimbursement in trend, but not always in magnitude.
A Novel Transrectal Ultrasound Robot: Development and Evaluation of its Reproducibility

Kazumi Kamoi, Georges-Pascal Haber, Clement Vidal, Philippe Koenig, Andre Berger, John Kefer, Antoine Leroy, Pierre Mozer, Monish Aron, Robert Stein, Jihad Kaouk, Mihir Desai, Inderbir S. Gill

Introduction: Prostate biopsies and local treatment such as brachytherapy are generally performed under imaging control by transrectal ultrasound (TRUS). However, current ultrasound technique requires manual control for the needle insertion guidance and is not reproducible. A robot would enable various trajectory directions towards any location in the prostate with high reproducibility. We developed a novel TRUS robot and evaluated its feasibility and reproducibility in a fresh human cadaver.

Methods: Robotic manipulation of TRUS probe was achieved by modifying a novel endoscope manipulator (TIMC-IMAGE Laboratory Institute Albert Bonniot, La Tronche, France). A commercially available TRUS probe (Type 8818 transducer, B-K Medical, Herlev, Denmark) was manipulated by the robot. A fresh human cadaver was used to evaluate: (1) safety profile of TRUS movement, (2) visualization of the prostate with 2-D image, (3) construction of 3-D image using automated acquisition, and (4) accuracy of targeting. Targeting accuracy was tested using prostatic calcification as a fiducial point. After adjusting the fiducial point (A0) as one point on the trajectory line, the probe was randomly and remotely commanded to move to another point (X), and then the robot was asked to “go back” to the fiducial point (A1). The distance between points A0 and A1 was measured three-dimensionally (\(\partial x\), \(\partial y\), \(\partial z\)) and registration error was calculated as \(\sqrt{(\partial x^2 + \partial y^2 + \partial z^2)}\). Accuracy of return to original target was repeated 10 times and average registration error determined.

Results: The set-up of the TRUS robot within the rectum was straightforward. The robot successfully moved within its full range of motion in all degrees of freedom. The entire prostate was well visualized in 2-D images. Automated 3-D image acquisition was successful. The fiducial point registration error ranged from 0.23 mm to 0.90 mm (mean 0.58 mm). There were no unexpected robotic movements or any rectal injury.

Conclusion: We have developed and tested a novel robotic device to perform safe TRUS examination of the prostate. The robotic device successfully achieved 2-D and 3-D images of the prostate. Most importantly, it could target a specific location within the prostate with high reproducibility (0.58 mm accuracy). This has significant clinical implications for diagnosing and focal therapy of prostate cancer.
Transrectal Ultrasound Measurement of Membranous Urethral Length as a Predictor of Urinary Continence after Laparoscopic Radical Prostatectomy

Kazumi Kamoi, Osamu Ukimura, Tsuneharu Miki, George-Pascal Haber, Philippe Koenig, Andre Berger, and Inderbir S. Gill

Introduction: We previously described the technical aspects of real-time transrectal ultrasound (TRUS) monitoring and guidance during laparoscopic radical prostatectomy (LRP). Herein, we determined whether TRUS-measured membranous urethral length (MUL) on TRUS is predictive of urinary continence after LRP.

Methods: MUL was measured on preoperative and immediate postoperative TRUS in 133 consecutive patients who underwent LRP by a single surgeon. Patients filled out self-administered International Continence Society questionnaires at 1, 3, 6, 12, and 18 months after surgery. Postoperative continence data were available in 100 cases. Continence was defined as the use of 0 to 1 pad per day.

Results: Mean pre and postoperative length of membranous urethra (MUL) measured by TRUS were 14.7 ± 1.7 and 13.0 ± 1.7 mm, respectively. On multivariate analysis, postoperative MUL was the only independent variable predictive of continence status at 12 months after surgery. Eighty-three patients with MUL > 11 mm had 100% continence rate at 12 months. In contrast, of 17 patients with a postoperative MUL ≤ 11 mm, the continence rate was 35%.

Conclusion: TRUS-measured membranous urethral length is predictive of continence after LRP. Membranous urethral length > 11 mm after surgery is associated with excellent continence at 12 months.

<table>
<thead>
<tr>
<th>Time after surgery</th>
<th>Preoperative MUL &gt; 13 mm (N = 73)</th>
<th>Preoperative MUL ≤ 13 mm (N = 27)</th>
<th>Postoperative MUL &gt; 11 mm (N = 83)</th>
<th>Postoperative MUL ≤ 11 mm (N = 17)</th>
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<td>1 month</td>
<td>17 (23)</td>
<td>1 (4)</td>
<td>18 (22)</td>
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<tr>
<td>3 months</td>
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<td>73 (100)</td>
<td>16 (60)</td>
<td>83 (100)</td>
<td>6 (35)</td>
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<tr>
<td>18 months</td>
<td>73 (100)</td>
<td>17 (64)</td>
<td>83 (100)</td>
<td>7 (41)</td>
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Risk Factors to Predict Positive Surgical Margins during Trus-Guided Laparoscopic Radical Prostatectomy (LRP)

Kazumi Kamoi, Osamu Ukimura, Tsuneharu Miki, George-Pascal Haber, Philippe Koenig, Andre Berger, and Inderbir S. Gill

Introduction: Real-time transrectal ultrasound (TRUS) guidance has significantly decreased our incidence of positive surgical margins (PSM) during LRP, yet considerable number of patients still have PSM. Herein, we sought to identify risk factors to predict PSM in patients undergoing TRUS-guided LRP.

Methods: TRUS measurements were documented during LRP in 215 consecutive patients with prostate cancer. TRUS findings and various clinical parameters were compared with pathological outcomes.

Results: Twenty nine PSM (13%) occurred in 215 LRP specimens. Commonest locations of positive surgical margins were apical and postero-lateral aspects of the prostate (45% and 38%, respectively). Intra-operative TRUS demonstrated hypoechoic lesion (HEL) in 120 (56%) of the patients in those 60 (28%) were suspicious for ECE. Multivariate logistic regression analysis demonstrated that the appearance of HEL was the only significant variable to predict PSM. In patients with HEL, the chance of PSM was 23%, while only 1% without HEL (p < 0.0001). In 61 patients with suspicion of extracapsular extension by TRUS, 14 (23%) unilateral and 16 (27%) bilateral dissection of neurovascular bundles were performed to avoid PSM and successfully achieved negative surgical margin in 43 (70%) of these high risk patients.

Conclusion: Negative ultrasound findings at LRP enable us to ensure the safe postero-lateral and apical dissection of the prostate. Since most of PSM arose in patients with abnormal findings on TRUS, site-specific wider excision at the high risk area of ECE should be considered to secure negative margins.
Prostate Mono Brachytherapy (I-125) is an Effective Treatment Option for Small Volume Gleason 7 Prostate Cancer

Craig Zippe, Geetu Pahlajani, Marwan Ali, Arul Mahadevan, Jay Ciezki

Introduction and Objective: Prostate mono brachytherapy (PMB) is an accepted treatment option for Gleason 6 prostate cancer. In individual cases, patients with Gleason 7 cancer with concerns of erectile dysfunction often elect to undergo PMB. Retrospectively, we analyzed our database with the hypothesis that PMB can be an accepted treatment option for Gleason 7 cancer.

Methods: We identified 59 patients from the Cleveland Clinic database (1997-2003), that underwent PMB for a Gleason 7 cancer and had a minimum follow up of 4 years. We compared it to 63 patients with Gleason 6 cancer from the author’s personal series in the same time period. We subdivided the Gleason 7 cancers into extensive and minimal disease. Extensive disease was defined as 2 or more positive biopsy areas (apex,mid,base), or >50% of any one core, or Gleason 4+3 cancers. In our Gleason 7 group, we found 36/59 (61%) had extensive disease and 1/3 of these 36 patients had Gleason 4+3. In the Gleason 6 group, 19% of the patients had extensive disease. In the Gleason 7 group bilateral disease was present in 11%; in the Gleason 6 group, 23%. The mean age of the patients in Gleason 7 group was 69 years; in Gleason 6, 64.8.

Results: The mean baseline PSA of both the groups were comparable; Gleason 6 - 6.63; Gleason 7 - 6.65. In Gleason 6 group, the mean PSA at 4 years was 0.38±1.4 with a 3.1% biochemical failure rate (ASTRO). In Gleason 7 group with minimal disease, the mean PSA at 4 years was 0.15±0.93 with a 0% biochemical failure rate. In Gleason 7 group with extensive disease, the mean PSA at 4 years was 0.98±0.78 with a 13.8% biochemical failure rate. There were 5 failures in the Gleason 7 group and 2 failures in Gleason 6 - all 7 occurring between 2 and 3 years. All the 5 failures in Gleason 7 cancer had extensive disease; 3 had positive core biopsy > 75-90% level and 2 had Gleason 4+3.

Conclusions: Our intermediate data indicates that prostate mono brachytherapy is an acceptable treatment option for Gleason 7 cancers, in particular those with minimal disease. Our biochemical cure rate for minimal Gleason 7 cancer at 4 years is 100% and for extensive Gleason 7 is 86%. This data should impact positively on our selection criteria for prostate mono brachytherapy, such that minimal Gleason 7 cancers can be routinely recommended.
Long Term Urinary Function following Prostate Mono Brachytherapy

Geetu Pahlajani, Marwan Ali, Craig Zippe

Introduction and Objective: With earlier detection, the incidence of prostate cancer continues to rise in the younger population. Due to the potential side effects from radical prostatectomy, via an open or robotic approach, more and more patients are choosing prostate brachytherapy as their treatment of choice for localized prostate cancer. We felt it was important to look at the potential long-term urinary side effects of patients undergoing prostate brachytherapy.

Methods: We analyzed data of 43 patients from an individual surgeons database (2000-2003) that had a minimum 4 years follow up (mean 4.4 yrs). We recorded the baseline AUA symptom and bother scores, the need for intermittent self catheterization (ISC), and gland size measurements. We assessed the incidence and duration of patient use of alpha blockers and the percentage of patients who discontinued medical therapy at 4 years. The mean age of the patients was 68±5.8 years; the mean PSA was 7.3; 60% had Gleason 6 cancers; 32.5% had Gleason 7.

Results: The mean baseline AUA symptom score was 8.1±7.4. With a mean follow-up interval of 4 years, the symptom score was 9.3±6.1 (p > 0.1). The baseline bother score was 1.9±1.1, and at 4 years, the mean bother score was identical at 1.9±0.9. A bother score of 2.0 reflects a patient who is mostly satisfied. In the perioperative period, 69.7% took alpha blockers for an average of 9 months; 30.2% did not take any medications. In analyzing the group who were on alpha blockers, 32.5% took it for <6 months, 37.2% took it for >6 months. At 4 years, only 27.9% (12/43) were on medical therapy. Following seed placement, 21% of the patients required ISC. When analyzing the ISC and the non-ISC group for the following variables (i.e. prostate volume, prostate length, radiation units), no differences could be demonstrated.

Conclusions: The long-term results show no urinary dysfunction following prostate mono brachytherapy. Patients had similar AUA symptom and bother scores at 4 years compared to their baseline. Long-term, 72% of the patients were able to discontinue all prostate medications. In the perioperative period, 21% of patients required ISC. We failed to demonstrate any variables to predict which patients required intermittent self catheterization.

The Relationship between Prostate Size and Biochemical Progression-Free Survival in Patients with Prostate Cancer

Robert Abouassaly, MD, Alwyn M. Reuther, MPH, Chandana Reddy, MS, Jay Ciezky, MD, Patrick A. Kupelian, MD, Eric A. Klein, MD

Introduction and Objective: Previous studies have suggested that prostate size may be an important prognostic variable in patients with prostate cancer. Patients with smaller glands have been shown to harbor higher grade, more advanced disease, and a greater risk of progression after radical prostatectomy (RP) or interstitial brachytherapy (PI). Some have suggested that this is merely a reflection of PSA density. Our aim is to determine if prostate size is an independent predictor of biochemical recurrence using the large prostate cancer database at our institution.

Methods: Patients with prostate cancer treated between January 1987 and August 2007 with either RP (2,969 patients) or PI (795) were included in the study. Those who received neoadjuvant or adjuvant treatment were excluded from the analysis. We evaluated the association between prostate size, T-stage, biopsy Gleason score, pretreatment PSA, PSA density, age, and biochemical progression-free survival (bPFS) using Cox proportional hazards regression.

Results: In the univariate Cox regression, when used as a continuous variable, prostate volume was not significantly associated with bPFS for RP alone or when combining RP and PI. However, a significant association was found between prostate volume and bPFS for PI alone. In the multivariate analysis, only T-stage and PSA density were found to be significant (p=0.01 & 0.0004 respectively). Interestingly, if PSA density is not included as a variable, prostate volume becomes significantly associated with bPFS (p=0.006). The figure demonstrates 10 year Kaplan-Meier estimates of bPFS by prostate volume grouping (log-rank p=0.54).

Conclusions: When controlling for PSA density, prostate volume does not appear to be a significant predictor of biochemical failure in patients treated with either radical prostatectomy or brachytherapy.
Staging Saturation Biopsy in Patients with Prostate Cancer on Active Surveillance

R. Abouassaly, M.D., J. S. Jones, M.D., F.A.C.S

Introduction and Objectives: One option for patients with low grade, low volume prostate adenocarcinoma is to delay curative treatment until evidence of disease progression exists. Our aim is to determine whether saturation prostate biopsy can provide a more accurate assessment of extent of disease, in order to determine what patients would be candidates for active surveillance.

Methods: Between July 2000 and February 2007 we identified 64 patients initially treated with delayed intervention for low grade, low volume disease.

Results: Patients had a median age of 70 years (range 51 – 89), with a median PSA of 5.4 ng/dl (range 0.3 – 19) at the time of diagnosis. Fifty-six of the patients underwent subsequent staging saturation 20-core biopsy a median of 286 days after the initial biopsy (range of 16 – 4823 days). Twenty-two patients had an upstaging of their disease as defined by an increase in Gleason score or volume of disease, leading to a recommendation of active treatment. Patients who were upstaged had significantly fewer cores taken at initial diagnostic biopsy (9.1% with ≥ 20 cores compared to 47% in patients with stable disease, p = 0.003).

Conclusions: Twenty-core saturation biopsy may lead to a more accurate assessment of extent of disease in men with prostate cancer on an active surveillance protocol.

Risk of Prostate Cancer on Re-biopsy following Atypia on Saturation Biopsy

Robert Abouassaly, J. Stephen Jones

Introduction and Objective: Atypical focus suspicious but not diagnostic of malignancy is a descriptive term used by pathologists on prostate needle biopsy when there is insufficient cytologic or architectural atypia to establish a definitive diagnosis of prostate adenocarcinoma. This finding is present in approximately 5% of biopsies, and carries a 40% risk of prostate cancer on subsequent biopsy. Our aim is to determine the risk of malignancy in patients with atypia diagnosed on saturation biopsy.

Methods: We queried the institutional review board approved prostate biopsy database at our institution, and identified 58 patients with a diagnosis of atypia who underwent a repeat biopsy between January 2001 and August 2007. Charts were reviewed for clinical and pathologic information. Statistical comparisons were performed using tests for non-parametric data. The Wilcoxon/Kruskal Wallis test was used for continuous data, and the Fisher Exact test was used for nominal data.

Results: Patients had a median age of 62 years (range 46-79). Of the 58 patients, 20 (34%) had atypia diagnosed on saturation biopsy (≥ 20 cores) (group 1), whereas 38 (66%) had atypia diagnosed with a more traditional biopsy technique (≤ 12 cores) (group 2). All patients subsequently underwent saturation repeat biopsy a median of 5 months after their original biopsy. Eight (40%) of the patients in group 1 were found to have cancer on re-biopsy, compared to 15 (39.5%) of the patients in group 2 (p = 1.00). Whereas only 1 of the 8 patients (12.5%) with cancer in group 1 had a Gleason score ≥ 7, this was found in 5 of the 15 patients (33%) in group 2 (p = 0.37). There was no significant difference between the number of positive cores and the maximum % of the cores involved between the groups (p = 0.59 & 1.00, respectively).

Conclusions: The finding of atypia on prostate biopsy is associated with a high likelihood of underlying malignancy. Although the risk of cancer on re-biopsy appears to be the same for atypia regardless of the number of cores taken on initial biopsy, there was a trend to lower grade cancer in those with this finding on saturation biopsy.
Predictors of Clinical Metastases in Prostate Cancer Patients on Androgen Deprivation Therapy

Robert Abouassaly, Alan Paciorek, Eric A. Klein, Charles J. Ryan, Peter R. Carroll

Introduction and Objective: Virtually all patients with prostate cancer on androgen deprivation therapy (ADT) will ultimately develop evidence of resistance to treatment. The prognosis for patients who develop metastatic disease on ADT is poor, with overall survival estimated to be 24 to 36 months. Our aim is to identify predictors of clinical disease progression in patients with prostate cancer on ADT.

Methods: Of the 13,740 men with biopsy proven prostate cancer enrolled in the CaPSURE database from 1995-present, we identified 4008 men treated with ADT after diagnosis without evidence of metastases at treatment initiation. These men were followed for a median of 3.7 years, with the primary endpoint being the development of bone metastases. Other treatments combined with ADT (radical prostatectomy vs radiation vs none), age, clinical risk category at diagnosis, percent of biopsies positive, BMI, race and number of comorbidities were compared between patients who developed metastases and those that did not using Chi-square tests in a Cox proportional hazards regression model.

Results: In addition to ADT, 1397(35%) were treated with radiation, 653(16%) with RP, 89(2%) were treated with both, and 1869(47%) were treated with ADT alone. The majority of men were either high (43%) or moderate risk (34%) at diagnosis. Mean age of the men in the cohort was 70 years (range 39-94 years). One hundred and ninety-six men (4.9%) progressed to metastatic disease a median of 18 months from the start of ADT (range 1-139 months). On both univariate and multivariate analyses, risk category (p<.0001, HR=2.40), percent of biopsies positive > 33% (p<.0001, HR=6.43), and age ≤ 65 years at diagnosis (p=0.001, HR=1.65) were significantly associated with the development of metastatic disease after ADT.

Conclusions: The use of these variables may help identify candidates for clinical trials evaluating secondary treatments for patients with hormone-refractory disease. Interestingly in our cohort, men who had RP or radiation in addition to ADT did not appear to have a significantly different risk of progressing to metastatic disease.

Saturation Technique Does Not Reduce Cancer Detection during Follow-up after Initial Prostate Biopsy

Brian R Lane, Ayman S Moussa, Craig D Zippe, Robert Abouassaly, Lynn Schoenfield, Cristina Magi-Galluzzi, J Stephen Jones

Introduction and Objective: It has been reported that the prostate cancer detection rate in men with PSA ≥2.5 ng/ml undergoing saturation (≥20 cores) prostate biopsy (PBx) as an initial strategy is not higher than that of 10-12 core PBx. At median follow-up of 3.2 years, we report the cancer detection rate on subsequent PBx in men who underwent initial saturation PBx (sPBx).

Methods: sPBx was used as an initial biopsy strategy in 257 men between 1/02 and 4/06. Cancer was initially detected in 43% of patients that underwent sPBx. In the 147 men with negative initial sPBx, follow-up including DRE and repeat PSA was recommended at least annually. Persistently elevated PSA or rise in PSA was seen as an indication for repeat sPBx.

Results: During median follow-up of 3.2 years after negative initial sPBx, 121 men (82%) underwent subsequent evaluation with PSA and DRE. Median PSA remained ≥4.0 ng/ml in 57% and rose by ≥1 ng/ml in 23%. Cancer was detected in 14 of 59 (24%) men undergoing repeat PBx for persistent clinical suspicion of prostate cancer. No significant association was demonstrated between cancer detection and initial or follow-up PSA or the finding of atypia, and high-grade PIN at initial sPBx. Cancers detected at repeat PBx were more likely to be Gleason 6 and organ-confined at prostatectomy than were those diagnosed with initial sPBx.

Conclusions: Previous experience suggested that while office-based saturation PBx improves cancer detection in men that have previously undergone a negative PBx, it does not improve cancer detection as an initial biopsy technique. We now report that the false negative rate on subsequent PBx after initial sPBx is equivalent to that following traditional PBx. These data provide further evidence against the use of saturation PBx as an initial strategy.
Low Pretreatment Total Testosterone Levels are Associated with a Predominance of Pattern 4 Prostate Cancer at Prostatectomy and Risk of Biochemical Recurrence

Brian R Lane, Andrew J Stephenson, Alwyn M Reuther, Michael W Kattan, Michael W Kattan, Cristina Magi-Galluzzi, Ming Zhou, Milton M Lakin, Eric A Klein

Introduction and Objective: Androgens play a key role in the development and progression of prostate cancer. Three retrospective studies suggest that low pretreatment total testosterone (T) is an independent predictor of adverse pathology in patients with localized prostate cancer. In a prospective study, the association of serum T with pathologic endpoints and risk of biochemical progression was evaluated.

Methods: Based on the mean T of OCD and NOCD groups from the study by Isom-Batz et al, we powered our study to 90% in our primary outcome measure (risk of biochemical recurrence). Routine preoperative T values were measured in 380 consecutive patients with clinically localized prostate cancer who underwent radical prostatectomy by a single surgeon between February 2003 and September 2006. The association of T levels (defined \textit{a priori} as < 220 ng/dL) with pathologic endpoints and risk of biochemical recurrence was evaluated in univariable and multivariable analyses using logistic and linear regression, respectively. Risk of biochemical recurrence was defined using a validated postoperative nomogram based on pretreatment PSA, primary and secondary surgical Gleason grade, extracapsular extension, positive surgical margins, seminal vesicle invasion, positive lymph nodes, and year of surgery.

Results: In univariable analysis, low T analyzed as a categorical variable was associated with predominant Gleason pattern 4 or 5 disease (p=0.049) and risk of biochemical recurrence (p=0.044). In multivariable analysis, nonsignificant trends were observed with regard to both predominant high grade disease (OR: 2.7; 95% CI: 0.9-8.4; p=0.084) and risk of biochemical recurrence (p=0.077). No association with tumor volume was observed in univariate or multivariable analyses (p=0.9; p=0.8).

Conclusions: In this prospective study, no significant association between low pretreatment T and high grade prostate cancer and risk of biochemical recurrence was observed after adjusting for established prognostic parameters. These and previous data suggest that alterations in the hormonal milieu during the initiation of prostate cancer may contribute to the development of aggressive prostate cancer. Based on our results, we cannot rule out a potential prognostic role of serum T in patients with clinically localized prostate cancer, but the prognostic and predictive utility of T for disease progression after definitive local therapy appears marginal and its routine use is not warranted.

Role of PSA and Saturation Biopsy Scheme in Prostate Cancer Detection among Patient Undergoing Repeat Biopsies

Ayman S. Moussa, Jianbo Li, Nelly Tan, Brian Lane, J Stephen Jones

Introduction and Objective: The optimal strategy for patients requiring repeat prostate biopsy is undefined, so we sought to determine the role of PSA as an indication for repeat biopsy and the best biopsy strategy regarding the number of cores needed for those patients.

Methods: We evaluated a total of 996 patients with no history of prostate cancer that had undergone repeat TRUS biopsy between 2000-07. Patients were divided into those undergoing their initial repeat (second overall) biopsy (n=668, Group 1) and those who requiring multiple repeat biopsies (n=328, Group 2). We stratified patients according to PSA, and limited the analysis to those with PSA ≤ 10 or > 10 based on similarities in cancer detection rates within those thresholds. In addition, we considered 8-19 cores to be extended biopsy, and 20+ cores to be saturation biopsy. All were performed in the office setting using periprostatic block.

Results: In the first repeat biopsy group (table 1) there was no significant improvement in cancer detection with saturation biopsy when PSA was ≤ 10 (P=0.845). However, if PSA was > 10 there was a trend towards improved cancer detection, but the difference did not achieve statistical significance, presumably based on limited number of patients (P=0.3682).

In patients with more than one repeat biopsy (table 2) there was significant improvement in cancer detection with saturation biopsy when the PSA was ≤10 (P=0.0105), and a marked improvement in cancer detection when PSA > 10 (P=0.0047).

Conclusions: There is limited improvement in cancer detection for the first repeat biopsy, especially if PSA is below 10. However, if a third or greater biopsy is required based on clinical suspicion, saturation biopsy offers vastly improved cancer detection, especially when PSA >10.

Table (1)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cores</th>
<th>8-19</th>
<th>&gt; 20</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA ≤10</td>
<td>N = 217</td>
<td>N = 344</td>
<td>0.845</td>
<td></td>
</tr>
<tr>
<td>Positive: 70 (32.2%)</td>
<td>Positive: 115 (33.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA &gt; 10</td>
<td>N = 51</td>
<td>N = 56</td>
<td>0.3682</td>
<td></td>
</tr>
<tr>
<td>Positive: 9 (17.6%)</td>
<td>Positive: 15 (26.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

continued
Introduction and Objective: A significant proportion of prostate cancer patients with biopsy Gleason scores (GS) ≥7 are upgraded or downgraded on interpretation of radical prostatectomy (RP) specimens. As biopsy GS plays a critical role in treatment decisions, we sought to identify the clinical and pathological parameters that predict pathological upgrading or downgrading in this population.

Methods: We retrospectively evaluated a total of 1133 patients who had undergone TRUS biopsy revealing ≥GS 7 (GS 7=963 patients, GS 8=133, GS 9=36, GS10=1) that underwent RP at our institution from 2000-07. Complete relevant information was available for all.

A multivariable logistic regression analysis was applied to identify predictors of pathological grading changes.

Results: Overall the mean age was 61.2 y with a mean PSA of 7.6 ng/ml. The mean number of cores in a biopsy was taken 11.6. Of the 1133 patients, surgical GS was upgraded in 297 (26.2%), downgraded in 211 (18.6%), and remained the same in 625 (55.2%). We found that biopsy characteristics which predicted surgical GS downgrading included the presence of inflammation (p=0.013), perineural invasion (p=0.0012) in the biopsy specimen in addition to large prostate volume (p=0.0012) and low maximum percentage of cancer in any core (p=0.016). The absence of prostatic intraepithelial neoplasia (PIN) (p=0.0317) or presence of perineural invasion in the biopsy in addition to fewer numbers of cores taken at biopsy (p=0.0006) were predictors of surgical GS upgrading. A greater number of cores positive with small prostate volume was the most likely to predict no change in GS in the RRP specimen.

Conclusion: Men with large prostate volume, low numbers of positive cores, with perineural invasion are most likely to have inaccurate biopsy GS. Low maximum percent of cancer in any core and presence of inflammation can predict a higher likelihood of downgrading. A low number of biopsy core obtained and the absence of PIN are associated with upgrading. It is important to determine correctly prostate volume, to have at least 10-12 cores in order to determine the likelihood that biopsy pathology will predict the true extent and GS of the entire tumor in order to assist in treatment decisions.

<table>
<thead>
<tr>
<th>CORES</th>
<th>8-19</th>
<th>&gt; 20</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &lt; 10</td>
<td>N= 95</td>
<td>N= 131</td>
<td>0.0105</td>
</tr>
<tr>
<td>Positive : 13 (13.68%)</td>
<td>Positive : 38 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA &gt; 10</td>
<td>N= 41</td>
<td>N= 61</td>
<td>0.0047</td>
</tr>
<tr>
<td>Positive : 8 (19.5 %)</td>
<td>Positive : 30 (49.1 %)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table (2)
Prostate Cancers Diagnosed at Repeat Biopsy are Smaller but Not Less Likely to Be High-Grade

Nelly Tan, Brian R Lane, Jianbo Li, Ayman S Moussa, Meghan Ross, J Stephen Jones

Introduction: We investigated whether prostate cancer (PC) diagnosed on initial biopsy had worse pathological outcomes compared to repeat biopsy.

Methods: We reviewed 905 newly diagnosed PC on TRUS biopsy from 2000-07. Patients were categorized by number of previous biopsies (NPB): initial (n=690), 2nd (n=142) and 3rd or more (n=73). We analyzed Gleason sum (GS), number of cores (NOC) taken, NOC positive, percent of NOC positive and bilaterality of PC among the 3 groups. Clinically insignificant cancers (CIC) were defined as those with 1 or 2 positive cores, ≤50% maximum cancer in a core and GS ≤6.

Results: PC was diagnosed in 57%, 20% and 19% of cases during 1st, 2nd and ≥3rd biopsies, respectively. Initial biopsy had higher NOC positive, percent NOC positive and maximum percent of PC involved in a core. More initial biopsies were positive bilaterally and fewer were CIC (p<0.01). However, ≥3rd biopsies had the highest percent (14%) of GS ≥8 (p<0.01). In multivariable analysis accounting for PSA, DRE, age, biopsy schema, and prostate volume, NPB was an independent predictor of NOC positive, percent NOC positive and maximum PC involved in a core, bilaterality and CIC (p<0.01). Only PSA, DRE and age (but not NPB) independently predicted GS (p<0.01).

Conclusions: PC diagnosed on initial biopsy had higher volume than on repeat biopsy. However, there were a significant number of high-grade PC’s detected on ≥3rd biopsies underscoring the importance of repeat biopsy in the setting of elevated or rising PSA despite negative previous biopsies.

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down grade Predictors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate volume</td>
<td>+1.3474569</td>
<td>0.0012</td>
</tr>
<tr>
<td>Inflammation</td>
<td>+0.5284539</td>
<td>0.0138</td>
</tr>
<tr>
<td>Max. cancer in one core</td>
<td>-0.0084835</td>
<td>0.0163</td>
</tr>
<tr>
<td>Perineural</td>
<td>+0.6922030</td>
<td>0.0012</td>
</tr>
<tr>
<td>Upgrade Predictors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIN</td>
<td>-0.6937399</td>
<td>0.0317</td>
</tr>
<tr>
<td>Number of cores</td>
<td>-2.1214907</td>
<td>0.0006</td>
</tr>
<tr>
<td>Perineural</td>
<td>+0.9788652</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>For all changes Predictors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate volume</td>
<td>+0.76045828</td>
<td>0.0270</td>
</tr>
<tr>
<td>Number of positive cores</td>
<td>-0.55521439</td>
<td>0.0155</td>
</tr>
<tr>
<td>Percent of positive cores</td>
<td>+0.01978424</td>
<td>0.00025</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>+0.78335879</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Does Transrectal Ultrasound Probe Really Matter? End-Fire versus Side-Fire: Prostate Cancer Detection Rates

Christina B. Ching, Ayman S. Moussa, Jianbo Li, Nelly Tan, Brian Lane, J. Stephen Jones

Introduction and Objective: Transrectal ultrasound (TRUS) biopsy of the prostate is a gold standard for diagnosing prostate cancer but still lacks 100% sensitivity. We compared the two most commonly used types of probes (end-fire and side-fire) used in TRUS biopsy to see if the type of probe affected prostate cancer detection rates.

Methods: We retrospectively evaluated a total of 1563 patients who had undergone TRUS biopsy between 2000 and 2007. Only patients with normal rectal exam undergoing initial prostate biopsy were included. The patients were divided into those whose biopsies were performed using an end-fire probe (n=801) and those whose biopsies were with a side-fire probe (n=762), evaluating if the type of probe used affected prostate cancer detection rates. The biopsies were performed by a total of ten different Urology staff all at the same institution. All pathology was reviewed at our institute's pathology department.

Results: Mean patient age was 64.7 years old in the side-fire arm and 64.4 in the end-fire arm. Patient PSA and number of biopsy cores were variable. There was a significant difference in the overall prostate cancer detection rate in the end-fire arm versus the side-fire arm (45.5% vs. 37.9% respectively, p=0.0026). When stratified for PSA ≤10 or PSA >10, there was a significant difference in detection rate between end-fire and side-fire in patients with PSA >10 (67.6% vs. 41.2% respectively, p=0.0001). There was also a significant difference in detection rates between end-fire and side-fire in those biopsies with less than 20 cores (45.5% vs. 38.0%, p=0.0082).

Conclusions: Type of probe does significantly affect overall prostate cancer detection rates, particularly in patients with a PSA >10 or undergoing TRUS biopsy with less than 20 cores. This is possibly due to the end-fire probe allowing better visualization and mechanical sampling of the apex and lateral most regions of the peripheral zone where cancer is most likely to reside.

<table>
<thead>
<tr>
<th>Probes</th>
<th>Side Fire</th>
<th>End Fire</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA ≤ 10</td>
<td>Total: 636</td>
<td>Total: 699</td>
<td>0.0661</td>
</tr>
<tr>
<td>Positive: 237</td>
<td>Positive: 296</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent: 37.26%</td>
<td>Percent: 42.34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA &gt; 10</td>
<td>Total: 126</td>
<td>Total: 102</td>
<td>0.0001</td>
</tr>
<tr>
<td>Positive: 52</td>
<td>Positive: 61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent: 41.2%</td>
<td>Percent: 67.64%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cores &lt; 20</td>
<td>Total: 628</td>
<td>Total: 639</td>
<td>0.0082</td>
</tr>
<tr>
<td>Positive: 239</td>
<td>Positive: 291</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent: 38%</td>
<td>Percent: 45.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cores ≥ 20</td>
<td>Total: 134</td>
<td>Total: 162</td>
<td>0.1823</td>
</tr>
<tr>
<td>Positive: 50</td>
<td>Positive: 74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent: 37.3%</td>
<td>Percent: 45.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A Multicenter VA Study of Zolendronic Acid in Men on Androgen Deprivation Therapy for Prostate Cancer with Preexisting Osteoporosis

M. Pandya, N. Bhoopalam, P. Iyer, P. Vanveldhuizen, S. Krasnow, H. Garewal, N. Friedman, T. Moritz, D. Reda, S.C. Campbell

**Background:** Prolonged androgen deprivation therapy (ADT) for men with prostate cancer (CAP) carries an increased risk of osteoporosis and fracture. Zoledronic Acid (Z) is a potent IV bisphosphonate that has been shown to improve bone mineral density (BMD) in patients with CAP who are just initiating ADT (duration < 1 year). However, the potential benefit of Z has not been investigated in patients who have pre-existing osteoporosis on ADT, who are at greatest risk for fracture.

**Methods:** We enrolled 27 patients with M0 CAP and preexisting osteoporosis (defined by a baseline BMD T score < -2.0) on ADT, in this open label, single arm trial to assess the impact of Z on bone health. All patients were started on supplemental vitamin D and calcium and were counseled about lifestyle modifications to optimize bone health. BMD was measured by DEXA scan at enrollment, 6 months, and 12 months. The primary endpoint was percent change in BMD at the lumbar spine at 12 months compared to baseline.

**Results:** Mean age was 73.0 years, 74% were Caucasian, and mean BMI was 28.4. The majority of patients were former smokers, moderate users of ETOH, and most were sedentary. Most patients were taking supplemental calcium and vitamin D at the time of enrollment. After 12 months of Z, lumbar spine BMD increased an average of 5.11% (p<0.0001) compared to baseline. Right hip BMD increased 2.14% (p=0.0014); left hip BMD increased 2.89% (p=0.0043), right femoral neck BMD increased 2.79% (p=0.0022); and left femoral neck BMD increased 2.93% (NS). Z infusion was well tolerated with minimal effect on renal function.

**Conclusions:** Zoledronic Acid improves BMD in men with CAP who have pre-existing osteoporosis on ADT. This novel finding demonstrates that bisphosphonate therapy can positively impact bone health in CAP patients with pre-existing osteoporosis who are at highest risk for fracture.

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A Phase III Trial of Zoledronic Acid (Z) to Prevent Osteoporosis in Men on Early vs. Prolonged Androgen Deprivation Therapy (ADT) in a High Risk VA Population

W. Broderick, S.C. Campbell, H. Garewal, P. Iyer, S. Krasnow, T. Moritz, D. Reda, P. Vanveldhuizen, N. Friedman, N. Bhoopalam

**Background:** ADT for prostate cancer (CAP) is associated with osteoporosis and an increased risk of fracture. Previous studies with Z have shown prevention of bone loss in patients just initiating ADT (duration < 1 year); however, this has not been investigated in patients on prolonged ADT or in older patients with multiple risk factors for osteoporosis.

**Methods:** We randomized 93 MO CAP patients in this double blind, placebo (P) controlled trial to evaluate the effect of Z in patients on ADT for various periods of time in the VA health care system. Mean age was 70.5 years. 55% were Caucasian, 41% African American, and 4% Hispanic, and mean BMI was 29.4. Preplanned strata (Str) included 50 on ADT <1 year (Str 1) and 43 on ADT for >1 yr (Str 2). All patients had baseline bone mineral density (BMD) T score ≥ -2.0. In each stratum, patients were randomized to receive either Z 4mg IV q3 months for 4 treatments or IV P on the same schedule. All men started calcium, vitamin D and weight-bearing exercise. BMD was measured by DEXA scan at baseline, 6 and 12 months. The primary endpoint was the % change in BMD at the lumbar spine.

**Results:** Patients were well matched within the strata across the treatment arms with respect to age, race, BMI and risk factors for osteoporosis. The majority of patients were ex-smokers, moderate ETOH intake, and were not taking calcium/vitamin D supplements or doing weight bearing exercise prior to enrollment. In Str 1, spine BMD increased 5.95% in the Z arm and decreased 3.23% in the P arm (p=0.0044). In Str 2, spine BMD increased 6.08% in the Z arm and only increased 1.57% in the P arm (p=0.0005). BMD also increased significantly in both hips for both strata for patients receiving Z compared to P. Treatment was well tolerated with minimal impact on renal function.

**Conclusions:** Zoledronic Acid improved BMD in older VA patients with MO CAP at high risk for osteoporosis, on ADT for < 1 yr or >1 yr. This represents a novel finding which indicates that bisphosphonate therapy is effective even if it is initiated later in the course of ADT, and is efficacious even in high risk populations.
Section 2
Renal Disease/
Laparoscopy
A Novel Telesurgical Endoscopic Guidance System and Contingency Plan for Treatment of Obstructive Nephrolithiasis during Space Exploration

Kefer JC, Desai MM, Aron M, Haber-Pascal G, Thomas J, Greenberg N, Gill IS

Introduction and Objective: The microgravity environment encountered during space exploration leads to an increased risk of nephrolithiasis. We describe a novel endoscopic guidance system allowing a novice to reliably place ureteric stents under telesurgical guidance from a ground-based urologist.

Methods: We engineered an endoscopic guidance system allowing flexible cystoscopy in a stable, calibrated, non-motorized guidance platform. The technical feasibility, efficiency and reproducibility of stent placement was assessed. Telesurgical flexible cystoscopy with placement of bilateral ureteric stents was performed in 5 acute swine (10 kidneys). Positional stability of the guidance platform was also assessed. Urologists directed telesurgical cystoscopy through two-way audio-video communication from a remote location.

Results: The telesurgical endoscopic guidance system allowed a novice assistant to place bilateral guidewires and stents in an efficient, reliable manner. Stent placement was confirmed using ultrasound transmitted remotely to the urologist through a wireless broadband network. Time for localizing the ureteric orifice and placement of a guidewire was 4 to 35 min (mean 18), and from guidewire to stent placement was 4 to 32 minutes (mean 17). On a visual analog scale of 1-10 (10=best), guided recognition of the ureteric orifices with stent placement was rated a 9. Positional stability of the endoscopic guidance system was rated a 10. All guidewires and stents were ultrasonographically visualized in the renal pelvis.

Conclusions: Our system allows a novice bedside assistant to reliably place ureteric stents in a safe reliable manner. This protocol represents a novel contingency plan for treatment of urolithiasis during space exploration, as well as other remote environments such as rural emergency clinics or health care systems in developing countries.
A Novel Device for Intraoperative Identification of the Ureter: Using Proximity Sensors to Prevent Inadvertent Ureteric Injury

Kefer JC, Gill IS, Kuban B, Waters K, Desai M

Introduction: Inadvertent intraoperative ureteric injury remains a significant concern during gynecologic, colorectal and vascular surgical procedures. Preoperative placement of standard passive ureteric stents can assist the non-urologic surgeon in tactile localization of the ureter, but the overall efficacy of standard ureteric stents for this application is limited. Here, we report a prototype intraureteric stent emitting a moderate magnetic field, and utilizing a linear output Hall Effect transducer (Honeywell Intl. Inc., Morristown, NJ) as an intraoperative magnetic proximity sensor, thereby precisely localizing the intraureteral stent. One major design challenge was to integrate a moderate yet stable magnetic field within the full length of the stent without compromising the detection capabilities or sensitivity of the Hall transducer. This stent and proximity sensor system may be used intraoperatively to localize the ureter, and may serve to reduce inadvertent ureteral injury.

Methods: A schematic drawing of the Hall effect transducer is shown below (Figure 1). Our stent design incorporates rare-earth neodymium-iron-boron (NdFeB) disc magnets (diameter 3.2mm x thickness 1.6mm) placed within the stent lumen at an offset 90° configuration, generating multiple magnetic fields along the length of the stent. Dual DC power supply at 8V excitation powered the Hall transducer. Magnetic field proximity detection was quantified using a 500 MHz oscilloscope set at 50 MHz. The stent was fixed in place ex vivo, and the Hall sensor approached the stent from 7 cm to 2 cm distance at 1 cm intervals, and then at 0.1 cm intervals from 2.0 to 1.0 cm proximity from stent (Table 1). The sensor approached the stent from all exposed sides, and changes in sensor current and standard deviation were recorded.

Results: The Hall transducer reliably detected increased magnetic field strength from 7 cm distance to 1 cm distance from the stent. This increase in detected field strength with increasing proximity was noted from all vectors, including parallel or perpendicular to the stent, making this device design suitable for localizing the ureter intraoperatively.

Conclusion: We report a novel stent design allowing precise localization of the ureter during intra-abdominal and pelvic surgeries utilizing a proximity sensor to detect magnetic fields from within the ureteric stent. This stent may serve to decrease the rate of inadvertent intraoperative ureteral injury, and allows the non-urologic surgeon the ability to actively identify the ureter during surgical procedures.

Laparoscopic Partial Nephrectomy for Select Central Tumors: Omitting the Bolster

Christopher J. Weight, M.D., Brian R. Lane, M.D., Ph.D., Inderbir S. Gill, M.D. M.Ch.

Objective: Laparoscopic partial nephrectomy (LPN) for central tumors often requires a substantial resection including collecting system entry. In such cases, renal reconstruction typically requires overseeing the tumor defect and bolstered renorrhaphy. In an effort to reduce warm ischemia time, we describe an alternative technique of performing LPN on select central tumors without bolstered renorrhaphy.

Methods: Following tumor excision, the tumor bed defect in 23 selected patients was closed with intra-parenchymal sutures and biological gelatin matrix thrombin sealant (FloSeal™), without bolstered renorrhaphy. Data regarding perioperative and postoperative outcomes were collected prospectively.

Results: Median tumor size was 2.5 cm (1.7-5). Median warm ischemia time was 20 minutes (9-44), estimated blood loss was 150 mL (50-1000), and on average, 80% (45-95%) of the kidney was spared. Complications occurred in 4 patients (17%): post-operative hemorrhage in a patient with a lateral tumor requiring surgical re-exploration (1), urine leak resolved spontaneously (1), post-operative anemia (1), and atrial fibrillation (1).

Conclusions: In properly selected patients with a central tumor extending to the collecting system, reconstruction of the LPN defect can be performed safely with a running intra-parenchymal hemostatic stitch and FloSeal™ without bolstered renorrhaphy. The operation is simplified and warm ischemia time significantly reduced. A laterally-located tumor, wherein the resultant LPN defect faces away from the surgeon, precluding uniform contact of FloSeal™ with the entire tumor bed, has the potential for postoperative hemorrhage, and is a contraindication for this technique.
Correlation of Radiographic Imaging following Radio Frequency Ablation and Cryoablation

Christopher J. Weight, Jihad H. Kaouk, Nicholas J. Hegarty, Eric Remer, Charles M. O’Malley, Brian R. Lane, Inderbir S. Gill, Andrew C. Novick

Introduction: Radio Frequency Ablation (RFA) and cryotherapy of small enhancing renal lesions are becoming increasingly more common. Because no tissue is available for pathologic analysis, the only measurement of successful tumor ablation has been the absence of contrast enhancement on post-treatment MRI or CT. We hypothesize that adding a post treatment biopsy would offer significant additional information regarding oncologic outcome in these relatively new renal cancer treatment paradigms.

Methods: From April 2002 to March 2006, 109 renal lesions in 88 patients were ablated with percutaneous RFA, and from Sept 1997 to Jan 2006, 192 lesions in 176 patients were treated with laparoscopic cryoablation. Patients were followed with radiographic imaging on post-operative day 1, and typically at 3, 6, and 12 months, and then annually thereafter. Routine post-ablation biopsy was scheduled at 6 months. Post-ablation biopsy was not done in patients who had complicating factors such as kidney remnant, or on anticoagulation.

Results: Radiographic follow up at 6 months was available in 73 RFA and 139 cryoablation patients. Radiographic success at 6 months was 85% (n=62) and 90% (n=125) for RFA and cryoablation respectively. Pathologic follow-up at 6 months was available in 37 RFA and 97 cryoablation patients. At six month biopsy, success in the RFA cohort dropped to 64.8% (n=24) while cryoablation success remained high at 93.8% (n=91). Of 13 patients with a 6-month positive biopsy after RFA, nearly half 46.2%(n=6) demonstrated no enhancement on post treatment MRI or CT. In patients treated with cryoablation, all positive biopsies demonstrated post-treatment enhancement just prior to biopsy.

Conclusions: Radiographic imaging is inadequate for determining successful treatment of kidney tumors with RFA. We recommend that a routine post treatment biopsy should be added to RFA follow up protocols due to significant risk of residual renal cell cancer without radiographic evidence. We continue to restrict RFA to high risk patients in the setting of an IRB protocol. In contrast, radiographic images of renal lesions treated with cryotherapy appear to correlate adequately in our series.

Matched-Pair Comparison of Baseline Demographics and Renal Function between Kidney Cancer Patients and Live Kidney Donors

Philippe Koenig, Inderbir S.Gill, Kazumi Kamoi, Monish Aron, Ayesha B. Singh, Christopher J. Weight, Mihir M. Desai, Jihad H. Kaouk, David Goldfarb, Emilio D. Poggio

Purpose: To evaluate baseline demographics and renal function in patients with kidney cancer and live kidney donors.

Methods: From 2 prospectively-maintained databases of patients undergoing surgery for clinically localized kidney cancer (n=947) and live kidney donors (n=434) at a single institution, we retrospectively performed a non-matched and a matched-pair (n=226 in each group) analysis correcting for disparities in age, sex, and ethnicity. Demographic data at presentation were compared as regards general medical condition, comorbidities, and baseline renal function.

Results: Non-matched comparison revealed kidney cancer patients were older and less healthy, with a higher incidence of hypertension, diabetes mellitus, and coronary artery, pulmonary, gastrointestinal, hematological, and endocrine disease (p<0.0001 for all). Even after the matched-pair analysis, these disparities remained significant. Kidney cancer patients had poorer renal function in the non-matched (24% higher serum creatinine, 30% lower Modification of Diet in Renal Disease(MDRD) estimated Glomerular Filatration Rate (GFR); p<0.0001) and in the matched-pair analysis (7% higher serum creatinine (p=0.06), 16% lower MDRDeGFR (p<0.0001). Multivariate analysis identified age, sex, ethnicity, American Society of Anesthesiologists score, smoking, and kidney cancer as independent predictors of eGFR<60mL/min. Within the kidney cancer cohort, tumor size did not correlate with comorbidity or renal functional status.

Conclusion: Even after matching for age, sex, and ethnicity, patients with kidney cancer have poorer baseline renal function and more risk factors for developing chronic kidney disease after unilateral nephrectomy compared to kidney donors.
The Impact of Minimally Invasive Techniques on Open Surgical Partial Nephrectomy: A Single Institutional Experience Over 10 Years  
Christopher J. Weight, Amr F. Fergany, Paul W. Gunn, Brian R. Lane, Andrew C. Novick  

Introduction: With the advent of minimally invasive nephron sparing surgical (NSS) options, we hypothesize that the indications, perioperative parameters and complication rates of open partial nephrectomy (OPN) may have changed significantly over a 10 year period.

Methods: OPN during two 3-year periods were compared. From 1994 to 1996 (before laparoscopic partial nephrectomy, cryoablation and radiofrequency ablation) 208 cases were compared against 347 OPN performed from 2004 to 2006 with regard to indication, perioperative parameters and complication rates.

Results: There were no significant differences between the groups with regard to age (59 vs. 58 years), gender (65.5% male vs. 65.0% male), and tumor size (3.9 cm vs. 3.6). The tumors removed in the recent era were more often in a solitary kidney (40.0% vs. 15.6% p<0.0001), centrally located (55.6% vs. 37.3% p <0.0001) and the pathology was more often higher grade (Furhman 3-4) (43.1% vs. 27.8% p<0.0001). In spite of the increased technical difficulty, the ischemia time in the more recent era was shorter (19.1 min vs. 40.6 min p=0.0000) and urologic and overall complication rates were statistically similar (7.5% vs. 8.9%, p=0.6071 and 19.1% vs. 14.4%, p=0.1723 respectively).

Conclusions: At a tertiary referral center, the introduction of minimally invasive NSS techniques has drawn away the less complicated, less aggressive tumors, reserving the bulk of the more complicated central tumors for OPN without decreasing the total number of open cases. With experience, these more difficult central tumors are being successfully treated with decreasing warm ischemia time and comparable complication rates to historical series.

Factors Affecting Renal Function after Laparoscopic Partial Nephrectomy  
Monish Aron, Burak Turna, Rodrigo Frota, Kazumi Kamoi, Georges-Pascal Haber, Inderbir S. Gill  

Objective: To determine the factors affecting kidney function after laparoscopic partial nephrectomy (LPN)

Methods: Between 09/1999 and 10/2006, 657 patients underwent LPN at our institution. A total of 103 patients undergoing unilateral LPN in the setting of bilateral functioning kidneys for a single mass in one kidney were identified with documented paired split renal function. Estimated GFR (eGFR) was calculated to assess global renal function. Multiple factors were assessed using univariate and multivariate analysis to identify risk factors for change in renal function. For sub-analysis, the study population (n=103) was stratified into 3 groups based on warm ischemia time (WIT; <30 min, 30-40 min, >40 min).

Results: On logistic regression analysis, only WIT was a significant predictor for decrease in eGFR at 6 months. Only percent kidney parenchyma excised was predictive of decline in differential renal function at 3 months. Although preoperative serum creatinine, preoperative eGFR and tumor size were significant in terms of decrease in eGFR on univariate analysis, these were not independent risk factors on multivariate analysis. Likewise, presence of hypertension and preoperative serum creatinine were significant on univariate but not on multivariate analysis.

On ROC analysis, a threshold value for WIT ≥36 minutes was associated with >20% decrease in eGFR. A cutoff value of ≥ 25% kidney parenchyma excised was associated with >20% decrease in the remnant kidney function on MAG-3 scan.

Conclusions: Increasing warm ischemia time and the amount of kidney parenchyma excised are the most important determinants of postoperative remnant function after LPN.
Laparoscopic Renal Cryoablation: Long-Term Oncologic Outcomes with Minimum 5-year follow-up

Monish Aron, Kazumi Kamoi, Georges-Pascal Haber, Mihir M. Desai, David Canes, Jihad H. Kaouk, Inderbir S. Gill

Introduction: We present 5-10 year oncologic outcomes after laparoscopic renal cryoablation (LRC).

Methods: Between 09/1997 and 09/2007, we performed renal cryoablation in 288 patients. Of these, 88 patients treated before 09/2002 (all laparoscopic) have minimum 5-year follow-up (table 1). Follow-up involved MRI imaging on postoperative day 1, 3 months, 6 months, 12 months, and then annually, with cryolesion biopsy at 6-months. All data were prospectively accrued.

Results: In the 88 patients with minimum 5-year follow-up, mean age was 67 years. Of these, 82 patients had a sporadic single renal mass (table 2), while 6 had multiple lesions. Mean tumor size was 2.3 cm (0.9-5.0 cm). Median ASA score was III, while mean BMI was 28. Overall, 5 patients developed local recurrence (1 of these had multiple tumors at initial presentation), 2 had local recurrence with metastases, and 7 had distant metastases without local recurrence (1 of these had multiple tumors at initial presentation). Overall, there were 6 cancer deaths, 6 of these in patients with a sporadic single mass at presentation (table 3). In the 82 patients with sporadic single renal mass (median follow-up 83 mos; range 60-120 mos), 5-year actual overall, cancer-specific, and disease-free survival is 83%, 95%, and 78%, respectively, while 10-year Kaplan-Meier overall, cancer-specific, and disease-free survival are 57%, 88%, and 51%, respectively.

Conclusions: Laparoscopic renal cryoablation is effective oncologic treatment for renal mass in select patients. Cancer-specific survival of 95% at 5-years and 88% at 10-years is possible.

---

Table 1: Demographic and perioperative data in 88 patients with minimum 5-year follow-up after LRC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Number</td>
<td>88</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>66.8 (28-88)</td>
</tr>
<tr>
<td>Number Male (%)</td>
<td>59 (67)</td>
</tr>
<tr>
<td>Median ASA score</td>
<td>3 (1-4)</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>28.0 (16.6-61.2)</td>
</tr>
<tr>
<td>Kidney status (%)</td>
<td></td>
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<tr>
<td>Normal Contralateral</td>
<td>41 (47)</td>
</tr>
<tr>
<td>Compromised Contralateral</td>
<td>26 (29)</td>
</tr>
<tr>
<td>Solitary Kidney</td>
<td>21 (24)</td>
</tr>
<tr>
<td>Mean serum creatinine (mg/dl)</td>
<td>1.29 (0.6-3.4)</td>
</tr>
<tr>
<td>No. renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (23)</td>
</tr>
<tr>
<td>No</td>
<td>68 (77)</td>
</tr>
<tr>
<td>Pre-op Mean Tumor Size(cm)</td>
<td>2.3 (0.9-5.0)</td>
</tr>
<tr>
<td>LRC Approach (%)</td>
<td></td>
</tr>
<tr>
<td>Transperitoneal</td>
<td>62 (70)</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>26 (30)</td>
</tr>
<tr>
<td>Mean Blood Loss (ml)</td>
<td>106 (10-800)</td>
</tr>
<tr>
<td>Mean Operating Time (min)</td>
<td>187 (75-420)</td>
</tr>
<tr>
<td>No. cryoprobes used (%)</td>
<td></td>
</tr>
<tr>
<td>1 Cryoprobe</td>
<td>64 (81)</td>
</tr>
<tr>
<td>2 Cryoprobes</td>
<td>13 (16)</td>
</tr>
<tr>
<td>3 Cryoprobes</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Mean Hospital Stay (hours)</td>
<td>47.2 (23-302)</td>
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Table 2: Oncologic outcomes in 82 patients with single sporadic tumor

<table>
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<th>Parameter</th>
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<tbody>
<tr>
<td>No. of Patients</td>
<td>82</td>
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<tr>
<td>Median Follow-up (Months)</td>
<td>83 (60-120)</td>
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<tr>
<td>Recurrences (local or distant or both)</td>
<td>12</td>
</tr>
<tr>
<td>Cancer Deaths</td>
<td>6</td>
</tr>
<tr>
<td>5 Year Overall Survival (Actual)</td>
<td>83%</td>
</tr>
<tr>
<td>5 Year Cancer-Specific Survival (Actual)</td>
<td>95%</td>
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<tr>
<td>5 Year Recurrence-Free Survival (Actual)</td>
<td>78%</td>
</tr>
<tr>
<td>10 Year Overall Survival</td>
<td>57%</td>
</tr>
<tr>
<td>10 Year Cancer-Specific Survival</td>
<td>88%</td>
</tr>
<tr>
<td>10 Year Recurrence-Free Survival</td>
<td>51%</td>
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</tbody>
</table>
Intermediate and Long Term Oncologic Outcomes after Laparoscopic Radical Nephrectomy (LRN) for Locally Advanced (PT2-PT4) Renal Cell Carcinoma (RCC)

Monish Aron, Antonio Finelli, Jose R Colombo, Jr, Mihir M Desai, Jihad H Kaouk, Inderbir S Gill

Introduction: Although publications of the oncologic efficacy of LRN include subsets of patients with pT2 or 3a disease, a substantial experience with pathologically advanced RCC has not been described to date.

Methods: Between 12/1997 and 05/2004, 380 LRN were performed for patients with a renal mass. Of these, 106 (28%) had pathologic advanced disease without metastases (pT2-4, N0/X, M0). Lymphadenectomy was not routinely performed. All specimens were removed intact.

Results: Median patient age was 62 years (33-100). The median ASA class and BMI were 3 and 29.3, respectively. Mean tumor size was 7.9 cm (2.5-16 cm). Mean specimen weight was 826 g (72-1763 g). All procedures were completed laparoscopically without conversion. The distribution of disease stages for patients included: pT2 in 45 patients, pT3a in 44 patients, pT3b in 16 patients, and pT4 in 1 patient. Positive surgical margins were noted in two patients (1.4%) with pT3b disease. Median follow-up in 95 evaluable patients is 4.3 years (IQR 2.8 – 5.3). For pT2, pT3a, and pT3b, the overall survival was 82.8%, 68.5%, and 79.5%; and cancer-specific survival was 95.8%, 91%, and 81.4%, respectively. Disease progression occurred in 3, 5, and 3 patients in the pT2, pT3a and pT3b groups at a mean time of 24, 13, and 16 months, respectively.

Conclusions: The intermediate oncologic outcomes for this cohort of patients are in keeping with those published for open radical nephrectomy.
Impact of Gender in Renal Cell Carcinoma: An Analysis of the SEER Database

Monish Aron, Mike M. Nguyen, Robert J. Stein, Inderbir S. Gill

Purpose: To evaluate gender differences in initial presentation, pathology, and outcomes with renal cell carcinoma (RCC).

Materials and Methods: The 1973-2004 Surveillance Epidemiology and End Results (SEER) 17 registries database was analyzed for renal tumors from 1988 to 2004 coded as primary site “kidney and renal pelvis”. After various exclusions, a final study group of 35,336 cases with complete data was obtained. Demographic variables analyzed included age, sex, and race. Tumor variables included size, stage at diagnosis, grade, and histology. Primary outcome variables included overall and cancer-specific survival.

Results: Of the patients, 22,288 were male (63%). Females presented with smaller tumors (5.9 vs. 6.1cm, p<0.0001) of lower grade (p<0.0001). Males had a higher incidence of regional or metastatic spread of renal carcinoma (p<0.0001). Median overall survival from time of diagnosis was 130 months for females vs. 110 months for males (p<0.0001). Comparing males and females, 5-year cancer specific survival was 78% versus 81%, and 5-year overall survival was 65% versus 69% (p<0.0001). On multivariate analysis, cancer specific survival was similar (H.R. 1.00, p=0.960) (fig 1), while overall survival was significantly longer for females (H.R. 0.92, p<0.0001) (fig 2). Older age at diagnosis, larger tumor size, higher grade, higher SEER historic stage, and sarcomatoid, collecting duct, or “other” histology were related to worse cancer-specific and overall survival.

Conclusions: Men present with larger, higher stage, higher grade RCC than women. Overall survival is better in women while cancer specific survival is not significantly different.

continued
### Multivariate Cox proportional hazards model of overall survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Haz Ratio</th>
<th>95% Confidence Interval</th>
<th>p</th>
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<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>1.03</td>
<td>1.03 - 1.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tumor Size (cm)</td>
<td>1.04</td>
<td>1.04 - 1.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>0.92</td>
<td>0.08 - 0.96</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1.06</td>
<td>1.00 - 1.13</td>
<td>0.044</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1.59</td>
<td>1.49 - 1.70</td>
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<tr>
<td>Grade 4</td>
<td>2.28</td>
<td>2.10 - 2.47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>Caucasian race</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>African American race</td>
<td>1.29</td>
<td>1.20 - 1.39</td>
<td>&lt;0.0001</td>
</tr>
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<td>American Indian/Alaskan Native</td>
<td>1.05</td>
<td>0.90 - 1.32</td>
<td>0.335</td>
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<td>Asian Pacific Islander</td>
<td>0.85</td>
<td>0.77 - 0.93</td>
<td>0.001</td>
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<tr>
<td>Other</td>
<td>0.56</td>
<td>0.43 - 0.73</td>
<td>0.228</td>
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<tr>
<td>Unknown</td>
<td>0.27</td>
<td>0.19 - 0.38</td>
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<td>SEER Historic Stage</td>
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<td>Localized</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>Regional</td>
<td>1.92</td>
<td>1.83 - 2.02</td>
<td>&lt;0.0001</td>
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<td>Distant</td>
<td>7.69</td>
<td>7.28 - 8.12</td>
<td>&lt;0.0001</td>
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<td>Histology</td>
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<tr>
<td>Clear Cell/Conventional</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Papillary</td>
<td>0.83</td>
<td>0.72 - 0.95</td>
<td>0.008</td>
</tr>
<tr>
<td>Granular</td>
<td>0.99</td>
<td>0.92 - 1.11</td>
<td>0.016</td>
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<tr>
<td>Chromophobe</td>
<td>0.60</td>
<td>0.47 - 0.76</td>
<td>&lt;0.0001</td>
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<tr>
<td>Sarcomatoid</td>
<td>1.55</td>
<td>1.33 - 1.81</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Collecting Duct</td>
<td>1.95</td>
<td>1.82 - 2.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>1.92</td>
<td>1.77 - 2.08</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Figure 2. Kaplan-Meier overall survival after diagnosis of renal carcinoma. Mean survival time for female patients was significantly prolonged compared with male patients (p=0.0001). Numbers at risk listed below graph.

![Survival Curve](image)

Continued
Laparoscopic Interaortocaval Metastasectomy for RCC

Andre Berger, Monish Aron, Kazumi Kamoi, Phillipe Koenig, Raj Goel, David Canes, Georges-Pascal Haber, Leonardo G. Lopes, Marcelo Miranda, Inderbir S. Gill

Introduction and Objectives: Patients with metastatic renal cell carcinoma (RCC) have a reported 5-year survival of 0% to 20%. Commonest site of metastasis is the lung. Patients undergone a curative resection for lung metastasis have a 54% survival rate at 5 years. Retroperitoneal lymphadenopathy was associated with shorter survival in patients with metastatic RCC. Complete surgical resection of metastatic lesions may bring survival benefits even in poor prognostic patients who are not candidates to systemic therapy. The combination of surgery and vascular endothelial grow factor targeted therapies will perhaps improve the outcomes in the management of advanced RCC. In this video we demonstrate a laparoscopic excision of an interaortocaval mass for RCC mets.

Methods: The patient is 84 year old female underwent to a right radical nephrectomy for RCC. Final pathology revealed PT3N0M0 Fuhrman 2 in 2002. In 04/07, on a routine follow –up CT a 5 cm interaortocaval hypervascular mass near the third part of the duodenum compressing the IVC was found. No other site of mets on CT abdomen, CT chest and bone scan. On 7/07, a laparoscopic excision of the mass was performed. The patient had previous atrial fibrillation and was taking Coumadin®. For this reason, she was bridged to heparin perioperatively.

Results: The patient was positioned in the right 45-degree flank position for metastasectomy. A 5 port approach was applied (four 12 mm ports, one 5 mm port), with configuration similar to employed during right partial nephrectomy. The adhesions from prior operation were lysed and the great vessels were widely exposed. The interaortocaval mass was identified and totally excised using metal clips, weck clips and suture for hemostasia.

Total operative time was 174 minutes. Estimated blood loss was 700 ml. She received 3 units of fresh plasma and 1 unit of red blood cells. The post-op course was uneventful and the hospital stay was 2 days. Histopathology revealed metastatic clear cell RCC with negative margins. At a 4-month follow up, the patent was on Sutent® therapy with no evidence of disease recurrence.

Conclusions: To our knowledge this is the first ever report of laparoscopic excision of interaortocaval mass for RCC. A laparoscopic approach for excision of RCC metastases in the vicinity of the great vessels is technically feasible. Nevertheless it should be reserved for laparoscopists with advanced skills.

Laparoscopic Partial Nephrectomy in Octogenarians

Anil A Thomas, Monish Aron, Inderbir S Gill

Introduction and Objective: As the U.S population ages, an increasing number of elderly patients will present with small renal masses. While active surveillance is a preferred option for many elderly patients, some are candidates for nephron-sparing surgery. We present our single-institution experience examining the outcomes of laparoscopic partial nephrectomy (LPN) in octogenarians.

Methods: From September 1999 to August 2007, 808 LPN were performed at our institution. Demographics, operative data, and perioperative complications in patients aged 80 years and older were compared with those in younger patients. Categorical variables were compared with Fisher’s exact test and continuous variables were analyzed using the Wilcoxon rank-sum test.

Results: A total of 772 patients younger than 80 years (range 17-79) (Group 1) and 36 patients aged 80 years and older (range 80-88) (Group 2) underwent LPN. Compared to younger patients, octogenarians had similar demographics including percent of male patients (61% vs. 72%, p = 0.2). Octogenarians tended to have larger mean tumor size (2.9 vs. 3.1 cm, p = 0.06), higher American Society of Anesthesiology (ASA) score (46% vs. 75% patients with ASA ≥ 3, p = 0.001) and higher preoperative serum creatinine (1.0 vs. 1.2 mg/dL, p = 0.0003). Mean operating time (217 vs. 217 minutes, p = 0.8), warm ischemia time (30 vs. 28 minutes, p = 0.2), estimated blood loss (267 vs. 271 ml, p = 0.4), and intraoperative complications (8% vs.6%, p = 0.8) were similar. Octogenarians tended towards increased postoperative complications (25% vs. 39%, p = 0.1), longer hospital stay (3.3 vs. 4.9 days, p = 0.07), and lesser transfusion requirements (4% vs. 0%, p = 0.3). Pathology confirmed renal cell carcinoma in 73% vs. 63%, in group 1 and 2, respectively (p = 0.5).

Conclusions: Active surveillance is the front-line option in the octogenarian population. However, in select patients, laparoscopic partial nephrectomy can be performed safely. Age alone, should not be a contraindication to LPN.
Five Year Outcomes of Laparoscopic Partial Nephrectomy

Brian R Lane, Inderbir S Gill

Introduction and Objective: Laparoscopic partial nephrectomy (LPN) is increasingly a definitive therapeutic option for patients with a small renal mass. Intermediate-term oncologic outcomes after LPN are excellent up to a mean follow-up of 3 years. Herein, we present outcomes in 56 patients, each of whom have now completed a minimum of 5 years of follow-up after LPN.

Methods: Of the 557 LPN performed at our institution, 58 patients with a localized tumor have completed >5 years since surgery. Clinical and renal functional data regarding 56 patients (97%) were obtained from medical records, radiographic reports, and patient contact via telephone.

Results: Patients averaged 64 years of age and 9% were symptomatic at presentation. Average tumor size was 2.9 cm. On histopathology, renal cell carcinoma was confirmed in 37 cases (66%), and pathologic tumor stage was pT1a in 32 patients (86%). Final surgical margin was positive for cancer in 1 patient. Median serum creatinine (sCr) pre- and post-operatively was 0.9 mg/dl and 1.0 mg/dl. No patient with normal baseline sCr undergoing elective LPN developed chronic renal insufficiency (sCr >2 mg/dl). At median follow-up of 5.7 years (5.0 to 6.9), no distant recurrence (0%) and a single local recurrence (2.7%) have been detected. Overall and cancer-specific survival was 86% and 100% at 5 years.

Conclusions: This is the initial report in the literature of oncologic and renal functional outcomes at 5 years after LPN, with excellent results comparable to open nephron-sparing surgery. At our center, LPN is an established alternative to open partial nephrectomy.

Perioperative Outcomes of Laparoscopic Partial Nephrectomy for Renal Tumors greater than 4 cm in Size

Matthew N. Simmons, Benjamin I. Chung, Inderbir S. Gill

Introduction: Laparoscopic partial nephrectomy (LPN) is gaining in application and acceptance. Herein we report our experience with LPN for renal tumors >4 cm, and compare perioperative outcomes with tumors <4 cm.

Methods: LPN was performed in 425 patients by a single surgeon between September 1999 and December 2005. Patients were grouped according to tumor diameter: <2 cm (Group I: n=89), 2-4 cm (Group II: n=278), or >4 cm (Group III: n=58). Demographics, operative data, and outcomes data within 30 days of surgery were compared.

Results: Mean tumor size was 1.5 cm, 2.9 cm, and 6 cm in groups I, II, and III, respectively. Tumor size directly correlated with central location (p<0.001), ASA score (p=0.05), intraparenchymal depth (p<0.001), and incidence of pelvicical repair (p=0.004) and heminephrectomy (p<0.001). Mean warm ischemia times were 30, 32, and 38 minutes in each group (p=0.007). Operative blood loss (219 v. 240 v. 284 ml; p=0.52) and duration of hospital stay (2.6 v. 3.7 v. 3.5 days; p=0.06) were equivalent. Carcinoma was present in 62%, 80%, and 53% of cases in each group (p=0.002). Positive cancer margins occurred in 1 and 2 patients in groups 2 and 3, respectively (0.4% vs. 3%; p=0.2). The mean postoperative serum creatinine increase in each group was 0.15, 0.23, and 0.26 (p=0.12). Mean postoperative estimated GFR in each group decreased by 11, 14, and 22 ml/min (p=0.01). The percentage of patients with preoperative >Stage 3 CKD in each group was 31%, 35%, and 44% (p=0.15). Postoperatively this increased to 52%, 55%, and 63% (p=0.27). Patients in Group III who had preoperative >Stage III CKD had increased risk for CKD stage advancement (RR = 8; p<0.001). The intraoperative complication rate was 8% in all groups. Total postoperative complication rates for each group were 11%, 24%, and 24% (p=0.03). GU complication severity and frequency did not correlate with tumor size.

Conclusions: Appropriately selected patients with renal tumors >4 cm in size can safely and efficaciously undergo LPN with outcomes comparable to those achieved for smaller renal tumors. Adequate laparoscopic expertise is a prerequisite.
Long-term Oncologic and Renal Functional Outcomes for Laparoscopic Partial versus Laparoscopic Radical Nephrectomy for RCC >4cm

Matthew N. Simmons, Christopher J. Weight, Benjamin T. Larson, Inderbir S. Gill

Introduction: To evaluate long-term oncologic and renal functional outcomes in patients undergoing laparoscopic partial nephrectomy (LPN) and radical nephrectomy (LRN) for pT1b, T2, and T3a renal cell carcinoma (RCC) >4cm.

Methods: Data were analyzed from a prospectively-maintained database for patients undergoing LPN (n=35) or LRN (n=75) for RCC over a 5-year period (2001–2005). All 110 patients had a radiological tumor size >4cm and pathologically-confirmed primary RCC. Patients with pre-existing nodal involvement, metastasis, or stage 5 chronic kidney disease (CKD) were excluded.

Results: Patient demographics and preoperative renal function were equivalent in all groups. LRN was performed more commonly in the first 3 years (60% LRN vs. 37% LPN) while LPN was performed more commonly in the latter 2 years (63% LPN vs. 40% LRN). The LRN group had a mean tumor diameter of 5.3cm compared to 4.9cm in the LPN group (p=0.04). Mean warm ischemia time in the LPN group was 37 minutes. Stage pT1b tumors were more common in the LPN group (83% vs. 57%; p<0.001), and pT3a tumors were more common in the LRN group (33% vs. 9%; p<0.001). Clear cell pathology accounted for 86% and 66% of tumors in the LRN and LPN groups, respectively (p=0.006). Median follow-up was 3.3 years (range: 2-6.7) in the LPN group, and 4.4 years (range: 2-6.5) in the LRN group (p=0.1). Both groups had similar overall mortality (11% in both groups), cancer-specific mortality (3% vs. 1%; p=0.3), and recurrence rates (6% vs. 3%; p=0.3). Estimated GFR was better preserved in the LPN group compared to the LRN group (decreases of 13ml/min vs. 24ml/min; p=0.03). More LRN patients experienced a 2-stage increase in CKD stage from baseline (12% vs. 0%; p<0.001).

Conclusions: In appropriately selected patients with T1b and T2 renal cancer, LPN provides long-term oncologic efficacy comparable to LRN. Renal outcomes are superior after LPN indicating functional preservation compared to LRN. Given our recent further decrease in warm ischemia times during LPN to 14 minutes (J Urol, in press February 2008), improved renal functional outcomes following LPN can be anticipated in the future.

Diaphragmatic Repair and/or Reconstruction during Upper Abdominal Urological Laparoscopy

Monish Aron, Jose R Colombo Jr, Burak Tuma, Robert J Stein, Georges-Pascal Haber, Inderbir S Gill

Purpose: To present our experience with and the technique of laparoscopic mesh reconstruction or suture repair of intentional resection or intraoperative injury of the diaphragm.

Materials and Methods: In a 10-year (1997-2006) review of 1850 upper abdominal renal and/or adrenal laparoscopic procedures at our institution, 13 patients (0.7%) sustained a diaphragmatic entry. These included iatrogenic injury (n=7, 0.4%), deliberate laparoscopic excision of a portion of the diaphragm (n=2), and diaphragmatic incision during transthoracic adrenalectomy (n=4). Laparoscopic repair techniques involved primary suture-repair (n=11) and primary reconstruction with a synthetic graft (n=2). A red rubber catheter and water-seal system was employed to primarily evacuate the pneumothorax. Our technique of laparoscopic repair of diaphragm is shown in figure 1.

Results: Inadvertent diaphragmatic injury (n=7) occurred during transperitoneal (n=6) or retroperitoneal (n=1) laparoscopy (partial nephrectomy-4, radical nephrectomy-2, adrenalectomy-1). Diaphragmatic breach occurred due to hook electrocautery (5), trocar insertion (1) and liver retraction (1). Deliberate diaphragmatic excision and mesh reconstruction (n=2) was performed after en bloc excision of diaphragm during radical nephrectomy (n=1) and during excision of a metastatic diaphragmatic nodule (n=1). Four transthoracic transdiaphragmatic adrenalectomies (TTA) were completed successfully without any intraoperative complications. All cases were completed laparoscopically without open conversion. Chest tube was placed prophylactically in the initial 2 patients undergoing TTA. Patient details are shown in table 1.

Conclusions: Laparoscopic and transthoracic repair/reconstruction of the diaphragm is safe and effective.

continued
### Section 3

**Female Urology/Voiding Dysfunction**

#### Table 1: Laparoscopic repair of iatrogenic injury to the diaphragm during upper abdominal urological laparoscopy

<table>
<thead>
<tr>
<th>S.No</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Surgery</th>
<th>Side</th>
<th>Approach</th>
<th>Cause of diaphragm injury</th>
<th>Other injuries</th>
<th>Postoperative pneumothorax</th>
<th>Chest tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>Radical Nephrectomy</td>
<td>Left</td>
<td>Retro</td>
<td>Throat placement</td>
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<td>2</td>
<td>74</td>
<td>F</td>
<td>Partial Nephrectomy</td>
<td>Right</td>
<td>Trans</td>
<td>Liver retractor</td>
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<td>3</td>
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<td>M</td>
<td>Radical Nephrectomy</td>
<td>Left</td>
<td>Trans</td>
<td>Hook electrocautery</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>4</td>
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<td>Partial Nephrectomy</td>
<td>Left</td>
<td>Trans</td>
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<td>Right</td>
<td>Trans</td>
<td>Hook electrocautery</td>
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<td>Hook electrocautery</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>65</td>
<td>M</td>
<td>En bloc excision of portion of diaphragm during radical nephrectomy for synchronous RCC</td>
<td>Left</td>
<td>Trans</td>
<td>Deliberate excision</td>
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<td>9</td>
<td>55</td>
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<td>En bloc excision of portion of diaphragm during radical nephrectomy for synchronous RCC</td>
<td>Right</td>
<td>Trans</td>
<td>Deliberate excision</td>
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<td>10</td>
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<td>M</td>
<td>Transperitoneal adrenalectomy</td>
<td>Right</td>
<td>Thoracic</td>
<td>Deliberate incision</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td>11</td>
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<td>M</td>
<td>Transperitoneal adrenalectomy</td>
<td>Right</td>
<td>Thoracic</td>
<td>Deliberate incision</td>
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*Retro-Retropitoneal, Trans-Transperitoneal, RCC-renal cell carcinoma*
Robotic Abdominal Sacrocolpopexy / Sacrouteropexy Repair of Advanced Female Pelvic Organ Prolapse: Utilizing POP-Q based Staging and Outcomes

Daneshgari F, Kefer JC, Kaouk J

Objectives: To assess the management of advanced pelvic organ prolapse (POP) with robotic-assisted abdominal sacrocolpopexy (RASC) and evaluate outcomes using the POP quantification scale (POP-Q).

Patients and Methods: Women with symptomatic stages III and IV POP were evaluated at our institution. After complete clinical assessment, including POP-Q-based physical examination and urodynaminc studies, the patients underwent RASC with or without anti-incontinence surgery in the presence (sacrouteropexy) or absence of uterus (sacrocolpopexy). Follow-up examinations at 3 and 6 months included a POP-Q-based examination.

Results: Fifteen women were consented for RASC; 12 underwent successful RASC, one required conversion to laparoscopic ASC, one to open ASC, and one to transvaginal repair. The mean (range) patient age was 64 (50–79) years. Before surgery, the mean POP-Q stage was 3.1 (3–4) and the POP-Q values for the anterior (Aa, Ba), posterior (Ap, Bp) and apex (C) of the vagina were: Aa - 0.9, Ba + 1.0, Ap - 1.0, Bp + 1.3, and C +2.1. After surgery, the mean POP-Q stage was 0 and the POP-Q values had improved to Aa – 2.29, Ba – 2.29, Ap – 2.65, Bp – 2.65, and C – 8.28. The mean (range) estimated blood loss during surgery was 81 (50–150) mL. The mean hospital stay was 2.4 (1–7) days. Seven patients had concurrent placement of a mid-urethral sling and one patient had a concurrent Burch colposuspension.

Conclusions: These early results show that RASC is safe and efficacious, and that its anatomical outcomes compare favourably to the reported results for open or laparoscopic ASC.
Urethral Diverticula: A Clinicopathological Study of 50 Cases

Anil A Thomas, Una Lee, Sandip Vasavada, Howard Goldman, Raymond R Rackley, Donna E Hansel

Introduction and Objective: Urethral diverticula are extremely uncommon and occur predominantly in females. Although the majority of surgically resected urethral diverticula are benign, there are reports of malignant transformation. We examined a large series of surgically resected urethral diverticula at our institution to determine associated histopathologic findings and subsequent clinical outcomes in this population.

Methods: A total of 50 patients underwent urethral diverticulectomy at our institution between 1981 and 2006. The clinical findings and outcomes were determined by retrospective analysis of medical records. Pathologic slides were reviewed from all cases to determine associated histopathologic findings.

Results: Patient age ranged from 2 to 75 years (mean 44 years, median 42 years), with peak incidence occurring in the 3rd and 4th decades. Forty-seven patients were female and 3 patients were male. The majority of patients were Caucasian (33/50; 66%), whereas only one third of patients were African-American (17/50; 33%). Clinical signs and symptoms were reported in 38 patients (76%). The most common clinical presentations included urinary incontinence (18/38; 47%), dysuria (14/38; 37%), recurrent urinary tract infection (9/38; 24%), pelvic and urethral pain (9/38; 24%), frequency (8/38; 21%), and dyspareunia (6/38; 16%). Diverticular size was reported in 32 cases (32/50; 64%) and ranged from 0.5 to 3.6 cm (mean 2.0 cm). Six cases circumferentially involved the urethra. On histopathologic examination, most cases demonstrated reactive findings, including acute inflammation (10/50; 20%), chronic inflammation (35/50; 70%), squamous metaplasia (15/50; 30%), and erosion with granulation tissue formation (16/50; 32%). Seven cases demonstrated the presence of nephrogenic adenoma (7/50; 14%). Although no carcinoma was identified in these specimens, 1 patient demonstrated extensive intestinal metaplasia (1/50; 2%) and 1 patient demonstrated a villous adenoma with low-grade dysplasia (1/50; 2%). Clinical follow-up was available on 38 patients (38/50; 76%) and ranged from 1 to 251 months (mean 54 months, median 17 months). No patient demonstrated subsequent recurrence or malignant transformation on follow-up.

Conclusions: Most cases of surgically resected diverticula demonstrate reactive changes. Only 2 patients demonstrated atypical findings, including extensive intestinal metaplasia and villous adenoma. Long-term follow-up demonstrated a benign course in all patients examined.

Colpocleisis for the Treatment of Stage IV Pelvic Organ Prolapse: Key Points in the Surgical Technique

Una J Lee, Sarah McAchran, Sandip Vasavada

Introduction and Objective: Pelvic organ prolapse (POP) remains a challenging clinical problem for the elderly. This video presents the key points in the surgical technique for total colpocleisis for the correction of symptomatic stage IV POP in an elderly woman.

Methods: The patient in this video is a 91 year old woman with multiple medical comorbidities, a previous hysterectomy, and who did not desire coital function. She has urinary symptoms of daytime frequency and nocturia. By physical exam, she had complete eversion of the vagina, Stage IV POP. She was unable to retain a pessary. She was an ideal candidate for this obliterator procedure.

Results: Colpocleisis is performed in lithotomy position. Foley, rectal pack and Scot ring retractor are placed. A four quadrant incision was marked prior to denudement of the vaginal epithelium. The incision is extended to just below to the bladder neck, distally toward the apex, and posteriorly toward the rectum. The lateral extent is anterior to the lateral sulcus. The extent of the cystocele and enterocele is demonstrated. After hydrodissection, the vaginal epithelium is completely excised from the underlying vaginal muscularis and endopelvic fascia. A combination of blunt and sharp dissection is used to mobilize the vaginal wall, with care not to enter the enterocele sac. Vaginal skin is excised, and careful hemostasis is achieved. The POP is everted with a series of circumferential purse string sutures of 2.0 PDS. The suture is tied as the prolapse is reduced. This is repeated until the entire POP is reduced. Anterior colporrhaphy stitches are placed for correction of the remaining cystocele. A concomitant mid-urethral sling can be placed for the treatment of stress urinary incontinence. Cystoscopy is performed to confirm bilateral ureteral patency and no bladder injury. Posterior perineal colporrhaphy and levator placcation are performed, to provide a buttress of support to prevent recurrent POP. The remaining vaginal depth is approximately 3-4 cm. This patient had a successful repair and no post op complications or recurrence. The literature reports success rates of 91-100%. A 2007 prospective study by Barber et al demonstrated colpocleisis results in a high quality of life with minimal regret.

Conclusions: For the treatment of POP in the medical unstable, sexually inactive elderly women with severe symptomatic POP, colpocleisis may be the preferred procedure for its low morbidity and consistently durable results. Colpocleisis should be in the every reconstructive surgeon’s armamentarium.
Comparison of Two Methods of Teaching the Pelvic Organ Prolapse Quantification (POPQ) Scale

Una Lee, MD, Sarah McAchran, MD, Firouz Daneshgari, MD

Introduction and Objective: Evaluation and quantification of the degree of POP remains a clinical challenge. In 1996, the International Continence Society (ICS) and International Urogynecological Association (IUGA) developed a standardized method, termed the pelvic organ prolapse quantification scale, the POPQ. Despite the strength of evidence for reproducibility of the POPQ, it has not been widely used by urologists. A method of teaching the POPQ is needed that is simple and effective in order to increase its use. The ABCs of POPQ is a pneumonic to help people remember the anatomic points of the POPQ. The objective is to compare the efficacy of two teaching methods for the POPQ.

Methods: The participants of the 2007 National Urology Resident Preceptorship Program in Female Pelvic Medicine & Reconstructive Surgery were given instruction on the POPQ using two methods (1) ABCs of POPQ lecture and (2) the ICS POPQ video in a cross over design. Participants were randomized to one of two groups, determining whether they received the ABC's of POPQ lecture first or the ICS video first. After each method, the participants answered a questionnaire which included: age, gender, PGY level, previous exposure to the POPQ, time since exposure to the POPQ, questions regarding their understanding and confidence of the POPQ, and two clinical cases of POP. Associations of carryover effect and calendar effect were evaluated with Pearson Chi Square test or Fisher's exact and Wilcoxon rank sum test. Associations of the method effect were performed with McNemar Chi Square test and paired t-test. P<0.05 was considered significant. This study was approved by the IRB.

Results: Of the total 41 participants, 23 participants were in group one and received the ABC's of POPQ lecture first. 18 participants were in group 2 and watched the ICS video first. There were no significant differences in age, gender, PGY level, or prior POPQ exposure. The largest represented group was PGY 4 urology residents. The groups were 70-72% male, and 28-30% female. Given that there is evidence for carryover effect, the overall results for the first time period are presented. There were no significant differences in outcomes of understanding and confidence, as well as in demonstrating the learned knowledge on 2 cases. The ABC's of POPQ lecture produced equivalent outcomes when compared to the ICS video.

Conclusion: Simplified validated teaching methods are needed for effective medical education. The ABC’s of POPQ is as effective a teaching method as the video produced by the ICS to teach the POPQ.

Outcomes of Obstructing Slings for Treatment of Incontinence in Women with Multiple Sclerosis

Mia A. Swartz, Wesley G. Kong, Raymond R. Rackley, Sandip P. Vasavada, Howard S. Goldman

Introduction and Objective: Women with multiple sclerosis (MS) and incontinence are challenging patients. Severe cases are sometimes treated with urinary diversion and obstructing slings. However, our review of the literature did not reveal any studies that addressed the use of obstructing urethral slings in this population. Our aim was to review use of obstructing slings in women with multiple sclerosis and refractory urge or mixed incontinence that have had previous urinary diversion.

Methods: Following institutional review board approval, we performed a retrospective study with follow-up telephone calls. We identified all women with MS from 2002 to present who underwent an obstructing sling procedure. A chart review was performed where comprehensive peroperative data was collected. The operative outcome was considered a failure if urine leakage was subjectively the same as before surgery or a further anti-incontinence surgery was required.

Results: We identified seven women with a mean age of 52.1 years (range 41-61). Most (N=4) had a suprapubic tube or an iliovesicostomy diversion (N=3), and the majority (71.4%) were on anticholinergic medication. Treatment with an obstructing sling was performed if they had refractory urge or mixed urinary incontinence despite urinary diversion. The mean postoperative follow-up after the obstructing sling was 26.4 months (range 5-60). The two patients (28.6%) with missing outcome data from the chart were successfully contacted. One patient (14.3%) was deceased, one (14.3%) declined to participate and three (42.9%) could not be contacted, but clear outcomes were available from the chart for all five of these patients. Three (42.9%) patients required a bladder neck closure–two were performed at 3 months and one at 32 months. Two (28.9%) patients had leakage postoperatively that was unchanged from preoperative leakage and declined further intervention. Two women (28.9%) are dry at 31 and 24 months of follow-up.

Conclusions: Use of obstructing slings for treatment of refractory urge or mixed incontinence in patients with MS with previous urinary diversion was not successful in 70.4% of our patients. It is difficult to perform large prospective studies in this population, and our study is limited by small sample size and retrospective design. However, we would advise future patients that the chance for incontinence cure is relatively low using an obstructing sling.
Is Diabetes a Risk Factor for All Components of Female Pelvic Floor Disorders?

Hardeep Phull, Wesley G Kong, Mia Swartz, Sarah McChran, Adrian V Hernandez, Firouz Daneshgari

Introduction and Objective: Female Pelvic Floor Disorders (FPFD) including pelvic organ prolapse (POP), Urinary Incontinence (UI), Stress Urinary Incontinence (SUI), and Fecal Incontinence (FI) often coexist and may share common risk factors. Diabetes mellitus (DM) is recognized as a key risk factor for UI and Sexual Dysfunction (SD). Our aim was to examine the cross sectional prevalence of all components of FPFD and SD among type I and II DM women in comparison to non-DM controls.

Methods: Female patients with or without the diagnosis of DM were recruited. Subjects without lower urinary tract symptoms (LUTS), including UI or SD, were recruited from the Department of Endocrinology (Group A), while those with LUTS were recruited from the Department of Urology (Group B), at the Cleveland Clinic. Euthyroid patients were recruited as age and sex matched controls (Group C). Subjects with other known causes of LUTS such as infection or neurogenic conditions were excluded. All subjects completed the Pelvic Floor Distress Inventory (PFDI) and Female Sexual Function Index (FSFI). Association between components of FPFD and SD among type I and II DM were examined by Fischer exact test to determine significant differences (p < 0.05) between the DM groups.

Results: A total of 106 women (range 30-76 y) were enrolled into Groups A (n=69), B (n=13), and C (n=24). The prevalence of FPFD was higher in Group B vs. Group A, but there was no significant difference overall: UI (69% vs. 45%), SUI (69% vs. 42%), POP (30% vs. 5%), FI (52% vs. 22%). Type II DM prevailed as the more common DM type (>80%) for each of the disorders and its occurrence was not significantly different among Groups A and B. However, type I DM was found exclusively in Group A for UI (20%), SUI (11%), and FI subjects (29%) (p < 0.02). There was no significant association between FPFD and DM duration. With regards to sexual function, there was no difference in desire, satisfaction, or pain between the DM groups and controls. However, there was less arousal for DM subjects with UI and SUI when compared to controls: 5.5 ± 7.3 vs. 10.8 ± 6.8 (p < 0.05), and 4.0 ± 6.6 vs. 11.0 ± 4.9 (p < 0.01), respectively. There was also less lubrication and orgasm among DM SUI patients compared to controls: 3.4 ± 6.4 vs. 13.9 ± 6.9 (p < 0.04), and 2.9 ± 5.3 vs. 9.7 ± 4.7 (p < 0.05), respectively.

Conclusions: UI (both urge and stress) and FI, but not POP are more prevalent in type I DM women for which DM duration is not a contributing factor. DM may play a role in SD by decreasing overall arousal, lubrication, and orgasm. The association between DM and components of FPFD and SD warrants further investigation.

Use of the Mid-Urethral Sling to Treat Stress Urinary Incontinence in Women with Multiple Sclerosis

Wesley G Kong, Mia A Swartz, Sandip Vasavada, Raymond R Rackley, Howard B Goldman

Introduction and Objective: Urinary incontinence is common among women with multiple sclerosis (MS). Incontinence is often due to neurogenic detrusor overactivity but can be multifactorial. This population is also at risk for developing stress urinary incontinence (SUI). Mid-urethral slings (MUS) are emerging as the new gold standard for treatment of SUI and little is known about their use in patients with MS. Our aim was to review outcomes of MUS placement in patients with stress urinary incontinence.

Methods: Following institutional review board approval, we performed a retrospective study. We identified all women with MS who underwent a MUS procedure from 2002 to present. A chart review was performed where comprehensive perioperative data was collected. A standardized telephone call was placed to each patient in order to administer questionnaires. We used the global assessment of severity and improvement (PGI-S and PGI-I, respectively) because these single-question instruments each represent patient-determined outcomes. The urogenital distress inventory-6 (UDI-6) was used to assess current urinary symptoms.

Results: We identified seven women with a mean age of 51 years (range 42-72) who had a MUS procedure with urodynamic (N=4) or subjective (N=3) SUI. The mean postoperative follow-up was 25.6 months (range 10-49). Four women (57%) were spontaneously voiding, two (28%) were on self-catheterization and one (14%) had an ileovesicostomy. All patients had preoperative urodynamics with normal bladder capacity. Six (86%) women reported no further SUI. Two women (29%) reported bothersome urge incontinence that was present preoperatively, and no patients had de novo urge incontinence. One patient (14%) experienced postoperative urinary retention which resolved within four weeks. Median score was 2 for PGI-S (range 1-4), 3 for PGI-I (range 1-5) and 8 for UDI-6 (range 0-15). Question 3 of the UDI-6 which asks about the symptom of stress urinary incontinence had a median value of 0 (0-3).

Conclusions: Use of the MUS to treat SUI in women with MS can be successful. While this population of patients may be at a higher risk for postoperative urinary retention, there were no cases of de novo urge incontinence. Based on our experience, we would counsel patients that while a tension-free sling may correct SUI, it will not address urge symptoms or cause global symptom improvement.
Role of Urodynamics on Clinical Decision-Making in Patients with Urinary Incontinence and Voiding Dysfunction

Hardeep Phull, Adonis Hijaz, Howard Goldman, Adrian Hernandez, Tara Frenkl, Courtenay Moore, Louis Moy, Raymond Rackley, Sandip Vasavada, Firouz Daneshgari

Introduction and Objective: The role of urodynamic studies (UDS) in the management of urinary incontinence (UI) and voiding dysfunction (VD) remains controversial. We conducted a prospective study to investigate how UDS influences clinical decision-making for women with these disorders and hypothesized that UDS alters physicians’ diagnostic impressions.

Methods: Female patients with VD, UI, or pelvic organ prolapse (POP) were recruited into this IRB-approved study. Subjects with pelvic pain, previously treated stress urinary incontinence (SUI), or disabilities were excluded. After completing the Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7), participants were randomly assigned to physicians and some underwent UDS as part of normal workup. Physicians rendered their clinical diagnosis, treatment plan, and level of confidence with their decision after: 1) initial physical exam 2) reviewing questionnaires 3) reviewing UDS results. Statistical analysis evaluated changes between these time points, using Wilcoxon Signed-Rank test and McNemar’s test for paired proportions, with p<0.05 indicating significant differences.

Results: Among the 141 patients recruited, median age and parity were 59 and 2.0, respectively. The most common initial diagnoses were mixed urinary incontinence (MUI) (23%), POP (15%), and VD (14%). Patients’ median UDI-6 and IIQ-7 scores were each 10.0. Exposure to questionnaires resulted in refinement of the diagnosis in 41 patients (28%) and treatment plan in 37 patients (26%), which was not significantly different. However, the physicians’ confidence level in their diagnosis and treatment plan significantly improved from 8.1 ± 1.2 and 7.9 ± 1.3 after initial exam to 8.5 ± 1.0 and 8.4 ± 1.0 after questionnaires, respectively (both p<0.001). UDS was completed in 76/141 (54%) of the patients and resulted in changes to the final diagnosis in 31/76 of the subjects (41%) and treatment plan in 20/76 (26%). There was an overall increase in diagnosis of SUI and VD, but a decrease in diagnosis of MUI (p<0.05). There was also an overall decrease in treatment with sling surgery and anticholinergic medications (p<0.05). The physicians’ confidence level further improved to 9.1 ± 1.1 and 9.0 ± 0.8 (p<0.001).

Conclusions: Validated questionnaires improved the confidence of the physician in the clinical diagnosis and treatment plan. Additional exposure to UDS improved confidence further and also changed the diagnoses of SUI, MUI, and VD as well as the treatment plan.

Mice Models of Obesity for Studies of Lower Urinary Tract Dysfunction and Pelvic Floor Disorders Associated with Obesity

Una Lee, Gregory Gasbarro, Yi Hao Lin, Guiming Liu, Mei Li, Michael Kavran, Firouz Daneshgari

Introduction: Obesity is one of important risk factors for urinary incontinence (UI), lower urinary tract dysfunction and female pelvic floor disorders (FPFD). However, the mechanisms of association between obesity and these common pathologies remain unknown. Animal models represent a valuable tool in the hierarchy of research for investigation of mechanisms of diseases. We have identified and bred offsprings of two mice models as the potential models for studies of FPFD and obesity; the ob/ob mouse which is a leptin-deficient hyper-insulinemic mouse that develops obesity at an early age due to type 2 diabetes, and the mouse homozygous for the Low Density Lipoprotein Receptor mutation (LDLR-/-) that are used to study atherosclerosis, hypercholesterolemia, and obesity with diet-induced diabetes. We hypothesized that the obese mice will have an abnormal voiding pattern compared to non-obese controls.

Methods: There were 4 groups of age matched female mice studied: Low Density Receptor Knockout (LDLR-/-), leptin deficient (ob/ob), double mutant (LDLR-/-; ob/ob), and C57Bl/6 control mice. Each of the LDLR-/-; ob/ob and LDLR-/- knockout mice strains were bred and confirmed to be knockout mice by genotyping. The obese mice were fed a high fat diet. The ob/ob and C57Bl/6 mice were obtained from Jackson Laboratories. The animals’ age, weight, and HgbA1c was recorded on day of testing. Each animal underwent 24 hour frequency voiding testing in mouse metabolic cages with free access to food and water. Urinary events were recorded during daytime and nighttime. Kruskal-Wallis test was used to compare medians across groups.

Results: There was no difference in the ages of the 4 groups of mice. Mean ages ranged from 11.9 to 13.4 weeks. There were significant differences in the weight of the 4 groups of mice (P<0.001). LDLR-/- ob/ob mice (n=7) and ob/ob mice (n=10) were 2.48±2.5 times the weight of controls. The LDLR-/- mice (n=18) did not show a significant increase in weight compared to controls. As expected, the obese mice with the ob/ob knockout (LDLR-/- ob/ob and ob/ob mice) demonstrated an elevated HgbA1c consistent with DMII (6-6.5), when compared to control and LDLR-/- mice (3.9) (p=0.03). For overall voiding characteristics across groups, the double mutant LDLR-/- ob/ob mice voided less frequently (p=0.1) and had less total urine output (p=0.003). This trend of fewer urinary events (p=0.08) and less total urine (p=.01) was also demonstrated in
the daytime for the LDLR−/− ob/ob mice. Nighttime voiding for the LDLR−/− ob/ob mice also demonstrated fewer urinary events ($p=0.2$) and lower total urine ($p=0.007$). The other obese mice model (ob/ob) with DMII demonstrated more frequent voiding and greater urine output overall ($p=0.1; p=0.003$) and during daytime ($p=0.08; p=0.01$), compared to the other three groups. There was a significant difference noted between daytime and nighttime voiding within the same groups for the ob/ob mice, LDLR−/− mice, and the control mice ($p<0.05$). There was no difference in mean void volume across groups.

**Conclusions:** Both obese mice models demonstrated abnormal voiding behavior. The obese mice with hypercholesterolemia and diabetes demonstrated less frequent voiding and less total urine output. The obese mice with diabetes demonstrated more frequent voiding and more total urine output. Further characterization of the lower urinary tract and pelvic floor function of our obese mice models is warranted.

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**Is Diabetes a Risk Factor for All Components of Female Pelvic Floor Disorders?**

*Hardeep Phull, Wesley G. Kong, Mia Swartz, Sarah McAchran, Adrian V. Hernandez, Firouz Daneshgari*

**Introduction and Objective:** Female Pelvic Floor Disorders including pelvic organ prolapse (POP), Urinary Incontinence (UI), and Fecal Incontinence (FI) often co-exist and may share common risk factors. Diabetes mellitus (DM) is recognized as a key risk factor for UI and Sexual Dysfunction (SD), and its incidence is rising. Our aim was to examine the cross sectional prevalence of all components of FPFD including UI, FI, POP and SD among type I and II diabetic women in comparison to non-diabetic controls.

**Methods:** Female subjects with or without the diagnosis of DM were recruited. Subjects without lower urinary tract symptoms (LUTS), including UI or SD, were recruited from the Department of Endocrinology (Group A), while subjects with LUTS were recruited from the Department of Urology (Group B), at the Cleveland Clinic. Age and sex matched control subjects were recruited from the Department of Endocrinology from a population of euthyroid patients (Group C). Subjects with other known causes of LUTS such as infection or neurogenic conditions were excluded. All subjects completed the Pelvic Floor Distress Inventory (PFDI) and Female Sexual Function Index (FSFI), which was stratified by the following domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. Association between components of PFDI including pelvic organ prolapse (POP), Urinary Incontinence (UI), Fecal Incontinence (FI) and sexual function were examined by Fischer exact test to determine significant differences ($p < 0.05$) between the DM groups, stratified by DM type and duration.

**Results:** A total of 106 women (range 10-76 y) were enrolled into Groups A ($n=69$), B ($n=13$), and C ($n=24$). Although the prevalence of FPFD was higher in Group B than Group A, there was no significant difference overall: UI (69% vs. 45%), SUI (69% vs. 42%), POP (30% vs. 5%), FI (52% vs. 22%). Type 2 DM prevailed as the more common DM type (>80%) for each of the disorders and there was no difference in its occurrence between Groups A and B. However, type 1 DM was found exclusively in Group A for UI (20%), SUI (11%), and FI subjects (29%) ($p < 0.02$). There was no significant association between FPFD and DM duration. With regards to sexual function, since there were no differences between DM groups, their FSFI scores were averaged and compared overall to control. Subsequently, there was no difference in desire, satisfaction, or pain between the DM group and controls. However, there was less arousal for DM subjects with UI when compared to controls ($5.5 \pm 7.3$ vs. $10.8 \pm 6.8$, $p < 0.05$). The same trend was observed for arousal in subjects with SUI ($4.0 \pm 6.6$ continued
vs. 11.0 ± 4.9, p < 0.01). There was also less lubrication and orgasm among SUI patients in the DM group compared to controls: 3.4 ± 6.4 vs. 13.9 ± 6.9 (p < 0.04), and 2.9 ± 5.3 vs. 9.7 ± 4.7 (p<0.05), respectively.

**Conclusions:** Urinary Incontinence (both urge and stress), and FI, but not POP are more prevalent in type I diabetic women for which the duration of diabetes is not a contributing factor. DM may play a role in sexual dysfunction by decreasing overall arousal, lubrication, and orgasm. The association between DM and components of FPFD warrants further investigation.

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**Mechanisms of Mid-urethral Sling Effects; Role of Suburethral or Lateral Support for Anti-Incontinence Effects**

*Sarah McAchran, Una Lee, Adonis Hijaz, Mike Kavran, Yi-Hao Lin, Margot Damaser, Firouz Daneshgari*

**Introduction and Objective:** Previous studies in a rat model of mid-urethral sling have suggested that the suburethral portion of the mid-urethral sling may not be necessary to produce the effect of increased urethral resistance as measured by leak point pressure (LPP), but may contribute to morbidities associated with slings including the voiding dysfunction (Hijaz, J of Urology 2005). In response to these findings, a composite sling model was developed to further test the hypothesis that the lateral support, rather than the suburethral support is all that is required to produce the anti-incontinence effects of the sling. The objective of this study was to evaluate the short and long-term efficacy of a novel composite mid-urethral type sling in a rodent model of stress urinary incontinence (SUI).

**Methods:** SUI was created in 28 female Sprague-Dawley rats by bilateral pudendal nerve transaction (PNT) under ketamine/xylazine anesthesia as described previously. The animals then were randomly assigned to short term (24 hours) or long-term (4 weeks) groups and underwent placement of either traditional mid-urethral sling (n=10) by placement of a 2 x 0.3cm strip of Prolene (Ethicon, Somerville, New Jersey) mesh at the mid-urethral level; a novel composite sling (n=10) where no vaginal dissection is performed and the sling is modified to have no suburethral effect; or sham sling (n=8). Within 24 hours or four weeks later, under urethane anesthesia, a suprapubic tube was placed and LPP was measured using a Crede maneuver, as described previously. In each animal LPP was measured 5-6 times and the mean was taken. Pairwise differences in LPP between the groups were calculated using the Wilcoxon signed rank test with p<0.05 considered significantly different.

**Results:** In the long-term group, the traditional sling increased LPP significantly compared to the sham group (54.83 vs. 38.16 cm H2O, respectively, p = 0.0017). The composite sling did not increase the LPP compared to the sham group (36.83 vs. 38.16 cm H2O, respectively, p=0.7072), as depicted below. Neither traditional nor composite sling increased the LPP above the sham in the short-term group.

**Conclusions:** Suburethral segment of sling is needed to restore the LPP in female rats models of SUI. In early studies, it does not appear that the sling without the suburethral support would be as effective at restoring LPP. Further refinements in design may help us to clarify the utility of this novel composite sling model.

continued
Virtual Reality Presentation of Normal Female Pelvic Floor

Li X, Veniero JC, Chen CCG, Barber M and Damaser MS

Introduction: Stress urinary incontinence and pelvic organ prolapse affect millions of American women. The cause still remains elusive and part of the reason is the limited knowledge of the anatomy of the female pelvic floor due to its complexity. In order to better understand the anatomy, we are building a virtual reality (VR) model of normal female pelvic floor based on high resolution magnetic resonance (MR) images. We present our initial results with different segmentation techniques as well as with building the model for virtual reality.

Methods: T2 weighted high resolution MR images were used to build the models of bladder, vagina, rectum, urethra, uterus and pelvic bones. Contrast agent-enhanced MR images were used to build the model of vessels. T2 weighted images together with out-of-phase images were used to build the models of obturator and levator ani muscles. The images were preprocessed with a nonlinear anisotropic filter and a local contrast enhancement filter. A contour-based semi-automatic segmentation method was used to segment the bladder as a test organ, since it has high contrast in T2 weighted images. Other organs such as vagina, urethra, uterus, rectum and muscles, we used manual segmentation. The 3D region grow method was applied for automated segmentation of vessels. The segmented organs, muscles and tissues were built into a VR model using Amira 4.11 and were verified by experts from radiology and gynecology.

Results: Three samples have been segmented and a VR model has been created. The results were verified by the experts from radiology and urology and a good result was achieved. The segmented organs can be viewed simultaneous with reviewing the original MR scans.

Conclusion: High resolution MR provides more information of the anatomy of female pelvic floor than other imaging methods; however, it still shows only limited details of soft tissue structures. Nonetheless, this method of viewing the pelvic floor organs and tissues may have the potential for application in research, education, and clinical practice.
Urodynamic Function and Expression of Neurotrophins after a Maternal Childbirth Injury Model of Vaginal Distension and Pudendal Nerve Crush in Rats

Damaser MS, Lin DL, Kerns JM, Sypert DF, Eggers L and Pan HQ

Hypothesis / Aims of Study: Clinically, during vaginal delivery of children, the muscles, nerves, ligaments and organs of the pelvic floor are compressed and injured. This includes the external urethral sphincter (EUS), the striated muscle of the urethra, which can become hypoxic during vaginal distension. In addition, the pudendal nerve, which innervates the EUS, courses through Alcock’s canal and can be trapped and injured during vaginal childbirth. Thus, the injuries incurred during vaginal childbirth represent a unique neuromuscular injury: one in which both the target organ (the EUS) and its innervation are injured simultaneously. These two injuries, along with injuries to other tissues of the pelvic floor are strongly correlated with later development of stress urinary incontinence (SUI). Neurotrophins are upregulated after nerve injury and down regulated after muscle injury and may provide the insight into mechanism of later SUI development due to pelvic floor injuries. Animal models of the maternal injuries in childbirth that can lead to pelvic floor dysfunction have focused on either vaginal distension (VD) or pudendal nerve crush (PNC). However, since the pudendal nerve is trapped and injured in Alcock’s canal and simultaneous with pelvic floor muscles injuries during vaginal distension, a dual injury model may best represent the injuries seen clinically. The objective of this project was to investigate urethral function, urethral anatomy, and expression of neurotrophins after a dual injury model consisting of both PNC and VD.

Study Design, Materials and Methods: Virgin Sprague-Dawley rats (n=140) were divided into 4 groups and underwent VD using a modified Foley catheter that was inserted into the vagina and filled with saline (3 ml) for 4 hours (VD). PNC consisted of a standardized bilateral compression of the nerve in the ischiorectal fossa (PNC), both injuries (PNC+VD), or neither (C). One day after injury, neurotrophin (BDNF, NT-4, Trk-B and NGF) expression in the external urethral sphincter (EUS) was investigated by immunohistochemistry (n=20). Four, 10, and 21 days after injury, urethral function was assessed by leak point pressure in all 4 groups: the bladder was slowly depressed while bladder pressure was measured via a suprapubic catheter implanted 2 days prior. The increase in external abdominal pressure at leakage, the leak point pressure (LPP), was taken to indicate urethral resistance to flow. Data was analyzed using a two ANOVA followed by a Student-Newman-Keuls test (p=0.05). Data is presented as mean ± standard error of the mean. Immediately after LPP measurement, the rats were euthanized and the urethra was dissected at each of the 4 time points and was used in qualitative histological analysis. Immunohistochemistry results were analysed qualitatively.

Results: There were no significant differences in LPP in the C group over time. Four days after injury, all 3 injury groups had significantly decreased Pabd compared to C rats. There were no significant differences in LPP between the injury groups. Ten days after injury, VD rats had recovered to C values but LPP of PNC and PNC+VD rats remained significantly lower than C rats. Three weeks after injury, all injury groups had recovered to C values. Histological evidence of injury was evident in the EUS of the VD and PNC+VD groups 1 day after injury. Four and 10 days after injury all injury groups showed evidence of striated muscle fiber disruption and atrophy in the EUS. Three weeks after injury the EUS had regenerated in the VD and PNC groups but remained disrupted in the PNC+VD group. All injury groups demonstrated evidence of connective tissue infiltration into the EUS. Immunohistochemistry demonstrated low expression of BDNF and NT-4 in the EUS of C rats. After VD, BDNF and NT-4 expression in the EUS was low and was not different from C animals. In contrast, BDNF and NT-4 expression was dramatically upregulated in the EUS of PNC rats. After PNC+VD, BDNF and NT-4 expression demonstrated downregulation in the region of EUS close to the vagina, although some animals showed upregulation of other regions in the urethra. Both NGF and Trk-4 showed either negative or slightly positive expression in the EUS of all 4 groups and had no significant difference between groups.

Interpretation of Results: LPP was significantly decreased in all 3 injury groups 4 days after injury, indicative of short-term decreased urethral resistance and urethral dysfunction. Ten days after injury, LPP significantly decreased only in the PNC and PNC+VD groups, indicating that these injuries needed longer time to recover compared to C animals. Twenty-one days after injury, LPP was not significantly different from C, indicating a return to normal function. Histological results demonstrated the muscle injuries in the urethra after either VD or PNC groups but dual injury may causes more severe injury to the EUS as disrupted muscle fiber only remained in the PNC+VD group 3 weeks after injury. Upregulation of BDNF & NT-4 after PNC indicates that BDNF & NT-4 are important for neuroregeneration. BDNF and NT-4 are not upregulated after VD suggesting that...
the lack of upregulation, possibly due to target organ (EUS) injury, may hamper neuroregeneration after simulated childbirth injuries. In addition, BDNF and NT-4 are not upregulated after PNC+VD suggesting that PN regeneration may be impaired after a double injury.

**Concluding Message:** Simultaneous PNC+VD provides a more severe injury than PNC or VD as indicated by histological assessment. The EUS may not upregulate neurotrophins enough for a strong neuro-regenerative response after PNC+VD, which may explain why the pudendal nerve does not appear to recover well in women with pudendal nerve injury after childbirth. Dual injury may provide a more clinically relevant injury model than previous ones.

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**The Effect of Vaginal Distension on Bladder and Urethral Function in Nulliparous Lysyl Oxidase Like-1 Knockout and C57Bl6 Mice**

**Gustilo-Ashby AM, Lee U, Daneshgari F, Li T and Damaser MS**

**Hypothesis / Aims of Study:** Female pelvic floor dysfunction (FPFD) is a complex and often debilitating group of conditions which include urinary incontinence, voiding dysfunction, pelvic organ prolapse, and anal incontinence. These disorders affect up to 75% of women, and require surgery in 11% of women, yet, little is known about their pathophysiology. Pregnancy and childbirth are well documented risk factors for FPFD, with urinary incontinence being particularly associated with a prolonged second stage of labor. Animal models of female pelvic floor dysfunction are limited. In rats, prolonged vaginal distension, using an inflated Foley catheter inserted into the vagina, leads to tissue hypoxia and reduced leak point pressures [1]. These findings suggest that urethral/vaginal trauma associated with ischemia during a prolonged second stage of labor may play a role in the pathophysiology of FPFD.

A new model of FPFD may help to elucidate the pathophysiology of FPFD associated with birth trauma. In 2004, Liu et al. noted that mice lacking the protein, lysyl oxidase-like 1 (LOXL1) routinely develop pelvic organ prolapse[2]. LOXL1 is required to synthesize elastin polymers from tropoelastin monomers in adult tissues. LOXL1 knockout (LOXL1 KO) mice develop pelvic organ prolapse after pregnancy and delivery or with aging, presumably due to an inability to maintain homeostasis of mature elastic fibers. In 2006, Liu et al. further characterized the FPFD seen in these mice [3]. LOXL1 KO mice develop overt prolapse 1-3 days post partum (Acute Stage), which retracts over 1-2 weeks, leaving a persistent perineal bulge with internal pelvic organ descent (Stable Stage). The vaginal wall was noted to be markedly distended with uterine descent into the upper vagina. Liu et al. also demonstrated that absence of LOXL1 leads to voiding dysfunction and possibly urinary incontinence in these mice. Parous prolapsed LOXL1 KO mice voided more frequently with smaller volumes than parous non-prolapsed wild type controls. The role of elastic fiber homeostasis in response to tissue trauma related to vaginal childbirth remains unclear. The objective of the study was to determine the effect of vaginal distension on voiding function and abdominal leak point pressures in Lysyl Oxidase Like 1 deficient (LOXL1 KO) and C57Bl6 mice.

**Study Design, Materials and Methods:** Nulliparous, virginal LOXL1 KO mice and C57Bl6 mice, aged 3-6 months, were assigned to either vaginal distension or no vaginal distension (control) groups. Mice in the vaginal distension group were
anesthetized and the vagina was serially dilated to accommodate a 12 Fr vaginal dilator. A modified pediatric Foley catheter was placed in the vagina and secured with silk suture. The balloon was distended with 0.5 ml of saline for four hours. After four hours of vaginal distension, the catheter was removed and the mice were allowed to awaken from anesthesia. Two days later, a suprapubic bladder catheter was placed under ketamine anesthesia. Two days after catheter placement, the mice underwent awake cystometrogram testing (CMG). Mice were then anesthetized with urethane and underwent abdominal leak point pressure testing (LPP). Control mice underwent catheter placement, followed by CMG and LPP testing two days later, as outlined above but did not undergo the vaginal distension procedure. The mean peak bladder pressures, baseline bladder pressures, fill time, fill volume, void volume, void pressure, voiding frequency, frequency of nonvoid contractions, and overall bladder contraction frequency were calculated from CMG data, and the mean peak bladder pressures, baseline bladder pressures, fill volume and abdominal leak point pressures were calculated from LPP data. Univariate testing was performed using Student t-tests for normative data and Wilcoxon Rank Sum tests for non-normative data. Differences between group mean values were compared using two way ANOVA testing. Pairwise multiple comparisons were performed using the Student-Neuman-Keuls method. A P-value less than 0.05 was considered statistically significant.

Results: Nine LOXL1 KO mice and 9 C57Bl6 mice were assigned to the vaginal distension group and 7 LOXL1KO mice and 15 C57Bl6 mice were assigned to the control group. LOXL1 KO mice had a significantly increased frequency of non-void bladder contractions after vaginal distension than LOXL1 KO mice in the control group (24.95 ± 5.58 contractions/hour vs. 5.39±6.32 contractions/hour, respectively. P=0.028). C57Bl6 also mice demonstrated an increase in non-void contraction frequency after vaginal distension compared with controls, although the results were not statistically significant (13.58±6.32 contractions/hour vs. 3.82±5.29 contractions/hour, respectively. P=0.25). No differences in fill volume, fill time, void pressure, void volume, or void frequency between the vaginal distension or control groups were identified on CMG testing. No differences were identified between LOXL1 and C57Bl6 mice within the vaginal distension or control groups. Abdominal leak point pressure testing revealed no differences within intervention groups in either mouse strain, however LOXL1 KO mice in the control group demonstrated a significantly greater abdominal leak point pressure than C57Bl6 controls (11.74±2.58 vs. 4.47±1.76 cm water, respectively. P=0.026). No mice developed acute pelvic organ prolapse up to four days after vaginal distension.

Interpretation of Results: LOXL1 KO mice demonstrate increased frequency of non-void bladder contractions after vaginal distension when compared with LOXL1 KO controls. These findings suggest that elastic fiber homeostasis after pelvic floor injury may play a role in the pathophysiology of detrusor overactivity. These findings are consistent with human studies which have shown decreased elastin gene expression in non-compliant human bladder tissue. Our findings contrast with published studies of vaginal distension in rats, where reduction in LPP is observed after vaginal distension. Neither Loxl1 KO nor C57Bl/6 mice demonstrate decreased LPP 4 days after vaginal distension. It is possible that in mice the bladder is more susceptible to injury from VD than the urethra, resulting in detrusor overactivity as opposed to stress urinary incontinence. Recovery rates may also differ between rats and mice. Longer term studies are needed to clarify this issue. Vaginal distension does not appear to induce acute pelvic organ prolapse in Loxl1-deficient mice. No mice demonstrated pelvic organ prolapse four days after vaginal distension. This may be explained by either insufficient pelvic floor injury or inadequate length of follow up to demonstrate this effect. Alternatively, POP may result from a multifactorial etiology, and may not be caused by mechanical injury alone. This study also suggests that different in mouse strains may demonstrate significant differences in bladder and urethral function. Baseline differences in LPP were demonstrated between Lox1 KO controls and C57Bl/6 controls, suggesting a difference in urethral function between strains without intervention. Future studies are needed to determine if the higher LPP seen in Lox1 KO mice are due to altered elastic fiber homeostasis or other genetic differences.

Concluding Message: We conclude that vaginal distension in LOXL1 KO mice may lead is associated with an increase in the frequency of nonvoid contractions, suggesting that altered elastic fiber homeostasis may play a significant role in the pathophysiology of detrusor overactivity.
MRI Anatomy of Lysyl Oxidase Like-1 Deficient (LOXL1 KO) Mice With and Without Pelvic Organ Prolapse (POP): A Pilot Study

Gustilo-Ashby AM, Lee U, Flask C and Damaser MS

Background: Female pelvic floor dysfunction (FPFD) is a complex and often debilitating group of conditions which include urinary incontinence, voiding dysfunction, pelvic organ prolapse, and anal incontinence. These disorders affect up to 75% of women, and require surgery in 11% of women, yet, little is known about their pathophysiology [4, 5]. In 2004, Liu et al. noted that mice lacking the protein, lysyl oxidase-like 1 (LOXL1) routinely develop pelvic organ prolapse [3]. LOXL1 is a copper-dependent monoamine oxidase required to synthesize elastin polymers from tropoelastin monomers in adult tissues. LOXL1 knockout (LOXL1 KO) mice develop pelvic organ prolapse after pregnancy and delivery or with aging, presumably due to an inability to maintain homeostasis of mature elastic fibers. In 2006, Liu et al. further characterized the FPFD seen in these mice [2]. LOXL1 KO mice develop overt prolapse 1-3 days post partum (Acute Stage), which retracts over 1-2 weeks, leaving a persistent perineal bulge with internal pelvic organ descent (Stable Stage). The vaginal wall was noted to be markedly distended with uterine descent into the upper vagina. These observations were made after animals were sacrificed. And it is unclear whether these changes are present and as pronounced in vivo. Furthermore, in humans, clinical examination has shown poor correlation with radiologic studies. Altman, Kenton. Lastly, because sacrifice is required to view the internal anatomy, longitudinal studies of changes in internal pelvic anatomy over time can not be performed. To date, no technique has been used to understand changes in internal pelvic anatomy in vivo in LOXL1 KO mice. If a feasible and accurate technique can be described, longitudinal studies can be performed using this animal model of FPFD.

Objective: To determine the feasibility of small animal MRI imaging to describe differences in female pelvic anatomy between live LOXL1 KO mice with and without POP.

Methods: Female LOXL1 KO mice with and without POP were used in the experiment. Prolapsed mice were parous and had stage III POP, and non-prolapsed mice were nulliparous and had stage 0 POP by the MOPQ staging system. Animals were anesthetized with isoflurane inhalation anesthetic and placed in a 7 Tesla Bruker Biospec MRI scanner. High resolution (600um x 200um x 200um) T1-weighted, fat-suppressed images were obtained with a turbo-spin echo sequence (TR/TE = 1500ms,20ms, 4 echoes) to visualize the pelvic anatomy in detail. Images were viewed serially using Volsuite 3.3.20 image processing software.

Mice were sacrificed after imaging. Gross anatomic dissections were performed, and digital images of the female pelvic structures were obtained.

Results: Age-matched mice with POP (n=2) and without POP (n=2) were studied. Qualitative analysis revealed increased variability in the size and location of the bladder in prolapsed mice compared with non-prolapsed mice, with the bladder below the pubic symphysis and distending the perineum in one mouse. The maximum bladder diameter was measured to be 14 mm, with noticeable bladder wall thickening of 0.4mm. In the second prolapsed mouse the bladder was located normally, however the vagina was markedly distended, leading to perineal distension. The rectum could be seen protruding outside the body in both prolapsed animals. The mice without POP demonstrated a uniform bladder size and location. In the mice without POP, the vagina, uterus, cervix, and rectum were observed in consistent anatomic positions.

Conclusion: MRI is a technically feasible investigational tool which is able to identify important anatomic differences between LOXL1 KO mice with and without POP. Future studies with larger numbers of animals and quantitative image processing techniques are warranted.
Parity is a Significant Determinant of Pelvic Organ Prolapse in LOXL1-Deficient Mice

Lee U, Gustilo-Ashby AM, Danashgari F and Damaser MS

Hypothesis / Aims of Study: Parity and vaginal delivery are known factors in the development of human pelvic organ prolapse (POP). With the recent introduction of genetic animal models for POP, it is important to characterize what factors significantly contribute to the development of prolapse in these animal models. In contrast to Fibulin 5-deficient mice who develop POP as nulliparous mice [1], LOXL1-deficient mice develop POP post partum. LOXL1 protein levels decrease at the end of pregnancy, and increase quickly after delivery to nonpregnant levels, highlighting LOXL1’s essential role in elastin remodeling in the postpartum period of mice [2]. The objective of this study was to describe the development of POP in LOXL1-deficient mice over time. We aim to describe the progression of POP, as well as factor(s) that significantly affect POP.

Study Design, Materials and Methods: LOXL1-deficient mice on a mixed C57Bl/6 and Sv129 background were bred with single pair mating and harem breeding. Female parous mice were observed over a 10 month period. Mouse Pelvic Organ Quantification (MOPQ) was used to measure grade of perineal bulge (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = grossly everted vagina) [1]. Kaplan-Meier Time to Prolapse curves were developed to describe the colony of LOXL1-/- female parous mice. Chi-square test was used with p values <0.05 indicating a significant difference.

Results: Female parous LOXL1−/− mice (n=39) were observed for a mean time of 20 weeks (range 15 to 67 weeks). Of the 39 mice, 25 have developed some degree of POP, and 14 are still being observed for development of POP. Of the 25 who have POP, 11/25 (44%) mice developed POP after the first delivery, 8/25 (32%) mice developed POP after the second delivery, 5/25 (20%) mice developed POP after the third delivery, and 1/25 (4%) mice after the fourth delivery. By 20 weeks of age, 50% of parous mice have developed POP. By 20 weeks of age, 15% of parous mice have developed grade 3 POP. For each unit increase in parity the estimate for the age at any prolapse decreases by 66.3% (Chi-square=0.0007). For each unit increase in parity the estimate for the age at any prolapse decreases by 55% (Chi-square=0.23).

Interpretation of Results: Parity is the significant factor that triggers POP in LOXL1-deficient mice. This provides further evidence that the LOXL1-deficient mouse model is a relevant genetic animal model for the study of POP because the POP develops and progresses over time after one or multiple pregnancies and deliveries, as is seen clinically.

Concluding Message: Parity is the significant determinant of pelvic organ prolapse in LOXL1-deficient mice.

Periurethral Inflammatory and Collagen Remodelling May Account for Preserved Anti-Incontinence Effects of a Cut Sling in a Rat Model

Chen CCG, Hijaz A, Drazba J, Daneshgari F and Damaser MS

Hypothesis / Aims of Study: It is estimated that more than 126,000 surgeries are performed each year for stress urinary incontinence (SUI) with sling procedures as the mainstay of surgical treatment. While sling procedure results in high success rates, it can also lead to complications including voiding dysfunction and urinary retention. Several series have demonstrated preservation of continence in approximately 80% of patients even after cutting the sling suburethrally to reverse iatrogenic obstruction. [1] It is thought that preservation of continence even in cut or removed slings result from fibrosis induced by the sling material. Although previous histologic analyses have demonstrated evidence of inflammation and fibrosis after implantation of different types of slings, it is unclear if there is specific evidence of collagen remodelling. Junqueira et al. first described analyzing Picrosirius red stained specimen using polarized light to evaluate collagen in different types of tissue. [2] Type I collagen form thick fibrils and birefringes as an intense orange to red colour. Type III collagen form thin fibers and has weak green birefringence. Although we have previously confirmed that cutting the sling suburethrally does not change its anti-incontinence effects in a validated rat model of SUI [3], we have not addressed potential etiologies of the continued anti-incontinence effects. Our aim was to determine if inflammatory responses or collagen remodelling in the urethro-vaginal tissue could have contributed to the preserved anti-incontinence effects of cut polypropylene sling.

Study Design, Materials and Methods: Institutional Animal Care and Use Committee approval was obtained. SUI was created in 60 age-matched female Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 250 to 300 gm by previously established method of pudendal nerve transection. The rats were then randomized into three equally sized groups according to surgical procedure: placement of a vaginal suburethral sling, placement of a vaginal suburethral sling in which the suburethral portion of the sling was immediately cut, and sham surgery without placement of the sling. Vaginal suburethral sling procedure was performed based on previously established methods and involved placement of a 3 x 20 mm polypropylene mesh. The sham surgery group underwent the vaginal dissection and needle passage without placement of the actual sling. Six weeks after surgery, the rats underwent placement of a suprapubic catheter for urodynamic measurements including leak point pressures (LPP) using previously published methods.

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After completion of LPP testing, the rats were euthanized, urethro-vaginal tissue harvested (cross-section of entire urethra and anterior vagina), immersion-fixed, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin-eosin, Masson’s trichrome, and Picosirius red stains. Qualitative histologic analyses of thirty hematoxylin-eosin and Masson’s trichrome stained specimens (ten from each treatment group) were made using a light microscope. Digital images of thirty Picosirius red stained specimens were obtained using an upright polarized light microscope (Leica DMR, Leica-Microsystems, Heidelberg, Germany). Quantification of the relative collagen content was assessed by analyzing the captured images (1.656 mm x 1.312 mm field size) using Image-Pro Plus 5.0 software (Media Cybernetics, Silver Springs, MD). A colour-segmentation profile was generated using the green-orange/red collagen birefringence of a Picosirius red stained lung sample as the standard. The colour-segmentation profile was then applied to a manually selected region of interest in each sample. The region of interest (urethro-vaginal tissue) was the fibromuscular connective tissue between the urethra and vaginal epithelium, which was further standardized with the striated muscles of the urethra as the superior and lateral borders and vaginal epithelium as the inferior borders. For each sample, the areas containing the birefringent collagen was measured and recorded as amount of collagen in square microns. As the region of interest was not a uniform size in all the specimens, the percentage of birefringent collagen/area was calculated. Potential differences between treatment groups were analyzed using the Kruskal-Wallis test. If the Kruskal-Wallis test was significant at the 0.05 level, Tukey multiple comparisons test was performed to evaluate which treatment groups differed. Statistical analyses were performed using JMP 5.0.1 (SAS Institute, Cary, NC).

**Results:** Median LPP values were similarly and significantly increased in animals with cut and intact vaginal slings compared with animals with sham surgeries (24.9 cmH2O, 27.9 cmH2O, 20.7 cmH2O, respectively, P < 0.001). Although individual histologic variations existed within the same treatment groups, inflammatory mediators and interstitial edema were similarly increased in cut and intact sling animals compared with sham surgery animals. Specimens from animals with cut and intact slings contained vacuoles that resulted from the fragmented polypropylene sling fibers. These vacuoles were surrounded by fibrosis and lymphocytes. Specimen from animals with cut and intact slings retained less of the aniline blue dye in the Masson’s trichrome stain, indicating edema. Under polarized light, specimens from the sham surgery animals appeared to be composed of collagen that predominately birefringed red to orange (typical of type I collagen) whereas cut and intact sling specimens appeared to contain collagen fibers that predominately birefringed green (typical of type III collagen). Specifically, the median percentage of collagen type I over the analyzed area in the cut and intact sling groups were similarly and significantly decreased compared with the sham surgery group (19.0%, 26.9%, 52.1%, respectively, P < 0.0001), while the median percentage of collagen type III over the analyzed area in the cut and intact sling groups were similarly and significantly increased compared with the sham surgery group (33.0%, 31.8%, 14.0%, respectively, P = 0.0008).

**Interpretation of Results:** In this rat model of SUI, animals with cut and intact slings had restoration of urinary continence as measured by similar and significantly increased leak point pressures compared with animals that underwent sham surgery. There was evidence of localized edema and chronic inflammatory reaction in animals that received suburethral slings (cut or intact) 6 weeks after the initial surgery. There was also evidence of collagen remodelling with similar and significantly decreased collagen type I and increased collagen type III in cut and intact sling animals compared with sham surgery animals.

**Concluding Message:** Incision of the sling at its suburethral section did not affect the anti-incontinence impact of the vaginal sling, as measured by LPP, in a rat model of SUI. The preserved anti-incontinence effects may be due to the presence of periurethral inflammation along with collagen remodelling as evidenced by an increase in collagen type III and decrease in collagen type I.
A Dual Injury Animal Model of Maternal Childbirth Injuries

Damaser MS, Lin DL, Kerns JM, Sypert DF, Eggers L and Pan HQ

Objectives: Multiple injury methods may best represent the complex maternal pelvic injuries of childbirth. The objective of this project was to investigate urethral function, urethrovaginal anatomy, and expression of neurotrophins after a dual injury model consisting of both vaginal distension (VD) and pudendal nerve crush (PNC).

Methods: Virgin Sprague-Dawley rats (n=140) were divided into 4 groups and underwent VD, using a modified Foley catheter inserted into the vagina and filled with saline (3ml) for 4 hours; PNC, consisting of a standardized bilateral compression of the nerve in the ischiorectal fossa; both injuries (VD&PNC); or neither injury (C). One day after injury, brain derived neurotrophic factor (BDNF) and neurotrophic factor 4 (NT-4) expression in the external urethral sphincter (EUS) were investigated by immunohistochemistry. Four, 10, and 21 days after injury, urethral function was assessed by leak point pressure in all 4 groups: the bladder was slowly depressed while bladder pressure was measured via a previously implanted suprapubic catheter. The increase in external abdominal pressure at leakage (Pabd) is used to measure urethral function. Data was analyzed using ANOVA (p=0.05). Qualitative histology of the urethra was also performed.

Results: Pabd in all 3 injury groups was significantly decreased 4 days after injury compared to C rats but was not significantly different compared to each other. VD rats recovered to C values 10 days after injury but Pabd of PNC and VD&PNC rats remained significantly decreased. All injury groups recovered to C values 21 days after injury. The EUS showed disruption in the VD and VD&PNC groups 1 day after injury. All injury groups showed evidence of striated muscle fiber disruption and atrophy in the EUS and nerve injury (Wallerian Degeneration) near the EUS. The EUS had regenerated in the VD and PNC groups 21 days after injury but remained disrupted and atrophied in the VD&PNC group. All injury groups demonstrated evidence of connective tissue infiltration into the EUS 21 days after injury. BDNF was dramatically upregulated in the EUS of PNC rats only. NT-4 was upregulated in the EUS of both PNC and VD&PNC rats.

Conclusions: Simultaneous PNC & VD provides a more severe injury than either PNC or VD, although urethral dysfunction follows the same timecourse as PNC, possibly due to compensatory mechanisms. The EUS may not upregulate neurotrophins enough for a strong neuroregenerative response after PNC & VD, likely due to simultaneous muscle and nerve injury. Dual injury may provide a clinically relevant injury model for use in further studies.

Loxl1-Deficient Mice Demonstrate Urinary Frequency after Development of Prolapse

Lee U, Gustilo-Ashby AM, Daneshgari F, Li T and Damaser MS

Introduction: Deficiency of Lysyl Oxidase Like-1 (LOXL1) results in impaired elastin remodeling in mice and pelvic organ prolapse (POP) following pregnancy and vaginal delivery of pups. Liu X. et al. (Nat Gen, 2006) and Liu G et al. (BJU Int, 2007) demonstrated that the absence of LOXL1 leads to increased voiding frequency in parous pelvic organ prolapsed mice compared to non-prolapsed nulliparous WT mice. It is unclear whether the differences in voiding pattern are due to the LOXL1 deficiency or the effect of pelvic organ prolapse. The objective of this study was to demonstrate the effect of pelvic organ prolapse on bladder function and abdominal leak point pressure in LOXL1-deficient mice with pelvic organ prolapse.

Methods: LOXL1-/- mice on a mixed C57Bl/6 and Sv129 background were maintained at the Cleveland VA Animal Facility, and bred with single pair and harem breeding. MOPQ quantification of the resulting POP was conducted. Parous LOXL1-/- mice with grade 3 POP and age and parity matched non-prolapsed (grade 0) LOXL1-/- mice (n=6) underwent conscious cystometry (CMG) and leak point pressure (LPP) testing two days after suprapubic tube implantation.

Results: The age of the mice ranged from 19 to 67 weeks and parity ranged from 1-5. There were no significant differences in the age and parity of the prolapsed and non-prolapsed LOXL1-/- mice. LPP between the two groups was not significantly different. However, the fill volume between prolapsed and nonprolapsed LOXL1-/- mice during LPP testing was significantly different (0.09 vs 0.06; p=0.008), demonstrating that the nonprolapsed LOXL1-/- mice have LPP collected at lower volumes compared to prolapsed LOXL1-/- mice.

Conclusions: Pelvic organ prolapsed LOXL1-/- mice have increased voiding frequency and decreased LPP. This animal model has potential for investigating the mechanism of POP.
Anal Sphincter Physiology after Pudendal Nerve Transection and Sphincterotomy: An Animal Model of Fecal Incontinence

Salcedo L, Zutshi M, Hull T and Damaser MS

Aim: To establish a reliable animal model to study anatomy and physiology of the anal sphincters and study the acute effects of both mechanical trauma and bilateral pudendal nerve transection.

Methods: 35 virgin female Sprague-Dawley rats were used and randomly allotted to four groups, 10 in control group (CG), 11 in sphincterotomy (AS) group, 9 in pudendal nerve transection (PNT) group and 5 for drug testing. Anorectal pressure (AP) was monitored using a saline-filled latex balloon connected through a saline filled PE-90 tubing to a pressure transducer, amplifier, and digital data recording system. Baseline resting pressures and anal contraction pressures were monitored. Electromyographic (EMG) signal was also recorded.

AS group received a sphincterotomy after initial AP and EMG recording and repeated after the injury. Rats in the PNT group had pudendal nerve isolation prior to the experiment and transected after initial AP and EMG monitoring, AP and EMG were recorded after unilateral and bilateral nerve transection. A separate group had drug testing using succinylcholine (S). Animals were euthanized and sent for histopathology. Pressure data was analyzed for resting pressure (RP), peak contraction (PC), number of peaks per contraction (NP), time to peak contraction (PT), and interval between contractions (CI).

Results: AP data showed consistent, rhythmic anal pressure contraction. EMG data showed regular rhythmic bursting pattern synchronized with AP recordings with an increase in frequency during pressure peaks. Only in the AS group did the NP show any significant difference when compared to the unilateral PNT (p=0.003) or bilateral PNT (p=<0.0001). There were no significant changes in NP immediately post-unilateral and bilateral pudendal nerve transection (p=0.14). S administration remarkably diminished all the EMG signal activity which paralyzed and inhibited the activity of the striated sphincter muscles. Histology showed rat anatomy similar to human anal anatomy. The AS group showed greater injury to the external sphincter muscles and less injury to the internal sphincter. PNT sphincter anatomy showed no change as compared to CG.

Conclusion: The female rat is a suitable and reliable model for studying the physiology of the anal sphincters and the mechanisms of incontinence and that the anal pressure wave is created by striated muscle contraction. The injuries inflicted in this animal model simulate the mechanisms of fecal incontinence in women.

A Simultaneous Myoneurophysiologic Study of the Guarding Reflex in Female Rats

Jiang H-H, Tang W, Damaser MS and Song B

Introduction: The guarding reflex participates in the maintenance of continence during coughing by inducing an external urethral sphincter (EUS) contraction. To evaluate this reflex and the peripheral nerves and muscles that participate, we simultaneously investigated the pelvic nerve and pudendal nerve, EUS and abdominal muscle electromyogram (EMG), and the detrusor cystometrogram (CMG).

Methods: 14 female adult Sprague-Dawley rats were studied under urethane anesthesia (1.2g/kg) by recording the pelvic nerve potential, motor pudendal nerve potential, EUS EMG and abdominal muscle EMG during filling CMG and isovolumetric CMG. For filling CMG, a PE catheter was inserted into the bladder via the urethra and warm saline (6ml/h) was infused. For isovolumetric CMG (at 0.8ml), a catheter was inserted through the bladder dome to monitor pressure after bladder neck ligation. A gradual pressure increase (15cmH2O or greater) was made by pressing a cotton swab on the bladder. The CMG, pelvic nerve & pudendal nerve signals, and abdominal muscle & EUS EMGs were recorded simultaneously by a multi-channel physiological recording system via a lower abdominal incision and after parts of the pubis and ischium were removed.

Results: During filling CMG (50 trials in 6 rats), a gradual increase in externally applied bladder pressure consistently caused increased pelvic nerve activity as well as a reflex response of the pudendal nerve. EUS EMG and abdominal muscle EMG activity also increased. The increased activities reached their peak at leakage. During isovolumetric CMG (64 trials in 8 rats), a passive pressure increase also caused an increased guarding response in the pudendal nerve, EUS EMG, and abdominal muscle CMG. Both at the end of filling CMG and isovolumetric CMG on 4 rats, bilateral pudendal nerves were transected which ended all EUS EMG activity. However, abdominal muscle EMG remained active.

Conclusion: The results indicate a passive pressure on the bladder induces a guarding reflex, not only to the EUS but also to abdominal muscle, even if no urine enters the proximal urethra. This simultaneous recording system provides a new method for studying neural control of continence and voiding.
Dual Injury May Provide a More Severe Childbirth Simulation than either Injury Alone

Pan HQ, Lin DL, Eggers L, Kerns JM, Sypert DF and Damaser MS

Introduction: During vaginal childbirth, the muscles, nerves and ligaments of the pelvic floor are compressed and injured. These injuries are strongly correlated with later development of stress urinary incontinence (SUI). Neurotrophins are upregulated after nerve injury and down regulated after muscle injury and may provide insight into the mechanism of later SUI development from pelvic floor injuries. Animal models of the injuries in childbirth have focused on either vaginal distension (VD) or pudendal nerve crush (PNC). The aim of this project was to test urethral function, urethral anatomy, and expression of neurotrophins after a dual injury model of both PNC and VD.

Methods: Virgin rats (n=140) were divided into 4 groups and underwent either VD using a catheter that was inserted into the vagina and filled with saline (3 ml) for 4 hours (VD), PNC consisting of a bilateral compression of the pudendal nerve (PNC), both injuries (PNC+VD), or neither (C). One day after injury, neurotrophin (BDNF, NT-4, Trk-B and NGF) expression in the EUS was tested by immunohistochemistry (IHC, n=20). Four, 10, and 21 days after injury, urethral function was assessed by leak point pressure, to indicate urethral resistance to flow. Data was analyzed using a two way ANOVA (p=0.05). Rats were then euthanized and the urethra was dissected for qualitative histological and IHC analysis.

Results: LPP was significantly decreased in all 3 injury groups 4 days after injury. Ten days after injury, LPP was significantly decreased only in the PNC and PNC+VD groups. Twenty-one days after injury, LPP was not significantly different from C. Histological results demonstrated muscle injuries in the urethra after either VD or PNC but these had recovered by 21 days. The dual injury may cause more severe injury to the EUS than either injury alone since it had not yet recovered histologically 3 weeks after injury. IHC showed strong upregulation of BDNF & NT-4 after PNC. BDNF and NT-4 are not upregulated after VD suggesting that the lack of upregulation, possibly due to target organ (EUS) injury, may hamper neuroregeneration after simulated childbirth injuries. BDNF and NT-4 are not upregulated after PNC+VD to the same extent as after PNC alone. Both NGF and Trk-4 showed either negative or slightly positive expression in the EUS of all 4 groups and had no significant difference between groups.

Conclusions: Simultaneous PNC+VD provides a more severe injury than PNC or VD alone although functional recovery follows the same time course as PNC. The EUS may not upregulate neurotrophins enough for a strong neuro-regenerative response after PNC+VD. Dual injury may provide a more clinically relevant injury model than either PNC or VD alone.

Recovery of Nerve Function after Simulated Childbirth Injuries in Female Rats

Jiang H-H, Pan HQ, Eggers L, Zaszczurynski PJ and Damaser MS

Introduction: The pudendal nerve and its target organ, the external urethral sphincter (EUS), can both be injured during vaginal childbirth and may not fully regenerate, contributing to development of resultant incontinence. We measured pudendal motor unit potential and EUS electromyograms (EMG) in rats to study nerve recovery after 3 different childbirth simulation injuries.

Methods: 32 female virgin Sprague-Dawley rats (200-300g) were randomly divided into 4 groups: vaginal distension (VD), pudendal nerve crush (PNC), both PNC and VD (PNC+VD), and controls. Animals in each group were studied 4 days (n=4) and 3 weeks (n=4) after injury. For VD, a modified 10F Foley balloon catheter was dilated to 3ml inside the vagina for 4 hours. For PNC, the pudendal nerve was crushed twice bilaterally for 30 seconds using a standardized instrument. Animals in the PNC+VD group received both of the above procedures. In each rat we simultaneously recorded the pudendal nerve motor branch potential, EUS EMG (using bipolar platinum electrodes) and the transurethral filling cystometrogram (CMG, 5ml/h) by removing parts of the pubis and ischium under urethane anesthesia (1.2g/kg i.p.). During filling CMG, a gradual bladder pressure increase was made by pressing a cotton swab on the bladder until leakage to test the response on pudendal nerve activity and EUS EMG.

Results: In control rats, both EUS EMG and pudendal nerve potential demonstrated activity during the storage phase of the CMG. The guarding reflex was positive since both pudendal nerve and EUS EMG increased activity with an increase in external pressure on the bladder. When voiding, there were bursting potentials (5-10Hz) in both pudendal nerve potentials and EUS EMG associated with high frequency oscillations (HFO) in bladder pressure. Four days after VD, the EUS EMG was weak; however pudendal nerve activity was near normal. During voiding, there was neither EUS EMG bursting nor bladder pressure HFOs but pudendal nerve activity demonstrated bursting. Three weeks after VD, EUS EMG and HFOs demonstrated signs of recovery. Four days after PNC, the EUS EMG, pudendal nerve activity and HFOs were all diminished but demonstrated recovery 3 weeks after injury. Four days after PNC+VD, the results were qualitatively similar to that of the PNC group but demonstrated less activity, indicating a more severe injury. Three weeks after PNC+VD, significantly less recovery was measurable than in the PNC group.

Conclusion: PNC+VD takes longer to recover nerve function than either PNC or VD alone. Slowed or incomplete nerve recovery may be the result of end organ injury from VD after dual injury.
Characterization of the Compliance and Frequency of Fluid-Filled Catheter Systems

Cooper MA, Zaszczurynski PJ, Damaser MS

There are many factors to take into account when designing a cystometry system. One often overlooked factor, although it is very important to the accuracy of measurements, is how the system performs dynamically. The focus of our research was dual fold: to determine both the compliance of polyethylene catheters with different lengths and gauges and the natural frequency of the system. This data will enable improved understanding of the function of catheter-based pressure sensing systems which will facilitate improved experimental and equipment design. We tested the compliance of the catheters by capping the end of the catheter while recording pressure and infusing saline to increase pressure and volume. We performed frequency response tests by popping a thin membrane and measuring the response from the catheter system using a pressure transducer. As expected, larger gauge tubings have increased compliance. For two meter tubing, the average compliance for one PE-90 catheter was 3.51289E-05 ml/cmH20 while the compliance for one PE-50 catheter was 2.85649E-05 ml/cmH20. The average frequency of a two meter PE-90 catheter is around 16.6 Hz. In further tests, we will analyze the effects of catheter length and gauge on the frequency.

Insulin-Like Growth Factor-1, Insulin-Like Growth Factor Binding Protein-3, Insulin-Like Growth Factor Receptor and Urodynamic Function after Pudendal Nerve Crush in Diabetic Female Rats

Pan HQ, Lin DL, Kuang M, Steward J, Sypert D, Rackley RR and Damaser MS

Introduction: Women with diabetes mellitus (DM) have a higher prevalence of lower urinary tract complications than women without DM. DM increases the risk of stress urinary incontinence (SUI) after vaginal delivery, contributing to the high prevalence of SUI. The pudendal nerve (PN) courses through Alcock’s canal and is particularly vulnerable to stretch and crush injury during childbirth, leading to denervation and atrophy of the external urethral sphincter (EUS), resulting in symptoms of SUI. Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3), through IGF-I receptors (IGF-IR), have considerable protective and regenerative functions in the nervous system in DM. However, the relationship between IGF-I, DM, birth trauma and SUI is poorly understood.

Objective: The aims of this study were to determine: 1. If PN crush in DM animals results in increased severity of SUI symptoms; 2. If these altered responses in DM animals are associated with IGF-I, IGFBP-3 and IGF-IR.

Methods: Seventy-six female virgin Sprague-Dawley rats were divided into DM, diuretic (DU) and untreated control (C) groups with 12-14 each. Each group was subdivided into PN crush (PNC) and sham PN (SPNC) groups. DM rats (8 weeks prior to PNC) were induced by injection (i.p) of streptozotocin (35 mg/kg). DU rats were given 5% sucrose in their drinking water for 8 weeks. For PNC, the PN was crushed twice bilaterally by closing a Castroviejo needle holder over it for 30 seconds. For SPNC, rats underwent a dorsal skin incision only. All rats underwent awake cystometry (CMG) and leak point pressure (LPP) testing 11 days after PNC or SPNC. At that time blood was intracardiacally obtained for assessment of IGF-I, IGFBP-3 and IGF-IR mRNA levels by semi-quantitative RT-PCR. The urethra, vagina, bladder and PN were dissected and embedded in paraffin for histological assessment.

Results: CMG data from DM group after PNC were not significantly different from that of SPNC, and from either C or DU animals. However, the leak point pressure during LPP testing was significantly decreased after PNC in DM animals compared to SPNC. There were no differences in leak point pressure between the C and DU groups after either PNC or SPNC. IGF-I mRNA level in DM rats was 40% lower than that of C rats but significantly increased 11 days after PNC.
compared to SPNC of both DM rats (7 times) and C rats (4 times). Within C and DU groups, IGF-I was moderately elevated after PNC compared to SPNC: 1.6 and 1.7 times, respectively. IGFBP-3 in DM rats was 2 times that of C rats but it was 40% decreased after PNC compared to SPNC, although it was relative higher (80%) when compared to C rats. IGF-IR showed no significant differences between the SPNC groups. It showed, however, a 30-40% decrease after PNC in all groups compared to SPNC. Pathology of the EUS, determined by histological assessment of urethral cross-sections, was increased in rats with PNC compared to rats with SPNC in all groups.

Conclusions: PNC leads to significantly decreased urethral resistance in DM rats as demonstrated by LPP. Therefore, PN injury may play an important role in the development of incontinence in DM. Elevated level of IGF-I and decreased levels of IGFBP-3 and IGF-IR after PNC in DM rats may contribute to the dysfunction and its recovery.

Lower Genitourinary Anatomy and Function of Lysyl Oxidase Like-1 Knockout (LOXL1 KO) Mice with and without Pelvic Organ Prolapse

Lee UJ, Gustilo-Ashby AM, Daneshgari F, Kuang M, Vurbic D, Lin DL, Flask C, Li T and Damaser MS

Introduction and Objectives: Female pelvic floor dysfunction (FPFD) is a complex and debilitating group of conditions which include urinary incontinence, voiding dysfunction, and pelvic organ prolapse (POP). Mice lacking the protein, lysyl oxidase-like 1 (LOXL1 KO) develop POP and demonstrate voiding dysfunction after pregnancy and delivery. Further characterization of the LOXL1 KO mouse model of FPFD is required to determine its relevance to FPFD in humans. The objective of this study was to compare anatomy and function of the lower urogenital tract (LUT) of LOXL1 KO mice with and without POP.

Methods: Parous LOXL1 KO mice on a mixed C57Bl/6 and Sv129 background were observed for POP (n=62). Degree of POP was quantified using the MOPQ quantification system. LUT anatomy in live anesthetized prolapsed (n=2) and non-prolapsed (n=2) mice was assessed using a 7 Tesla Bruker Biospec MRI scanner. High resolution T1-weighted, fat-suppressed images were obtained and examined qualitatively. Age and parity-matched LOXL1 KO mice were divided into two groups: prolapsed (n=11) and non-prolapsed (n=6). LUT function was assessed using conscious cystometry (CMG) and leak point pressure (LPP) testing. Quantitative histologic analysis was performed on mid-urethra samples stained with vonGieson (elastin) stain. Kaplan Meier curves described the development of POP over time with significant differences determined using a chi-square test. Univariate analysis was performed using t-test on normally distributed data, and Wilcoxon rank sum test on non-normally distributed data. Multivariate analysis was performed using two-way ANOVA. Pairwise multiple comparisons were performed using the Tukey test. P values < 0.05 were considered significant.

Results: By 25 weeks of age, 50% of parous LOXL1 KO mice developed POP. Parity significantly affected the age at which POP developed (p=.016). With each delivery, the age at development of POP decreased by 25%. MRI imaging demonstrated that LOXL1 KO mice without POP had a uniform size and location of the pelvic organs. In contrast, the LOXL1 KO mice with POP had increased variability in the size and location of the bladder and vagina compared with non-prolapsed mice. There were no significant differences in CMG values between age and parity matched LOXL1 KO mice with and without POP, however, multivariate analysis revealed lower LPP in the prolapsed mice compared with non-prolapsed mice when controlled for parity (23.1 ± 3.2 vs. 37.1 ± 4.1 cmH2O; p=0.02). Parity significantly contributed to reduced LPP both between groups and within
groups. There was a significant increase in the number of elastin clusters in the external urethral sphincter of LOXL1 KO mice with prolapse (28.7 ± 3.9) compared with LOXL1 KO mice without prolapse (17.8 ± 1.8) and C57Bl/6 controls (9.6 ± 2.9, p=.002).

**Conclusion:** The LOXL1 KO mouse model is a relevant genetic animal model for the study of FPFD. Parity is the significant factor that triggers POP in LOXL1 KO mice. As in humans, POP in LOXL1 KO mice develops over time, and is associated with one or multiple deliveries. LOXL1 KO mice with prolapse have variable internal pelvic anatomy which clinical examination may not accurately describe. Both parity and POP are associated with a significant decrease in LPP in LOXL1 KO mice. An increase in elastin clusters in the urethra of LOXL1 KO mice with POP suggests that elastin disorganization associated with POP mice may lead to functional abnormalities in animals with POP. Our findings support research that abnormal elastic fiber homeostasis plays an important role in the pathophysiology of FPFD.

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**Biomechanical Relationships between Urodynamic Pressures during Cough and Valsalva in Normal and Stress Incontinent Women**

*Spirka T, Damaser MS, Kenton K and L Brubaker*

**Introduction and Objectives:** Precision in relational descriptions between standardized urodynamic pressures during cough and valsalva events and the functional event (leakage) is likely to advance our understanding of the etiology of stress urinary incontinence. The objective of this study was to quantify the relationship between vesical, abdominal, and urethral pressures during cough and valsalva in continent and stress incontinent women.

**Methods:** Using an IRB-approved, NIH funded protocol, standardized urodynamic data, including vesical, abdominal, and urethral pressures, were acquired from 2 groups of women; (1) continent women had no incontinence symptoms or urodynamic findings; (2) stress incontinent women had symptoms and urodynamic findings of stress incontinence. Urodynamic pressure data were obtained during cough and valsalva maneuvers at maximum cystometric capacity. Phase plots were created by plotting simultaneous abdominal pressures versus vesical pressures and vesical pressures versus urethral pressures obtained every 0.2s during each cough and valsalva maneuver. Linear regression was used to fit linear trend lines to the corresponding phase plots for each event using the least squares method. Quality of fit was evaluated using the coefficient of determination. Data is presented as mean ± standard deviation. Slopes of linear trend lines were compared using the Mann Whitney Rank Sum Test with p<0.05 indicating a significant difference between groups.

**Results:** Twelve women were stress incontinent, and the remaining 11 were continent. The slope of trend lines fit to abdominal pressure versus vesical pressure phase plots for non-leaking events and leaking events were 0.94 ± 0.14 and 0.93 ± 0.10, respectively, and were not significantly different. The slopes for leaking and non-leaking valsalva maneuvers were 0.91 ± 0.08 and 0.95 ± 0.14, respectively. The slope for leaking coughs was 0.94 ± 0.12 and the slope for non-leaking coughs was 0.94 ± 0.14. No significant differences were observed when the slopes of the trend lines fit to phase plots of abdominal pressure versus vesical pressure for valsalva maneuvers was compared with the trend lines obtained from coughs when both leaking and non-leaking events were considered. The results were similar for the trend lines obtained for vesical pressure versus urethral pressure: slopes for leaking and non-leaking events were 1.24 ± 0.32 and 1.11 ± 0.28. The resulting slopes for trend lines associated with
leaking and non-leaking valsala maneuvers (1.08 ± 0.29 and 1.32 ± 0.39, respectively) and leaking and non-leaking coughs (1.14 ± 0.27 and 1.18 ± 0.25, respectively) were also not significantly different. The coefficient of determination was 0.979 ± 0.08 for trend lines used to define the relationship between abdominal and vesical pressure and 0.859 ± 0.15 for those used to define the relationship between vesical and urethral pressure.

Conclusions: The relationship between simultaneously recorded urodynamic pressures is highly consistent and does not vary during cough or valsala or between continent and stress incontinent subjects. The slope of the linear trend line fit to phase plot data is not significantly different from 1, indicating complete pressure transmission of abdominal pressure changes to the bladder and urethra. We conclude that pressure transmission changes are not a cause of leakage in stress incontinent patients.

Dual Simulated Childbirth Injuries Result in Slowed Recovery of Pudendal Nerve and Urethral Function

Jiang H-H, Pan HQ, Gustilo-Ashby AM, Glaab J, Zaszczyzynski PJ and Damaser MS

Introduction and Objectives: Both pelvic floor muscle trauma and pudendal nerve injury have been implicated in stress urinary incontinence (SUI) development after childbirth. We used animal models to investigate how combinations of these injuries affect the rate of neuromuscular recovery.

Methods: 60 female Sprague-Dawley rats were divided into 5 groups: vaginal distension (VD), pudendal nerve crush (PNC), PNC and VD (PNC+VD), pudendal nerve transection (PNT) and controls. Rats in each group were studied 4 days (n=5) and 3 weeks (n=6) after injury. For VD, a modified 10F Foley catheter was dilated to 3ml inside the vagina for 4 hours. For PNC, the pudendal nerve was crushed twice bilaterally for 30s. The PNC+VD group received both of the above procedures. For PNT, the pudendal nerves were transected bilaterally. We simultaneously recorded pudendal nerve motor branch potentials (PNMBP), external urethral sphincter electromyography (EUS EMG) and transurethral transurethral bladder pressure under urethane anesthesia (1.2g/kg i.p.). The presence of a guarding reflex (increased frequency & amplitude of PNMBP and EUS EMG activity) during leak point pressure (LPP) testing was determined by application of an external increase in bladder pressure in the absence of active bladder contraction.

Results: In controls, a guarding reflex was present as demonstrated by increased PNMBP and EUS EMG activity during LPP testing. Four days after VD, the EUS EMG activity was diminished, but PNMBP activity was near normal. After 3 weeks, EUS EMG showed a significant recovery in both frequency & amplitude. Four days after PNC, both EUS EMG and PNMBP activity were diminished, but demonstrated significant recovery after 3 weeks. Four days after PNC+VD, both EUS EMG and nerve activity were diminished, and little recovery was observed after 3 weeks. PNMBP and EUS EMG activity in the PNT group was similar to that of PNC+VD animals and did not recover. LPP results are consistent with the reduction in EUS EMG and PNMBP activity.

Conclusion: Urethral sphincter nerve and muscle function recovers more slowly after PNC+VD than after either PNC or VD alone. The pudendal nerve may regenerate more slowly after PNC+VD, explaining the slow recovery of nerve and muscle function. Future work will be aimed at testing methods to facilitate neuroregeneration and recovery after this clinically relevant dual injury.
Biomechanical Relationships between Urodynamic Pressures during Cough and Valsalva in Normal and Stress Incontinent Women

Spirka T, Kenton K, Damaser MS and Brubaker L

Introduction and Objectives: The goal of this study was to quantify the relationship between vesical, abdominal and urethral pressures during cough and valsalva in continent and stress incontinent women.

Methods: Following IRB approval, standardized urodynamic data, including vesical, abdominal and urethral pressure were acquired in 12 continent and 11 women with urodynamic stress incontinence during cough and valsalva maneuvers at maximum cystometric capacity. Phase plots were created by plotting simultaneous abdominal pressures versus vesical pressures and vesical pressures versus urethral pressures obtained every 0.2s during each cough and valsalva maneuver. Linear regression was used to fit trend lines to the corresponding phase plot for each event. Quality of fit was evaluated using the coefficient of determination. Data is presented as mean ± standard deviation. Slopes of linear trend lines were compared using the Mann Whitney Rank Sum Test with p<0.05 indicating a significant difference between groups.

Results: We did not detect a difference in the slope of the trend lines fit to abdominal pressure versus vesical pressure phase plots for non-leaking events and leaking events were 0.94 ± 0.14 and 0.93 ± 0.10 respectively. No significant differences were observed when the slopes of the trend lines fit to phase plots of abdominal pressure versus vesical pressure for valsalva maneuvers was compared with the trend lines obtained from coughs when both leaking and non-leaking events were considered. The results were similar for trend lines obtained for vesical pressure versus urethral pressure: slopes for leaking and non-leaking events were 1.24 ± 0.32 and 1.11 ± 0.28. The resulting slopes for leaking and non-leaking valsalva and coughs were also not significantly different.

Conclusions: The relationship between simultaneously recorded urodynamic pressures is highly consistent and does not vary during cough or valsalva or between continent and stress incontinent subjects. The slope of the linear trend line fit to phase plot data is not significantly different from the value 1, indicating complete transmission of abdominal pressure changes to the bladder and urethra, which strongly supports the hypothesis that pressure transmission changes are not a cause of urinary leakage in stress incontinent women.

Simulated Childbirth Injuries to the Pudendal Nerve and Urethral Sphincter Result in their Slowed Functional Recovery

Jiang H-H, Pan HQ, Gustilo-Ashby AM, Glaab JB, Zaszczurynski PJ and Damaser MS

Introduction and Objective: The injuries to the pudendal nerve and urethral have been implicated in stress urinary incontinence (SUI) development after childbirth. We used animal models to investigate how combinations of these injuries affect the rate of neuromuscular recovery.

Methods: 60 female Sprague-Dawley rats were divided into 5 groups: vaginal distension (VD), pudendal nerve crush (PNC), PNC and VD (PNC+VD), pudendal nerve transection (PNT) and controls. Rats in each group were studied 4 days (n=5) and 3 weeks (n=6) after injury. For VD, a modified 10F Foley catheter was dilated to 3ml inside the vagina for 4 hours. For PNC, the pudendal nerve was crushed twice bilaterally for 30s. The PNC+VD group received both of the above procedures. For PNT, the pudendal nerves were transected bilaterally. We simultaneously recorded pudendal nerve motor branch potentials (PNMBP), external urethral sphincter electromyography (EUS EMG) and the transurethral bladder pressure under urethane anesthesia (1.2g/kg i.p.). The presence of a guarding reflex (the activity increase in both PNMBP and EUS EMG) during leak point pressure (LPP) testing was determined by application of an external increase in bladder pressure in the absence of active bladder contraction.

Results: In controls, a guarding reflex was present as demonstrated by increased PNMBP and EUS EMG activity during LPP testing. Four days after VD, the EUS EMG activity was diminished, but PNMBP activity was near normal. After 3 weeks, EUS EMG showed a significant recovery in both frequency & amplitude (p<0.05). Four days after PNC, both EUS EMG and PNMBP activity were diminished, but demonstrated significant recovery after 3 weeks. Four days after PNC+VD, both EUS EMG and PNMBP activity were diminished, and little recovery was observed after 3 weeks. PNMBP and EUS EMG activity in the PNT group was similar to that of PNC+VD animals and did not recover. LPP results are consistent with the reduction in EUS EMG and PNMBP activity.

Conclusions: Urethral sphincter nerve and muscle function recover more slowly after PNC+VD than after either PNC or VD alone. The pudendal nerve may regenerate more slowly after PNC+VD, explaining the slow recovery of nerve and muscle function. Future work will be aimed at testing methods to facilitate neuroregeneration and recovery after this clinically relevant dual injury.
Insulin-like Growth Factor Expression and Urodynamic Function after Pudendal Nerve Injury in Diabetic Rats

Pan HQ, Lin DL, Kuang M, Sypert D, Steward J, Rackley RR and Damaser MS

Introduction and Objective: Women with diabetes mellitus (DM) have a higher risk of stress urinary incontinence (SUI) after vaginal childbirth than women without DM. The pudendal nerve (PN) passes through Alcock’s canal and is particularly vulnerable to crush injury during delivery. The injury may lead to denervation & atrophy of the external urethral sphincter (EUS) resulting in SUI symptoms. The aims of this study were to investigate if PN crush (PNC) in DM rats damages urinary function & if these altered responses are associated with increased levels of AGEs.

Methods: 252 female virgin Sprague-Dawley rats were divided equally into DM, diuretic (DU) & control (C) groups. Each group was then equally subdivided into PNC & sham PNC (SPNC). DM rats (blood glucose >300 mg/dL for 8 or 20 weeks prior to PNC) were induced by a Streptozotocin (35 mg/kg) injection. DU rats were fed with 5% sucrose in their drinking water. PNC was performed twice bilaterally by closing a needle holder over the PN for 30 seconds. SPNC rats underwent a dorsal skin incision only. All rats underwent awake cystometry (CMG) and leak point pressure (LPP) testing 4 or 13 days (with 8 wks of DM, n=14) & 4 days (with 20 wks of DM, n=14) after PNC or SPNC. The bladder, urethra, vagina & PN (8 wks-4d) were dissected separately & tested for levels of AGEs using gas chromatography/mass spectrometry (6/group) & en bloc (8/group) for histology.

Results: DM rats (8wks-4d) with SPNC had significantly increased voiding pressure & volume voided during CMG compared to both DU & C rats with SPNC. The duration or frequency of void was not significantly different in DM rats with SPNC compared to DU & C rats with SPNC. DM rats (8 wks-4d) with PNC had significant decreased voiding pressure & duration of voids compared to DM rats with SPNC. The volume voided by DM rats (8 or 20 wks) with PNC was not significantly different from that of rats with SPNC. The LPP testing was significantly decreased after PNC compared to SPNC & there were no differences between the C, DU, & DM groups after either PNC/SPNC. Furosine & carboxyethyl-lysion (CML) were significantly increased in all tissues tested in DM rats compared to C & DU rats. The disruption & pathology of the EUS was increased overall in rats with PNC compared to rats with SPNC.

Conclusions: DM rats even with SPNC require increased pressure to void since increased urinary volumes are typical of this pathology. DM rats with PNC likely have a highly distensible urethra, enabling them to void the same increased volumes with less voiding pressure. PNC leads to decreased urethral resistance to flow as demonstrated by LPP testing in all groups. The similarity of LPP between DM rats & both control groups suggests that PNC causes reduced LPP by denervation of the EUS regardless of the disease state. Therefore, PNC injury may play an important role in the development of SUI in DM. Elevated levels of certain AGEs may contribute to the dysfunction as well.

continued
Effect of Pudendal Nerve Crush on Urodynamic Function and Advanced Glycation End Products in Diabetic Female Rats

Pan HQ, Lin DL, Sypert D, Steward J, Monnier V and Damaser MS

Introduction and Objective: Crush injuries sustained by the pudendal nerve during child birth frequently cause denervation and atrophy of the external urethral sphincter (EUS) resulting in SUI symptoms. The aims of this study were to investigate if PN crush (PNC) in diabetic rats alters urinary function or the levels of advanced glycation end products (AGEs) when compared to non-diabetic rats.

Methods: 168 female virgin Sprague-Dawley rats were divided equally into diabetic (DM), diuretic (DU) & control (C) groups. Half of the animals in each group were subjected to PNC the other half to sham PNC (SPNC). Diabetes was induced in the DM group animals either 8 weeks or 20 weeks before PNC or SPNC by Streptozotocin injection (35 mg/kg). Diuresis in the DU group animals was induced by adding 5% sucrose to their drinking water. All rats underwent awake cystometry (CMG) and leak point pressure (LPP) testing 4 days after PNC or SPNC. The bladder, urethra, vagina and PN of the 8 week DM rats were extracted and tested for levels of AGEs using gas chromatography/mass spectrometry.

Results: CMG results showed that 8 week DM animals subjected to SPNC had significantly increased voiding pressure while those subjected to PNC had significant decreased voiding pressure and duration of voids. No significant difference was observed when the CMG results of 8 week and 20 week rats were compared. LPP was found to be significantly decreased in all animals subjected to PNC. Furosine & carboxyethyl-lysion (CML) was found to be significantly increased in DM animals in all of the tissues tested after PNC. AGEs levels were significantly increased after both PNC and SPNC in diabetic animals. Bladder weights and vagina weights were found to be significantly increased in DM rats. It was also found that only bladder weights significantly increased in DU. DM rats also exhibited significantly increased bladder cavities and significant decreases in bladder wall thickness. Diabetic rats also were found to have significant disruptions in the musculature of the EUS.

Conclusions: PNC results in the urethra becoming highly distensible in both DM and non –DM rats. This increased distensibility enables the animal to void the same increased volumes with less voiding pressure which leads to decreased urethral resistance to flow as demonstrated by the reduced LPP results in all groups. The similarity of LPP results in all groups suggest that reductions in LPP are caused by denervation of the EUS and not affected by DM.

Pelvic Floor Muscle: Does it contribute to Urinary Incontinence during a Stress to the Bladder?

Jiang H-H, Salcedo L, Gustilo-Ashby AM, Song B and Damaser MS

Introduction and Objective: Pelvic floor muscle (PFM) exercise has been regarded as a primary choice for treatment of stress urinary incontinence. To access if PFM activity contributes to urinary continence, we tested PFM electromyogram (EMG) response to an externally applied bladder pressure on female animals.

Methods: Thirty-one female adult Sprague-Dawley rats were studied under urethane-anesthetization with simultaneous recordings of filling cystometry (CMG; 5 ml/h) via transurethral catheter, PFM (pubo- or iliococcygeus muscle) EMG and external urethral sphincter (EUS) EMG. These muscles were accessed directly by the opening of pubic symphysis in a supine position. A pressure increase to urinary leakage (ΔP) was made by pressing a cotton swab on the bladder.

Results: During filling CMG, EUS EMG showed steady tonic activity during continence and bursting activity during voiding. For PFM EMG, some rats showed steady tonic activity (n=13) during continence and decreased activity (arrow c) during voiding. For other rats PFM EMG (n=18) showed no tonic activity, but activated by pinching the perineal skin. This activity could be maintained unless voiding occurred. The ΔP (45±5.45 cmH₂O) to leakage caused increased EUS EMG activity (arrow a). However, there was no such positive response in PFM EMG. 36% of the ΔPs caused a decrease in PFM EMG activity (arrow b). This may reflect a reflex intended to protect the bladder and upper urinary tract from high sudden pressure by allowing leakage.

Conclusions: PFM, unlike EUS, has no contribution to prevention of incontinence during an applied increase in bladder pressure (bladder-to-urethra guarding reflex). Probably, PFM exercise facilitates continence by reinforcing PFM to decrease the bladder neck mobility or prolapse, but doesn’t involve in the above mechanism.
Differential Gene Expression of Lysyl Oxidase Like-1 (LOXL1) Knockout (KO) Mice with Pelvic Organ Prolapse

Lee UJ, Gustilo-Ashby AM, Kuang M, Rackley R, Li T and Damaser MS

Introduction: Genes potentially associated with human pelvic organ prolapse (POP) or stress urinary incontinence (SUI) have been identified. The objective of this study is to investigate the differential expression of candidate genes implicated in human prolapse and upregulated genes implicated in human SUI in Lysyl Oxidase Like-1 (LOXL1) knockout (KO) mice with and without prolapse compared to C57BL/6 nonprolapsed mice in order to investigate the molecular mechanism of POP in LOXL1 KO mice.

Methods: Mouse vaginal tissue was collected from 3 groups: (1) LOXL1 KO parous mice with POP (n=5), (2) LOXL1 KO parous mice with no evidence of POP (n=5), and (3) C57Bl/6 nulliparous mice with no evidence of POP (n=5). The tissue was microdissected and flash frozen in liquid nitrogen and stored at -80 degrees. The following 11 genes were selected for targeted gene expression analysis: SGCB, MYO10, KIRT16, LAMC2, pKp1, MYBPC2, MYH14, NFI13, LAMC1, COL8A1, and HAS3 based on their described role in POP or SUI. Total RNA was extracted from the tissues. Quantitative real-time PCR was performed. Relative mRNA levels were determined by comparison to GAPDH internal control.

Results: Relative mRNA of the 11 selected genes in the vaginal tissue of the 3 groups was measured. There were no significant differences across the groups for the following 10 genes: SGCB, MYO10, KIRT16, LAMC2, pKp1, MYBPC2, MYH14, NFI13, LAMC1, and COL8A1. Hyaluronan synthase 1 (HAS1) was differentially expressed across the 3 groups (p<0.0469). HAS1 had increased expression in the prolapsed group and decreased expression in the non-prolapsed group, compared to control.

Conclusions: To determine what genes and molecular pathways are involved in the development of POP and urinary dysfunction, we used LOXL1 KO mice to investigate 11 genes that have been implicated in human POP or human SUI. Limitations and potential confounding factors of this study include controlling for age, parity, and estrus cycle. Nonetheless, we found that HAS1 gene expression was upregulated in prolapsed LOXL1 KO mice compared to C57Bl6 controls, and downregulated in LOXL1 KO mice without prolapse. HAS1 is involved in extracellular matrix and developmental regulation and important in wound healing and tissue structural integrity, and may warrant further investigation in the study of pelvic organ prolapse.

Mechanisms of Mid-urethral Sling Effects; Role of Suburethral or Lateral Support for Anti-Incontinence Effects


Introduction and Objective: Previous studies in a rat model of mid-urethral sling have suggested that the suburethral portion of the mid-urethral sling may not be necessary to produce the effect of increased urethral resistance as measured by leak point pressure (LPP), but may contribute to morbidities associated with slings including the voiding dysfunction (Hijaz, J of Urology 2005). In response to these findings, a composite sling model was developed to further test the hypothesis that lateral support, rather than suburethral support is all that is required to produce the anti-incontinence effects of the sling. The objective of this study was to evaluate the short and long-term efficacy of a novel composite mid-urethral type sling in a rodent model of stress urinary incontinence (SUI).

Methods: SUI was created in 28 female Sprague-Dawley rats by bilateral pudendal nerve transaction (PNT) under ketamine/xylazine anesthesia as described previously. The animals then were randomly assigned to short term (24 hours) or long-term (4 weeks) groups and underwent placement of either traditional mid-urethral sling (n=10) by placement of a 2 x 0.3cm strip of Prolene (Ethicon, Somerville, New Jersey) mesh at the mid-urethral level; a novel composite sling (n=10) where no vaginal dissection is performed and the sling is modified to have no suburethral effect; or sham sling (n=8). Within 24 hours or four weeks later, under urethane anesthesia, a suprapubic tube was placed and LPP was measured using a Crede maneuver, as described previously. In each animal LPP was measured 5-6 times and the mean was taken. Pairwise differences in LPP between the groups were calculated using the Wilcoxon signed rank test with p<0.05 considered significantly different.

Results: In the long-term group, the traditional sling increased LPP significantly compared to the sham group (54.83 vs. 38.16 cm H2O, respectively, p = 0.0017). The composite sling did not increase the LPP compared to the sham group (36.83 vs. 38.16 cm H2O, respectively, p=0.7072), as depicted below. Neither traditional nor composite sling increased the LPP above the sham in the short-term group.

Conclusions: Suburethral segment of sling is needed to restore the LPP in female rats models of SUI. In early studies, it does not appear that the sling without the suburethral support would be as effective at restoring LPP. Further refinements in design may help us to clarify the utility of this novel composite sling model.
Cytokine Expression after Vaginal Distension of Different Durations in Virgin Sprague-Dawley Rats

Hadley M. Wood MD, Mei Kuang, Lynn Woo MD, Adonis Hijaz MD, Marc Penn MD, PhD, Raymond Rackley MD, and Margot S. Damaser PhD

Introduction and Objective: Vaginal distension (VD) has been used to simulate injuries of vaginal childbirth in rat models. We have previously shown that VD results in upregulation of monocyte chemotactic protein-3 (MCP-3) in the vagina and urethra, which signals stem cell (SC) migration to injury sites. In this study, we investigate the effect of duration of VD on the differential expression of cytokines and cytokine receptors involved in SC homing and tissue repair to identify the factors most important for recovery from injury.

Methods: 20 10-week virgin Sprague-Dawley rats were divided into 4 groups: 1 hr VD, 4 hr VD, 6 hr VD, and 4 hr anesthesia without VD. Vagina, bladder, urethra and rectum were harvested immediately after VD and flash-frozen. Real-Time PCR was used to determine levels of expression of cytokines and receptors associated with SC homing and tissue repair. Mixed models analysis was used to determine associations between expression level and duration of distension, with significance considered at p<0.05.

Results: Positive associations between duration of VD and level of urethral expression were found for two of the CC chemokine receptors (CCR) of MCP-3 [CCR1 (p=0.0001) and CCR5 (p=0.032)], as well as, for MCP-3 (p=0.025), and hypoxia-inducible factor 1-α (HIF1-α, p=0.023). Duration of VD also resulted in upregulation of MCP-3 expression in rectal tissue (p=0.035). Urethral expression of CCR2, another receptor for MCP-3, approached significance (p=0.066). An inverse relationship between duration of VD and expression of IL8 was found in the bladder (p=0.0008). Trends in expression of stromal cell-derived factor 1 (SDF-1), another SC homing cytokine, and its receptor, CXCR4, were not significant in any of the pelvic organs with increasing duration of VD. Expression of CCR2, CCR3, and vascular endothelial growth factor (VEGF) also did not change significantly with increasing VD duration in any of the tissues studied.

Conclusions: There appears to be a strong relationship between duration of VD and expression of MCP-3 and two of its associated receptors (CCR1, CCR5) in the urethra immediately following VD. The increase in HIF1-α expression in the urethra with prolonged VD suggests a limited role of tissue ischemia in the immediate response of pelvic organs to VD. The inverse association between IL8 expression and duration of VD observed in the bladder suggests that the inflammatory response plays a limited role in bladder recovery from VD.

Impact of Delivery on Stem Cell Homing Factors after Rat Vaginal Distention

Hadley M. Wood MD, Mei Kuang, Lynn Woo MD, Adonis Hijaz MD, Marc Penn MD, PhD, Raymond Rackley MD, and Margot S. Damaser PhD

Introduction and Objectives: Rat vaginal distention (VD) has been used to study the effects of vaginal delivery, including stem cell (SC) homing. A comparison between virgin (V) and peripuerpural (P) rats after VD has not been made. We hypothesized that the parturition contributes to expression of SC homing factors and their receptors after VD as compared with virgin rats.

Methods: 72 Lewis rats were divided into 4 groups: 1) V w/o VD (control), 2) V w/ VD, 3) P w/ VD, and 4) P w/o VD. For groups 3 and 4, primigravid timed-pregnant rats were obtained and observed until delivery. Within 24 hrs of delivery, group 3 underwent VD for 4 hrs. At the same time, group 2 (age-matched V) underwent VD for 4 hrs. After delivery, group 4 underwent anesthesia w/o VD (4 hrs). Group 1 (age-matched V) underwent anesthesia w/o VD (4 hrs). Each group (N=18) was further randomized to euthanasia immediately (N=6), 3 days (N=6) or 7 days (N=6) after VD, at which time pelvic organs were dissected and flash-frozen. RTPCR was used to determine levels of expression of biochemicals associated with SC homing factors in the urethra. Our laboratory has shown that the majority of histological and biochemical changes that occur after VD affect the urethra and immediately adjacent tissues. Thus, we focused on expression of SC homing factors in the urethra. Mixed models analysis was used to evaluate associations between groups and chemokine/receptor expression.

Results: VD was a significantly correlated with urethral expression of SC homing factor, MCP3 (p<0.0001), two of the known receptors for MCP3 (CCR1, p=0.0013; CCR2, p=0.0016). Two additional related receptors (CCR3, p<0.0001; CCR5, p<0.0001), as well as pro-inflammatory mediators HIF-1α (p<0.0001) and VEGF (p=0.0009) also correlated with VD. While there was no association between SDF1 expression and VD, the SDF1 receptor, CXCR4, was significantly upregulated after VD (p<0.0001). The effect of VD was seen regardless of whether the animals were V or P. Peripuerpural status independently affected tissue expression only of CCR1 (p=0.008) and HIF1α (p=0.045).

Conclusions: Rat VD results in persistent upregulation of biochemicals associated with SC homing, independent of parturition, which may account for the findings of reduced LPP and functional recovery demonstrated previously. Parturition does not appear to provide additional protective benefit with regards to expression of most of these molecules (exception CCR1 & HIF1α). Since rat vaginal delivery (w/o VD) does not appear to result in reduced LPP, it is postulated that the additional intervention of VD is necessary to simulate the injury sustained during human vaginal delivery.
Section 4

Infertility
Presence and Possible Role of Poly (ADP-ribose) Polymerase (PARP) Homologues in Ejaculated Human Spermatozoa

Rakesh Sharma, PhD, Ashok Agarwal, PhD, Rejesh Jha, PhD, Reda Mahfouz, MD, Uwe Paasch, MD, Sonja Grunewald, Satya Yadav, PhD, Edmund Sabanegh, MD

Introduction and Objective: Sperm DNA damage plays an important role in the pathogenesis of male infertility. Poly (ADP-ribose) polymerases (PARP) have been involved in various sperm cell functions such as gamete differentiation (during spermiogenesis), spermatogenesis and chromatin remodeling. PARP cleavage has been reported as an apoptosis or necrosis marker in other cell types. However its presence on ejaculated sperm is unclear. Our objective was to investigate the presence of PARP and evaluate its function in ejaculated spermatozoa.

Methods: Study employed semen specimens from 18 healthy fertile donors and 12 infertile males. Double layer density gradient, protein extraction, detection, immunoblotting and exposure to PARP inducer staurosporine, or hydrogen peroxide with or without PARP inhibitor 3-aminobenzimide were used. PARP proteins were detected by MALDI-Tof-Tof and the corresponding protein was identified based on the peptide mass fingerprinting.

Results: Three distinct PARP homologues were detected (~75, ~63 and ~60 kDa). These were identified as PARP-1, PARP-2 and PARP-9 respectively (Table). PARP protein was positively related with sperm maturity. PARP proteins (75, 63 and 60 kDa) were modulated to varying extent in mature and immature fraction following induction of apoptosis by hydrogen peroxide and staurosporine exposure in the presence and absence of the PARP inhibitor (3-aminobenzenzamide)

<table>
<thead>
<tr>
<th>Band (kDa)</th>
<th>Query match/Percentage</th>
<th>Name of PARP homologue</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>31/40 (77%)</td>
<td>Poly [ADP-ribose] polymerase 1 (ADPRT) (NAD(+) ADP-ribosyl transferase 1) (PARP-1)</td>
</tr>
<tr>
<td>63</td>
<td>24/43 (55%)</td>
<td>Poly [ADP-ribose] polymerase 9 (PARP-9)</td>
</tr>
<tr>
<td>60</td>
<td>13/23 (56%)</td>
<td>Tankyrase-2 (TANK2)</td>
</tr>
</tbody>
</table>

Conclusions: Poly (ADP-ribose) polymerase (PARP) homologues (~75, ~63 and ~60 kDa) were identified as PARP-1 (~75 kDa), PARP-9 (~63 kDa) and PARP-2 (~60 kDa) respectively in ejaculated human spermatozoa. A positive correlation between the amount of PARP protein and sperm maturity suggests a role of PARP proteins in DNA damage/repair.
The Natural History of Low Level Leukocytospermia in Men Seeking Evaluation for Infertility

Edmund Sabanegh, MD

Introduction: Controversy exists regarding the impact of seminal leukocytes on fertility. Some studies find detrimental effects, while others find no effect or even beneficial effects. What concentration of leukocytes is significant is also unproven. Traditionally the WHO defines leukocytospermia as greater than 1M leukocytes/ml. Despite this definition, investigators have found that even very low levels of leukocytospermia have significantly higher levels of oxidative stress than samples with no detectable leukocytes and that at these lower levels, there is a significant decrease in sperm motility and DNA integrity.

Considering that low level leukocytospermia may impair sperm function in infertile males, we have begun to empirically treat patients with leukocytospermia > 0.1M/ml at our institution. In an effort to assess treatment of leukocytospermia, however, the natural history of semen leukocytes must first be assessed.

Objective: To define the rate of spontaneous resolution and variability of lower level leukocytospermia.

Method: Retrospective chart review was carried out and all patients with any level of leukocytospermia were identified. Those who had more than one semen analysis prior to treatment were evaluated to determine the variability in leukocytospermia as measured by the Endtz test.

Results: Average time interval between Endtz tests was 65 days (Range 21-179). When consecutive Endtz scores were analyzed, there were 12 increases in levels of leukocytes, six decreases, and two unchanged. Only 2 (10%) resolved spontaneously. Figure 1 shows the trends of Endtz scores among patients with at least 2 separate Endtz tests prior to undergoing any treatment.

Discussion: The rate of spontaneous resolution of leukocytospermia is relatively low (10%). Lackner et al have reported a spontaneous “resolution” rate of 43% when using a cut-off value of 1M/ml. Considering evidence exists for possible adverse effects of even low level leukocytospermia, this cut-off value may be too high. Our data suggest that absolute resolution of leukocytospermia is much less common at 10%. This provides background data for further studies on the treatment of low level leukocytospermia in that any treatment will need to demonstrate success rates significantly greater than 10%.

Conclusion: The true cut-off value for significant leukocytospermia is unknown, however when considering any level of leukocytospermia as possibly detrimental, only 10% of patients will spontaneously resolve.
Correlation of Kruger Morphology and Successful Intrauterine Insemination

Edmund Sabanegh, MD

Introduction and Objective: For couples undergoing Intrauterine Insemination (IUI), total motile sperm count correlates with IUI success. The significance of sperm morphology as it relates to IUI success, however, is less well defined. A few studies have suggested a positive correlation between Kruger morphology and success rates with IUI, but other data suggests that significant numbers of fertile men also have abnormal sperm morphology. In this review we aim to assess any relationship between sperm morphology and successful IUI outcomes.

Methods: 98 consecutive couples that underwent semen analysis and intrauterine insemination at our institution were identified. Each male’s first complete semen analysis was used as IUI analyses do not include assessment of morphology. Pregnancy rates per couple were analyzed in relation to sperm concentration, motility, total motile count, % normal Kruger morphology, total number of morphologically normal sperm, and the total normal motile sperm count (total motile count X % normal Kruger morphology). Univariate and multivariate logistic regression analysis evaluated the correlation between each factor and pregnancy.

Results: On univariate analysis, average male partner age was the only factor that was significantly different between the couples that did and did not achieve pregnancy (p=0.01). On multivariate analysis, sperm concentration, total motile count, total number of morphologically normal sperm, and the total normal motile sperm count all failed to show a significant correlation with pregnancy outcomes (p ≥ 0.05). Values in the table are presented as mean (SD).

Conclusions: In our model, motility and morphology failed to associate with IUI success. Though total motile count is accepted as a predictor of IUI success, the lack of correlation in our study is likely due to the fact that it is retrospective in nature. Therefore, men in our population had already met minimal standards for motility and concentration. Unlike total motile count, however, couples with poor morphology are not excluded from proceeding with IUI. Thus our study suggests that Kruger morphology does not predict IUI success. Furthermore, the novel parameter (total normal motile sperm count) does not appear to correlate with IUI outcome either.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Couples Not achieving pregnancy (n=61)</th>
<th>Couples achieving pregnancy (n=37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male age (yrs)</td>
<td>38.0 (5.7)</td>
<td>35.3 (4.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Female age (yrs)</td>
<td>34.0 (4.4)</td>
<td>33.1 (4.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Kruger morphology (% normal)</td>
<td>6.8 (9.3)</td>
<td>7.1 (10.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Total Motile Count</td>
<td>102.2 (110.0)</td>
<td>146.1 (137.0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Total Motile Normal Count</td>
<td>10.3 (19.3)</td>
<td>17.0 (30.0)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Conclusion: Kruger morphology may have little utility in predicting IUI outcomes. Live birth rate was high even with abnormal morphology. We did not find that poor sperm morphology negatively affected blastocyst quality. This is likely a result of being able to select individual normal sperm during the ICSI procedure itself.

Kruger Morphology, Blastocyst Formation, Live Birth Rate and other Clinical Outcomes of Intracytoplasmic Sperm Injection

Edmund Sabanegh, MD

Introduction and Objective: Kruger morphology may have little predictive value in the clinical setting of in-vitro fertilization (IVF) with Intracytoplasmic sperm injection (ICSI). ICSI negates many problems associated with poor morphology. Prior studies suggest poor sperm morphology is associated with decreased blastocyst formation. We evaluate the prognostic value of Kruger morphology on pregnancy outcomes and embryo development of ICSI cycles.

Methods: Outcomes for 1074 IVF /embryo transfer cycles from Jan. 2001 to Dec.2006 at Cleveland Clinic Fertility Center were evaluated. Patients older than 36 years were excluded. Embryos were cultured in HTF with 10% SSS. Embryos were selected for transfer on Day 3 based on standard criteria. Remaining embryos were cultured until day 5 or 6 and frozen at the blastocyst stage. The relationship between sperm morphology, embryo quality, development, implantation rate, and live birth rate was analyzed.

Results: The table compares Kruger morphology and outcomes in 1074 ICSI cycles. Excellent outcomes were achieved, even in sperm samples with 0% normal forms. This suggests that once introduced into the oocyte, sperm from morphologically abnormal samples have the same potential as those from specimens with normal morphology. It may be that during selection of sperm, embryologists eliminate morphology as a factor by selecting the “most normal” sperm within a population of abnormal sperm. The largest percentage of high quality blastocysts suitable for freezing was found in the group with 0% normal morphology and ranged from 26-37% between groups(p= 0.0026). This may be reflective of the cause of infertility itself. In groups with the most abnormal sperm and so male factor as the primary diagnosis, underlying female factors may have been less. Thus, once the impact of morphology was mitigated by the use of ICSI, these groups actually had better blastocyst development

Conclusion: Kruger morphology may have little utility in predicting ICSI outcomes. Live birth rate was high even with abnormal morphology. We did not find that poor sperm morphology negatively affected blastocyst quality. This is likely a result of being able to select individual normal sperm during the ICSI procedure itself.
Effect of Elevated Male Partner Body Mass Index on Outcomes of Intrauterine Insemination

*Edmund Sabanegh, MD*

**Introduction and Objective:** Little is known about the effect of elevated male partner Body Mass Index (BMI) on fertility. Initial reports suggest an inverse correlation between BMI and numbers of normal motile sperm, but no data on pregnancy outcomes has been reported. In this study, we attempt to define the effect of male partner BMI on the outcome of Intrauterine Insemination (IUI).

**Methods:** Charts of couples undergoing IUI at our institution between January and October of 2006 were reviewed and data gathered with respect to semen parameters, the age and BMI of both partners, and pregnancy outcomes. Semen parameters were obtained from both diagnostic semen analyses and IUI specimens, but pregnancy outcomes were only assigned to IUI specimens. Couples were grouped according to male partner BMI as Obese (BMI >30), Overweight (BMI 25-30), and Normal (BMI <25). The ANOVA test was used to assess differences in variables across BMI groups. Univariate and multivariate logistic regression analysis was performed to define any association of variables with pregnancy outcome.

**Results:** 71 couples had data on male partner BMI and were included in the study for a total of 381 Semen analyses of which 205 were IUI cycle analyses. Table 1 shows the differences in female BMI, female age and semen parameters across male BMI categories.

<table>
<thead>
<tr>
<th>Variables</th>
<th>All analyses (n=381)</th>
<th>Male BMI groups (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;25 (n=110)</td>
<td>25-30 (n=183)</td>
</tr>
<tr>
<td>Female BMI</td>
<td>26.2 (5.6)</td>
<td>25.8 (5.5)</td>
</tr>
<tr>
<td>Female Age (yrs)</td>
<td>35.4 (4.3)</td>
<td>35.1 (4.4)</td>
</tr>
<tr>
<td>Semen analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>2.9 (1.7)</td>
<td>3.1 (1.8)</td>
</tr>
<tr>
<td>Motility (%)</td>
<td>57.6 (20.4)</td>
<td>53.6 (19.5)</td>
</tr>
<tr>
<td>Concentration (M/ml)</td>
<td>52.7 (60.1)</td>
<td>45.6 (46.5)</td>
</tr>
</tbody>
</table>

All variables expressed as Mean (SD). P-values given are for comparison between BMI > 30 group and any other groups.

**continued**
Infertility

Semen Culture Analysis of Persistent Semen Leukocytes after Empiric Treatment with Doxycycline

Edmund Sabanegh, MD

Introduction: Genital tract infection has been shown to be deleterious to sperm function and spermatogenesis. The impact of subclinical infections is less clear and most studies show poor correlation between leukocytospermia (LSP) and bacteriospermia. The lack of correlation may be due in part to lack of standardized specimen collection, presence of fastidious organisms, and different patient populations. Though these studies compared semen culture results and LSP levels, to our knowledge no study has investigated these relationships in patients with persistent LSP after empiric treatment.

Objective: To describe the characteristics, particularly semen culture results, of patients with persistent LSP after empiric treatment with doxycycline.

Methods: At our institution, patients with LSP over 0.1M/ml are treated empirically with doxycycline. 3 months after treatment, if LSP does not resolve, a semen culture is recommended. We retrospectively reviewed patients who had undergone empiric doxycycline therapy and analyzed those who had persistent levels of LSP as measured by the Endtz test.

Results: Of a total of 142 patients, 58 (41%) had LSP greater than 0.1M leukocytes per ml. Of the patients empirically treated with doxycycline, 22 had at least one follow-up semen analysis. Of these, 10 (45%) had resolved LSP, 12 of 22 (55%) had persistent LSP despite empiric treatment and of these, 7 patients had a semen culture. Table 1 shows the semen parameters of this group.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>pH</th>
<th>Vol</th>
<th>Mot</th>
<th>Count</th>
<th>Kruger</th>
<th>WHO</th>
<th>Endtz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>7.8</td>
<td>4.3</td>
<td>53</td>
<td>37.1</td>
<td>5</td>
<td>21</td>
<td>5.82</td>
</tr>
<tr>
<td>Post empiric treatment</td>
<td>7.8</td>
<td>3.6</td>
<td>54</td>
<td>14.7</td>
<td>7</td>
<td>38.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Post culture directed</td>
<td>7.5</td>
<td>3.7</td>
<td>60</td>
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<td>7</td>
<td>34</td>
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</tr>
</tbody>
</table>

The results of the cultures were as follows: Normal flora (2), Enterococcus (2), Methicillin Resistant Staph Aureas (MRSA) (1), Gram negative Rods (1), Coag Negative Staph (1). After culture directed therapy, 1 of 7 (14%) had resolution of LSP, 2 of 7 (28%) had persistent LSP and 4 of 7 (57%) did not have a follow-up semen analysis.

Discussion: While some studies have suggested an inverse relationship between BMI and semen parameters, this was not observed in the present study. Men with a BMI over 30 tended to have partners who were older and who also had elevated BMI. To adjust for this, multivariate analysis was performed and revealed a trend towards decreasing pregnancy Odds Ratio (OR) in overweight and obese men, but it failed to reach statistical significance. Certainly a larger sample size might be expected to demonstrate statistical significance.

Conclusions: Elevated male BMI does not correlate with semen parameters, although there is a trend towards decreasing pregnancy rates with IUI in men with elevated BMI. Additional larger studies are needed to elucidate the effect of elevated male BMI on assisted reproduction outcomes.

Table 2 shows the results of the multivariate analysis evaluating the relationship of male partner BMI to fertility.

<table>
<thead>
<tr>
<th>Male BMI group</th>
<th>Pregnancy Rates</th>
<th>Multivariate OR for Pregnancy (95% CI) p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>17.5</td>
<td>1.0†</td>
</tr>
<tr>
<td>25-30</td>
<td>17.0</td>
<td>0.8 (0.3-2.0)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>7.5</td>
<td>0.3 (0.1-1.4)</td>
</tr>
</tbody>
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† Reference group

Semen Culture Analysis of Persistent Semen Leukocytes after Empiric Treatment with Doxycycline

Edmund Sabanegh, MD

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Infertility

Empiric Treatment of Low Level Leukocytospermia

Edmund Sabanegh, MD

Introduction and Objective: Leukocytospermia has traditionally been defined by the World Health Organization (WHO) as greater than 1 million (M) leukocytes per milliliter (ml) of seminal fluid. However, there is growing evidence that even much lower levels of leukocytospermia are associated with elevated levels of oxidative stress, and a significant decrease in sperm motility and DNA integrity.

This initial report describes the outcomes of empiric antibiotic therapy for patients with leukocytospermia of 1 M/ml or less.

Methods: A retrospective review of records of patients receiving infertility evaluation from Sept. 2006 to Sept. 2007 was conducted. Of 168 patients evaluated for leukocytospermia, 29 had seminal leukocyte levels between 0.2 and 1.0 M/ml as identified by the Endtz test and had received empiric short-course antibiotic therapy. 21 had follow-up analysis. The control group (n=24) was obtained by reviewing consecutive charts for a period immediately preceding the practice of routine treatment of low level leukocytospermia. A paired t test was used for comparisons between groups. Pregnancy data was obtained from record review and telephone interview. Its association with semen parameters was evaluated using logistic regression analysis. Pregnancies resulting from in-vitro fertilization were excluded from this analysis.

Results: Table 1 shows differences between treated patients before and after empiric antibiotic therapy.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-Tx</th>
<th>Post-Tx</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (M/ml)</td>
<td>42.6 (59.5)</td>
<td>51.8 (63.6)</td>
<td>0.9</td>
</tr>
<tr>
<td>Motility (%)</td>
<td>50.6 (22.3)</td>
<td>53.2 (22.1)</td>
<td>0.9</td>
</tr>
<tr>
<td>Total Motile Count (M)</td>
<td>49.9 (61.1)</td>
<td>88.8 (156)</td>
<td>0.5</td>
</tr>
<tr>
<td>Kruger (% NL)</td>
<td>3.3 (2.91)</td>
<td>3.7 (2.1)</td>
<td>0.9</td>
</tr>
<tr>
<td>Endtz (M/ml)</td>
<td>0.6 (0.2)</td>
<td>0.5 (0.6)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Numbers expressed as Mean (SD)

Discussion: There were no statistically significant differences in semen parameters among any category. This could be due to an actual lack of treatment effect or to the small sample size. There is an obvious trend towards decreasing levels of LSP with empiric antibiotic treatment after culture directed treatment. A larger sample size would likely reveal differences that were statistically significant.

The cultures reveal that a significant portion of patients with persistent LSP will harbor pathogenic bacteria. We consider Gram Negative Rods, Enterococcus and MRSA to be pathologic organisms and these organism accounted for 4/7 (57%) of the culture results.

Conclusion: Empiric antibiotics may reduce the numbers of semen leukocytes. In those patients where LSP does not resolve, semen culture is likely to identify significant pathologic bacteria.
Table 2 compares the pre-treatment semen parameters of treated patients with semen parameters of case-matched untreated patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treated (n=21)</th>
<th>Not treated (n=24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (M/ml)</td>
<td>42.6 (59.5)</td>
<td>52.4 (59.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Motility (%)</td>
<td>50.6 (22.3)</td>
<td>44.5 (23.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Total Motile Count (M)</td>
<td>49.9 (61.1)</td>
<td>69.7 (97.8)</td>
<td>0.4</td>
</tr>
<tr>
<td>Kruger (% NL)</td>
<td>3.3 (2.91)</td>
<td>4.2 (4.6)</td>
<td>0.6</td>
</tr>
<tr>
<td>Endtz (M/ml)</td>
<td>0.6 (0.2)</td>
<td>0.5 (0.2)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Numbers expressed as Mean (SD)

Treatment with antibiotic was associated with improved likelihood of achieving pregnancy with an Odds Ratio (OR) of 3.9, 95% CI 1.0-1.56, p=0.05 on univariate analysis. Multivariate analysis also yielded similar results: OR 4.1, 95% CI 0.9-18.6; p=0.06. The overall pregnancy rate was 9/21 (43%) for the treatment group and 4/24 (17%) for the untreated group.

Discussion: Semen parameters between the two groups were similar. Treatment with antibiotics tended to increase the total motile count, but this did not assume statistical significance. However, pregnancy rates showed marked improvement with empiric therapy for low level leukocytospermia, with an odds ratio of 3.9.

Conclusion: Treatment of low level leukocytospermia appears to improve pregnancy outcomes, though semen analysis appears minimally changed. Studies with larger numbers of patients are needed to confirm these findings.

Sexual Development and Fertility of LOXL1-/- Male Mice

Hadley M. Wood, Una J. Lee, J.H. Ross, E. Sabanegh, Tiansen Li, and Margot S. Damaser

Introduction and Objective: Lysyl oxidase-like protein 1 (LOXL1) is one several enzymes that oxidize primary amine substrates and participate in maintenance of elastic fiber homeostasis. Recent evidence suggests that LOXL1 may play a role in fetal development, tissue tumor suppression, cell motility, and cellular senescence, in addition to extracellular matrix remodeling. During breeding of LOXL1-/- for studies of pelvic organ prolapse in females, LOXL1-/- mouse pairs demonstrated subfertility relative to control pairs. The objective of this study was to investigate the genitourinary defects and fertility of the male LOXL1-/- mice, with particular attention to testicular, epididymal, gubernacular and penile histopathology and fecundity, which may lead us to a better understanding of the role of LOXL1 in male sexual development.

Methods: Morphometric evaluation of 6-9 month old male LOXL1-/- (N=26) gonads and genital organs were compared with male C57Bl/6 controls (N=24). These measurements included: age, body weight, scrotal development, evidence of feminization (nipples or vaginal pouch), penile malformations, anogenital distance (AGD), absence/presence of perineal bulge, and size of perineal bulge. Estimates of gonadocyte productivity were derived using a standard technique of gonadal homogenization. A breeding program was conducted to determine how much of the infertility observed in LOXL1-/- pairs was due to male-factor. Qualitative histopathological comparison of the genitourinary organs of male LOXL1-/- and control mice using H&E and von Gieson’s staining was undertaken.

Results: LOXL1-/- mice weighed less than their age-matched C57Bl/6 counterparts (p<0.001). Size-adjusted perineal bulge was larger (p<0.001) and resting location of the gonads were higher intraabdominally (p=0.048). Estimates of daily gonadocyte counts also suggested that the LOXL1-/- mice had lower gonadocyte productivity (p=0.048). The breeding program results suggested that the LOXL1-/- males paired with control females demonstrated relative fecundity values intermediate between LOXL1-/- pairs (lowest fecundity) and control pairs (highest fecundity), suggesting a component of male-factor infertility. No gross qualitative histological differences were noted on H&E or von Gieson’s staining of the gonads, gubernaculum and penis.

Conclusions: These findings suggest a subtle, possibly multifactorial, role of the LOXL1 protein in male sexual development and fertility.
Section 5

Sexual and Pelvic Health
Early Intervention with PDE-5 Inhibitors following Prostate Brachytherapy Improves Subsequent Erectile Function

Geetu Pahlajani, Marwan Ali, Rupesh Raina, Craig Zippe

Introduction and Objective: Prostate mono brachytherapy (PMB) is an accepted option for Gleason 6, low-volume Gleason 7 prostate cancers, and is being offered more frequently in younger patients. Unfortunately, erectile dysfunction can be a side effect from PMB, occurring frequently in the first 12 months following treatment. This study examines the use of early PDE-5 inhibitors (sildenafil citrate) in preventing subsequent erectile dysfunction following prostate brachytherapy.

Methods: We examined a single surgeon series of 69 patients that had undergone prostate mono brachytherapy from 2002-2005. All patients had a minimum 1-year follow up. Prospectively, patients had baseline, 6 and 12 month SHIM and IIEF-6 scores recorded. The 69 patients were divided into early sildenafil (31) and non sildenafil groups (38) and their SHIM and IIEF-6 scores were compared at 6 and 12 months. Daily sildenafil (25-50 mg) was given immediately in the perioperative period for a duration of 12 months. Overall, for the entire group, the mean PSA was 6.8; 78% had Gleason 6 cancer; 20% had Gleason 7 (3+4) cancer. The mean age in the early PDE-5 group was 62.8 years; in the non PDE-5 group, 66.0 years. The mean radiation units in the early PDE-5 group was 50.2; in the non PDE-5 group, 43.9U (p = 0.08).

Results: In the non PDE-5 group, the mean baseline SHIM score of 17.1 dropped quickly to 9.1 at 6 months and stayed at 9.3 at 12 months. In the early PDE-5 group, the mean baseline SHIM score of 21.8 decreased slightly to 17.6 at 6 months, and was maintained at 17.9 at 12 months. (p>0.01 vs baseline). Using the Wilcoxon Rank Sum Test, the 6 and 12 month SHIM scores in the early PDE-5 group differed from the non PDE-5 group (p< 0.001). The IIEF-6 questionnaire confirmed the SHIM analysis (see Table).

Conclusions: Following prostate mono brachytherapy, patients experience a significant decline in SHIM / IIEF-6 scores at 6 and 12 months. Our data indicates a 50% decrease in the quality of their erections. This gives us a window of opportunity to initiate an early intervention program with PDE-5 inhibitors, vacuum constriction devices or intraurethral alprostadil. In this study, the early use of sildenafil citrate following PMB maintained erectile function at both 6 and 12 months.
Early Incidence of Erectile Dysfunction following Prostate Brachytherapy

Zippe C, Pahlajani G

Introduction: Prostate brachytherapy is been chosen in somewhat same incidence as robotic prostatectomy for localized prostate cancer. Because of its rising popularity, our institution decided to look in closer details at the morbidity and side effects of this procedure.

Methods and Materials: We examined a single surgeon series of 59 patients that had undergone prostate brachytherapy from 2002 to 2005. All these patients had at least one-year follow-up. The patients had baseline SHIM scores performed as well as IIEF (6+3). The IIEF (6+3) included 6 questions on satisfaction plus 3 additional questions on change in intensity of orgasm, pain at orgasm and blood in the ejaculate. These scores were recorded at baseline, 6 months and 12 months. The mean age of this population was 65 and the mean PSA was 6.75. 46/59 (78%) had Gleason 6 tumor, 12/59 (20%) had Gleason 7 tumor and 1 patient had Gleason 8. The mean number of seeds placed in these patients was 108 with the mean radiation of 47.18 U.

Result: Baseline mean SHIM scores of the patients were 19, 6 months mean SHIM score were 12.0 and 12 months SHIM score were 12.13. This indicates a significant decline in erectile function that happens quiet early. When the IIEF 6 scores were seen, they were 23.3 at baseline, 14.19 at 6 months and 14.58 at 12 months. The second validated questionnaire confirms the acute incidence of erectile dysfunction. At 12 months, 2 patients had pain at orgasm and 6 patients had blood in the ejaculate. Majority (76%) of the patients noticed change in the orgasm. 21/59 number of the patients were placed on early Viagra program. The patients on the early Viagra program had their baseline SHIM score of 22.4 and the 6 months and 12 months score were 17 and 18.4 respectively. The patients who were not in the early program had their baseline SHIM score of 17.1 and their 6 and 12 months score of 9.1 and 8.4 respectively.

Conclusion: Patients of prostate brachytherapy who don’t enter in early PDE-5 inhibitors program experience a significant decline in their SHIM score at 6 months and 12 months. Our data indicates nearly 50% decrease in the quality of their erections. Majority of these patients can still have vaginal penetration but do suffer considerably in the quality of their erections. 76% had a change in orgasm but painful orgasm and blood in the ejaculate were not major issues. The implication of this data is that patients who left untreated with early intervention program had a significant decline in their sexual function in their first 6 and 12 months. This gives us the window of opportunity to initiate early intervention program such as PDE-5 inhibitors, vacuum constriction devices, MUSE.
VCD Revisited: Its Emerging Role in Preventing Erectile Dysfunction (ED)

Craig Zippe, Geetu Pahlajani

Introduction: There is considerable interest in early intervention protocols in use of VCD to encourage corporeal rehabilitation and prevention of post–RP veno-occlusive dysfunction. There are few randomized studies and the available literature focuses on VCD as a therapeutic option for ED. There are no reports on use in early penile rehabilitation programs.

Method: A search was done using PubMed, Medline and the Cochrane Library, Aug 1990-Sep 2007. Relevant studies assessing the role of VCD for management of ED following RP were analyzed. The outcomes sought were patient/partner satisfaction, preservation of penile length and girth and return of natural erection sufficient for vaginal penetration.

Result: Our study of 109 men randomized to VCD, or not, after RP for 9 mos. 74/109 men randomized to VCD (53 w/nerve sparing surgery), 60 actually used it w/constriction bands for vaginal intercourse twice/wk. In the VCD group 32% reported return of natural erections at 9 mos. With 17% having erections sufficient for vaginal intercourse. Observation group - 37% regained spontaneous erections; 11% had erections sufficient for vaginal intercourse; 26% sought adjuvant therapy. RP has a significant effect on penile length and girth. Munding (2001) and Savoie (2003) both reported 70% decrease in penile length after RP. In our study, in the observation group (no VCD) 63% reported a decrease in penile length and girth; in contrast, only 23% reported a decrease in the VCD group. Dalkin (2007) confirmed our study that early use of VCD – 10 minute daily sessions - reduced the likelihood of penile shortening from 48% in historical control to 3.5% in his study.

Conclusions: Evolving data suggests that early use of VCD facilitates early sexual intercourse, early patient/spousal sexual satisfaction and preservation of penile length and girth. These benefits of early VCD therapy are significant because of the length of neuropaxia that occurs following RP. Our current early intervention program following RP includes daily VCD therapy (10 minutes twice a day) and maximum use of oral PDE-5 inhibitors.

Lower Urinary Tract Syndrome and Sexual Function among Symptomatic and Asymptomatic Diabetic Men

Wesley G. Kong, Hardeep Phull, Mia A. Swartz, Adrian V. Hernandez, Firouz Daneshgari

Introduction and Objectives: There is increasing evidence indicating that lower urinary tract syndrome (LUTS) and sexual dysfunction may coexist in men at risk. Men with diabetes mellitus (DM) are considered as high risk for both conditions, as DM affects both urinary and sexual function. We aimed to examine the prevalence of sexual dysfunction and LUTS and their association with other risk factors among men with diabetes mellitus (DM).

Methods: Following institutional review board approval males with symptomatic and asymptomatic LUTS were recruited from the Cleveland Clinic Departments of Urology and Endocrinology, respectively. Inclusion criteria included established diagnosis of DM. Exclusion criteria included other known causes of LUTS including infection, and neurogenic conditions. All subjects responded to the International Prostate Symptom Score (IPSS) and the International Index of Erectile Function (IIEF). Data on age, race, and other demographic information were also collected. LUTS severity was categorized by AUASS as mild (<7), moderate (8-19) and severe (20-35). IIEF score stratified subjects as having no (25-30), mild (19-24), moderate (13-18), or severe (1-12) erectile dysfunction. The association between the severity of the LUTS and erectile dysfunction was analyzed with the Kruskal Wallis and Fisher exact tests.

Results: Seventy-eight male subjects with mean age of 54 years were recruited into this study. 45 (58%) had mild, 31 (40%) moderate (8-19) and severe (20-35), IIEF score stratified subjects as having no (25-30), mild (19-24), moderate (13-18), or severe (1-12) erectile dysfunction. The association between the severity of LUTS and erectile dysfunction was analyzed with the Kruskal Wallis and Fisher exact tests.

Conclusions: In our cohort of LUTS symptomatic and asymptomatic diabetic men, there was no linear association between severity of LUTS as measured by IPSS and erectile dysfunction as measured by IIEF. The claimed association between LUTS and ED needs further investigation.
New Paradigms for Implantable Penile Prosthetic Design

Matthew N. Simmons, MD, PhD, Drogo K. Montague, MD

Introduction and Objective: Inflatable penile prosthetics have yet to optimally mimic natural erection. Activation of current devices requires physical compression of a pump located within the scrotum, an unnatural process that can cause anxiety and discomfort. Additionally, multi-component prostheses can be difficult to implant, and have a higher risk for mechanical failure. Novel self-contained penile prostheses that more closely mimic natural erection are in high demand.

Methods: Two completely novel classes of penile prostheses were designed and constructed. Attributes of each device including size, physiologic compatibility, efficacy, and durability were assessed.

Results: The first prosthetic design obtains rigidity from a biologically-compatible heat-activated peptide hydrogel that reversibly transitions from a liquid to a gel state within a physiologic temperature range. Peptides with different theoretical polymerization kinetics were synthesized and analyzed using rheometry. A second prosthetic design utilizes an electronically-controlled miniature motor and sliding piston mechanism to regulate cavernosal pressure. The unique gear mechanism allows for a small motor to generate torque capable of increasing cavernosal chamber pressure to 250 cm H2O. Both hydrogel and motorized prototypes consist solely of two cavernosal implants connected by wires to a wafer-shaped control hub. The control hub would be implanted subcutaneously in a suprapubic location, and the low-voltage rechargeable battery within the hub would be recharged periodically using an externally-applied induction coil. Both prostheses were designed for extracorporeal electronic activation using a radiofrequency transmitter/receiver switch.

Conclusions: Hydrogels demonstrated rapid solidification upon temperature increase, and also demonstrated self-repair after gel disruption. However, gel strength was inadequate, and depolymerization time was on the order of hours. Future discovery of peptides with faster phase transition, higher strength, and expansile qualities could potentially allow this design to be developed. In regard to the motorized prosthesis, both proof-of-concept and formal prototype models have been constructed and have proven successful. The motorized design is currently being patent protected.
Section 6

Bladder Cancer
Predicting Occult Malignancy in the Prostate Prior to Radical Cystectomy
Kefer JC, Liu L, Klein EA, Campbell SC

Introduction: Risk of morbidity following radical cystoprostatectomy (RCx) influences some men towards bladder-sparing therapies with suboptimal oncologic control. Prostate-sparing could reduce post-RCx morbidity, but remains controversial. Here, we assess our ability to predict occult prostatic malignancy prior to RCx, and define a subset of men at low risk for prostatic malignancy.

Methods: We retrospectively analyzed 184 consecutive males undergoing both staging TURBT and RCx between 1995 and 2006 at our institution. Patients with known prostate cancer (CAP), non-urothelial carcinoma, or diverticular masses were excluded, and 171 patients were analyzed for risk factors of CAP and prostatic involvement of TCC (PI-TCC: carcinoma in situ (CIS), multifocal tumors (MF), and bladder neck/trigone involvement (BNTI)). Prostates were sectioned at 3 mm-intervals with representative sections assessed. Uni- and multivariate logistic regressions cross-tabulated risk factors with pathology findings to predict probability of occult malignancy.

Results: 55 patients (32%) had PI-TCC (33 with urethral, 26 with stromal, and 26 with ductal involvement). Cystoscopic findings of CIS (OR=2.16, 95% CI 1.11-4.20), multifocality (OR=2.11, 95% CI 1.10-4.06) or BNTI (OR=7.23, 95% CI 3.14-16.65) were predictive of PI-TCC. Presence of CIS (OR=2.44, p<0.02, 95% CI 1.17-5.10), and BNTI (OR=7.21, p<0.0001, 95% CI 1.17-5.10) were also predictive of PI-TCC on multivariate analysis. Interestingly, all patients with PI-TCC had one or more of these risk factors, and all 35 patients (20%) without these risk factors were also without PI-TCC (p<0.0005). We also found that PSA > 2.5, positive DRE, or age >60 predicted occult CAP. Of 62 patients with CAP, 60 had one or more of these risk factors, and the remaining two patients had low-grade, microscopic disease. Overall, 7 of 171 patients (5%) had no risk factors for PI-TCC or CAP, were without prostatic malignancy, and all were identified by preoperative parameters.

Conclusions: Our results validate clinical risk factors for predicting prostatic malignancy, and identify a subset of patients at low risk for occult malignancy who could be potential candidates for prostate sparing. This subset is small, however, and prospective validation will be required.
Comparison of Outcomes in Squamous Cell Carcinoma of the Bladder versus Urothelial Carcinoma with Squamous Differentiation

Anil Thomas, MD, Andrew J Stephenson, MD, Steven C Campbell, MD, Donna E Hansel, MD, PhD

Introduction and Objective: Squamous cell carcinoma of the bladder (SCC) is a rare tumor and its long-term prognosis has remained controversial. We examined a large series of patients who underwent radical cystectomy for SCC in order to identify histopathologic features and clinical outcomes associated with these tumors. In addition, we compared these patients to a subset of patients who underwent radical cystectomy for urothelial carcinoma with squamous differentiation (USD) in order to determine whether outcomes varied between these populations.

Methods: Of 2783 radical cystectomies performed between 1981-2006, 55 cases of pure SCC were identified (2%). In addition, 32 patients with a diagnosis of USD were identified and included 18 cases of extensive squamous differentiation and 14 cases of focal squamous differentiation.

Results: In the SCC population, patient age ranged from 38 to 83 years (mean 66 years) with a M:F ratio of 3:2. Fifty-three patients were Caucasian and 2 patients were African-American. No patient had a prior history of schistosomiasis; only 1 patient had a history of HPV. Thirteen patients presented with hematuria and 2 patients with dysuria. Tumor size ranged from 0.8 to 7 cm (average 3.6 cm). Invasion was present into the lamina propria (3/49), muscularis propria (15/49), perivesical fat (24/49) and adjacent structures (7/49). Metastases at surgery were identified in 16/55 patients (29%) to pelvic lymph nodes (13/55), mesentery (2/55) or pelvic sidewall (1/55). Clinical follow-up was available on 24 patients (1 to 184 mo, mean 44.9 mo). Five patients (21%) developed subsequent metastatic disease. Fifteen patients were alive without disease from 2 to 184 months postoperatively (mean 65 mo; 62%), whereas only 2 patients died of disease within 2 years of diagnosis. In comparison, the USD population demonstrated a similar patient age range (33-93 yr) and tumor size (0.3-9.5 cm). Invasion was identified into the lamina propria (3/49), muscularis propria (15/49), perivesical fat (24/49) and adjacent structures (7/49). Metastases at surgery were identified in 16/55 patients (29%) to pelvic lymph nodes (13/55), mesentery (2/55) or pelvic sidewall (1/55). Clinical follow-up was available on 24 patients (1 to 184 mo, mean 44.9 mo). Five patients (21%) developed subsequent metastatic disease. Fifteen patients were alive without disease from 2 to 184 months postoperatively (mean 65 mo; 62%), whereas only 2 patients died of disease within 2 years of diagnosis. In comparison, the USD population demonstrated a similar patient age range (33-93 yr) and tumor size (0.3-9.5 cm). Invasion was identified into the lamina propria (3/49), muscularis propria (15/49), perivesical fat (24/49) and adjacent structures (7/49). Metastases were identified in 10/32 patients (31%). In contrast to the SCC group, however, 8/24 patients (33%) developed subsequent metastases and only 50% were alive without disease on extended follow-up.

Conclusions: This study represents one of the largest series of SCC on radical cystectomy. Comparison to USD indicates that SCC demonstrates a slightly lower postoperative metastatic rate and better long-term disease free outcomes than USD.

Laparoscopic-Assisted and Open Radical Cystectomy in the Elderly

Andre Berger, Steven Campbell, Kazumi Kamo, Denilson Custodio, Georges P Haber, Monish Aron, Michael Gong, Mihir Desai, Jihad Kaouk, Inderbir S Gill, Amr Fergany

Introduction and Objective: Muscle-invasive bladder cancer often occurs in the elderly. Open radical cystectomy (ORC) is the gold standard treatment, with laparoscopic radical cystectomy (LRC) being an emerging minimally invasive alternative. Clinical outcomes of LRC amongst elderly patients have not been defined in the literature to date. We compare peri-operative and surrogate oncologic outcomes in patients 70 years or older managed with LRC or ORC.

Methods: A retrospective review was undertaken of 94 patients who underwent either LRC (urinary diversion performed extracorporeally through a 6-7 cm incision) or ORC between August 2005 and September 2007. Of these, 55 patients were ≥ 70 years old. Of these, we selected only patients with ileal conduit diversion (n=52) to maintain consistency of analysis in this study. Patients were divided in 2 groups: LRC (n=25) and ORC (n=27). Perioperative and surrogate oncologic outcomes were obtained from patient charts and a review of the Social Security Death Index.

Results: There were no significant differences between the LRC and ORC groups as regards mean patient age (77 vs 78 yrs), BMI (28 vs 27), ASA class, comorbidities, smoking history and indications for radical cystectomy. Perioperative and surrogate oncologic outcomes are illustrated in the table. LRC was associated with less blood loss (p=0.0002) and a marginally quicker recovery profile (p=ns). Extended LND was performed more often in the ORC group, as reflected in the nodal yields (21 for ORC vs. 12.1 for LRC). The percentage of patients with positive LN’s was higher for ORC than LRC (37% vs. 16%), likely reflecting selection bias.

Conclusions: In the elderly patients, LRC can provide reduced blood loss and our data suggests a marginally quicker recovery profile. Complication rates and surrogate oncologic outcomes were similar between the two groups. Nodal counts were lower in this initial LRC group.
Bladder Cancer

6

Bladder Cancer

Urinary Diversion-Related Complications: Laparoscopic versus Open Radical Cystectomy

Andre Berger, Amr Fergany, Kazumi Kamoi, Goroges Haber, Monish Aron, Denilson Custodio, Sebastien Crouzet, Mihir Desai, Jihad Kaouk, Michael Gong, Inderbir S Gill, Steven Campbell

Introduction and Objective:

LCR with extracorporeal reconstruction is an emerging minimally invasive alternative for the management of muscle-invasive bladder cancer. However, relatively short ureteral length and body habitus may make the diversion more challenging and could theoretically predispose to ureteral anastomotic strictures and other diversion-related complications.

Methods:

A retrospective review was undertaken of 94 patients managed with either LRC or ORC performed between August 2005 and September 2007. Diversion-related and other clinical parameters were obtained from patient charts and review of the Social Security Death Index.

Results:

There were no significant differences between the LRC (n=41) and ORC (n=53) groups with respect to mean patient age (70 vs. 69; p =0.75), BMI (27 vs. 26; p= 0.57), sex, ASA class, comorbidities, smoking history, operative indications, and pathologic stages. Distribution of urinary diversions was similar between LRC (32 conduit, 7 neobladder, 1 continent cutaneous) and ORC groups (45 conduit, 7 neobladder, 1 continent cutaneous). Number of lymph nodes retrieved was greater in ORC group (23 vs. 14, p=0.01). There were no differences between overall intraoperative complications (2% vs. 2%) and postoperative minor (12% vs. 17%, p=0.51) or major complications (8.0% vs. 7.4%, p=0.26).

Thirteen diversion related complications were identified including: LRC (n = 7; 17%) with 6 ureteral stenosis (7.3%) and total incontinence after neobladder requiring AUS; ORC (n = 6, 11%) with 3 ureteral stenosis (2.8%), 1 neobladder disruption requiring re-operative repair, and 2 parastomal hernias. On univariate analysis, only a higher nodal yield correlated with a lower risk of diversion-related complications. LRC trended towards higher ureteral stenosis rate, although this was not statistically significant.

Conclusions:

The perioperative outcomes and complications are as follows:

<table>
<thead>
<tr>
<th>Perioperative Outcomes</th>
<th>LRC</th>
<th>ORC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time (min)</td>
<td>381.3 ± 125.8</td>
<td>377 ± 108</td>
<td>0.92</td>
</tr>
<tr>
<td>Blood loss (cc)</td>
<td>537.2 ± 332.3</td>
<td>1103 ± 645.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>Transfusion rate</td>
<td>13%</td>
<td>51%</td>
<td>0.01</td>
</tr>
<tr>
<td>Oral intake (days)</td>
<td>4.8 ± 2.0</td>
<td>5.9 ± 5.9</td>
<td>0.81</td>
</tr>
<tr>
<td>Minor post op complications (%)</td>
<td>12%</td>
<td>18.5 %</td>
<td>0.51</td>
</tr>
<tr>
<td>Major postop complications (%)</td>
<td>8.0 %</td>
<td>7.4 %</td>
<td>0.93</td>
</tr>
<tr>
<td>Ambulation (days)</td>
<td>2.5 ± 1.5</td>
<td>3.9 ± 4.1</td>
<td>0.46</td>
</tr>
<tr>
<td>Lymph nodes retrieved (mean)</td>
<td>12.1 ± 8.0</td>
<td>21 ± 14.6</td>
<td>0.024</td>
</tr>
<tr>
<td>Positive lymph nodes (%)</td>
<td>16%</td>
<td>37%</td>
<td>0.08</td>
</tr>
<tr>
<td>Positive surgical margins (%)</td>
<td>0%</td>
<td>7.4%</td>
<td>0.16</td>
</tr>
<tr>
<td>Ambulation (days)</td>
<td>25 ± 20</td>
<td>30 ± 25</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Results: There were no significant differences between the LRC (n=41) and ORC (n=53) groups with respect to mean patient age (70 vs. 69; p =0.75), BMI (27 vs. 26; p= 0.57), sex, ASA class, comorbidities, smoking history, operative indications, and pathologic stages. Distribution of urinary diversions was similar between LRC (32 conduit, 7 neobladder, 1 continent cutaneous) and ORC groups (45 conduit, 7 neobladder, 1 continent cutaneous). Number of lymph nodes retrieved was greater in ORC group (23 vs. 14, p=0.01). There were no differences between overall intraoperative complications (2% vs. 2%) and postoperative minor (12% vs. 17%, p=0.51) or major complications (9% vs. 7%, p=0.26).

Thirteen diversion related complications were identified including: LRC (n = 7; 17%) with 6 ureteral stenosis (7.3%) and total incontinence after neobladder requiring AUS; ORC (n = 6, 11%) with 3 ureteral stenosis (2.8%), 1 neobladder disruption requiring re-operative repair, and 2 parastomal hernias. On univariate analysis, only a higher nodal yield correlated with a lower risk of diversion-related complications. LRC trended towards higher ureteral stenosis rate, although this was not statistically significant.

Conclusions: Diversion-related complications, particularly ureteral stenosis, were marginally increased with LRC compared to ORC (p=ns). Only higher nodal yields correlated with decreased incidence of diversion-related complications, suggesting that a more extended dissection may result in better proximal mobilization of the ureter, with less angulation under the sigmoid mesentery.

continued
### Risk factors for Urinary Diversion-Related Complications

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate Analysis $p$</th>
<th>Multivariate Analysis $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approach (lap vs. open)</td>
<td>0.42</td>
<td>NS</td>
</tr>
<tr>
<td>Age $\geq$ 70</td>
<td>0.16</td>
<td>0.76</td>
</tr>
<tr>
<td>BMI</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>ASA $&gt;$ 2</td>
<td>0.22</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.12</td>
<td>0.44</td>
</tr>
<tr>
<td>$\geq$ 15 lymph nodes retrieved</td>
<td>0.02</td>
<td>0.08</td>
</tr>
</tbody>
</table>

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### Introduction and Objective

A validated mouse model for superficial bladder cancer is warranted to enable preclinical studies on intravesical anticancer agents. We sought to improve upon our previously described orthotopic superficial bladder cancer mouse model with validation using in vivo ultrasound imaging.

### Methods

Using the murine bladder tumor (MBT-2) cell line, 11 C3H/HeJ female mice were inoculated with $5 \times 10^5$ MBT-2 cells in 50 uL serum-free RPMI via transurethral catheterization without electrocautery. Using the VisualSonics™ Vevo 770® ultrasound device, we performed transabdominal micro-ultrasound imaging 3, 6, and 15 days after tumor instillation. Imaging was also performed in all mice prior to tumor cell instillation. Tumors were measured using linear 2-dimensional measurements using sagittal and transverse imaging planes. Mouse bladders were subsequently harvested, formalin-fixed, embedded in paraffin, sectioned and stained with hematoxylin and eosin for confirmation of bladder tumors.

### Results

Superficial bladder tumors were evident on micro-ultrasound imaging starting on day 3 post-MBT-2 cell instillation in all mice. Multifocal tumors were seen in 27% of mice on day 3, 91% on day 6, and 100% on day 15. Average number of tumors found on days 3, 6, and 15 was 1.3, 2.4, and 3.5. Mean tumor size (max dimension of largest tumor) on days 3, 6, and 15 was 0.7mm, 1.1mm, 1.3mm. Histology sections on all mice confirmed presence of bladder tumors in all mice.

### Conclusions

Using abdominal micro-ultrasound, we validate the presence of superficial bladder tumors in our MBT-2 mouse orthotopic bladder cancer model. Our model is reproducible and can be used to evaluate the efficacy of various intravesical anti-cancer agents. Tumors can be followed longitudinally for progression or regression with micro-ultrasound imaging.
Lidocaine 2% Gel versus Plain Lubricating Gel for Pain Reduction during Flexible Cystoscopy – A Meta-analysis of Prospective Randomized Controlled Trials
Amit R. Patel, M.D., J. Stephen Jones, M.D., Denise Babineau, Ph.D.

**Purpose:** Current literature reports mixed results for the effectiveness of topical intraurethral lidocaine gel during flexible cystoscopy for local anesthesia. Our objective was to conduct a meta-analysis of randomized controlled trials examining the efficacy of 2% lidocaine versus plain gel in decreasing the amount of pain that male patients incur during flexible cystoscopy.

**Materials and Methods:** A search of the literature between 1950 to September 2006 yielded a total of 46 applicable papers. Search terms included: cystoscopy and pain. Study selection included randomized controlled trials, flexible cystoscopy, males, control groups receiving plain gel, and treatment groups receiving 2% lidocaine prior to cystoscopy. Data extraction included two reviewers (ARP, JSJ) who independently reviewed each study and were blinded to identifying features. Primary outcome measured was pain incurred by patient throughout entire cystoscopy as measured using a VAS.

**Results:** Data from 9 eligible trials (number of patients = 817) within 7 publications were included in the meta-analysis. Using a random effects model, the difference between the VAS pain scores from patients receiving 2% lidocaine and plain gel was estimated to be -4.61 with an approximate 95% CI of (-9.6, 0.385), indicating no statistically significant difference.

**Conclusions:** Based on a meta-analysis of 9 randomized controlled trials, there is no evidence to suggest a statistically significant difference in the efficacy of pain control between lidocaine gel and plain gel lubrication in men during flexible cystoscopy. This supports a conclusion that its benefit is limited to lubrication, and any other perceived benefit is consistent with placebo.

Pain Reduction during Office Cystoscopy with Intraurethral Lidocaine Jelly Injection versus Video-Monitor Viewing
Christina B Ching, Jianbo Li, J Stephen Jones

**Introduction and Objective:** Intraurethral lidocaine jelly injection has long been the standard used to decrease pain during office cystoscopy. A recent meta-analysis, however, failed to support this widely used practice. In contrast, another recent study demonstrated decreased pain scores in men who visualized their cystoscopy simultaneously with the surgeon. We investigated whether a patient’s ability to witness their cystoscopy on video-monitor helped alleviate a patient’s perceived “pain” during office cystoscopy in comparison to lidocaine jelly.

**Methods:** From June 2007 to October 2007, we prospectively collected data on 54 male patients undergoing office cystoscopy randomly assigned by computerized program to either premedication with intraurethral lidocaine jelly injection (n=26) 5 minutes prior to office cystoscopy or witnessing their cystoscopy on video-monitor (n=28). They were asked to score their pain on a 1-100 point scale during cystoscopy. Those in the lidocaine group also gave pain scores of the injection itself. We took into account initial versus repeat cystoscopy, patient age, and whether a resident or an attending physician performed the cystoscopy.

**Results:** The intraurethral lidocaine arm was composed of 26 patients with a mean age of 59.1 (± 14.4 SD) years. The video-monitor arm was composed of 28 patients with a mean age of 69.1 (± 11.0 SD) years. There was no difference (p=0.661) in pain scores between cystoscopy after lidocaine jelly injection (37.4 ± 22.8 SD) and video-monitor watching (29.2 ± 17.4 SD), taking into consideration initial vs. repeat cystoscopy, patient age, and performer training level (resident vs. attending). We also evaluated the pain of the lidocaine injection itself (29.6 ± 21.1 SD) as compared to the pain of subsequent cystoscopy or cystoscopy with video-monitoring. We found no difference in either (p = 0.491 and p = 0.508 respectively).

**Conclusions:** We found that pain scores during office cystoscopy with intraretral lidocaine injection versus those watching their cystoscopy on video-monitor were not significantly different. This further fails to demonstrate a benefit of premedication with transurethral lidocaine injection. At best, it is no better than simply allowing patients to understand their cystoscopy by visualizing the procedure on a video-monitor, suggesting that the morbidity associated with office cystoscopy may be dependent more on psychological trauma and anxiety than actual neuropathic pain.
Laparoscopic Cystoprostatectomy for Radiation Induced Hemorrhagic Cystitis

Ayman Salah Moussa and Amr F Fergany

Introduction and Objective: Severe hemorrhagic cystitis following radiotherapy is a rare but difficult problem to manage. The incidence of severe hematuria following pelvic irradiation is difficult to determine although most studies state an incidence of less than 5%, increasing with time since irradiation. Methods of treatment include simple bladder irrigation, cystoscopic coagulation, intravesical coagulants, hyperbaric oxygen therapy, internal iliac embolisation, or urinary diversion, with a stepwise progression in treatment intensity often employed and no management strategy being 100% successful. Cystectomy with urinary diversion remains the final definitive treatment when faced with refractory or life-threatening bleeding. Laparoscopic radical cystectomy has been used for treatment of patients with bladder cancer, and prior pelvic radiation is often considered a contraindication to laparoscopy. We report on 3 cases of hemorrhagic cystitis secondary to radiation treatment of prostate cancer treated successfully with laparoscopic cystectomy.

Methods: Three patients (ages 72-80) with severe persistent bleeding due to hemorrhagic cystitis after radiotherapy for prostate cancer presented after failure of different conservative methods. Laparoscopic cystectomy with urinary diversion was offered as a less invasive option to open cystectomy. A standard 4-port transperitoneal laparoscopic technique was used, and ileal conduit diversion was performed through a minilaparotomy.

Results: Mean (total) operating time was 285 minutes, no open conversion was necessary, and no intraoperative complications were encountered. Maximal blood loss was 200cc. One patient had a prolonged postoperative ileus in the absence of intra-abdominal pathology, and was discharged on the 15th postoperative day, the other patients were discharged 5 and 7 days after surgery. No other postoperative complications were encountered.

Conclusion: Radiation induced scarring with obliteration of tissue planes can present a significant contra-indication to laparoscopic pelvic surgery. We have successfully performed laparoscopic cystectomy in select patients with benign bladder pathology (irradiation cystitis) following pelvic radiation. It remains to be seen whether the use of laparoscopy in similar patients with bladder cancer will be feasible.
Sarcomatoid Differentiation of Renal Cell Carcinoma Renders a Poor Prognosis even for Small Renal Masses Amenable to Minimally Invasive Surgery

Patel, A.R., Gill, I., Kaouk, J., Fergany A.

**Background and Objectives:** Renal cell carcinoma (RCC) with sarcomatoid differentiation portends a poor prognosis, with patients presenting with larger renal masses and advanced disease. Given the increasing number of small renal masses diagnosed annually, we sought to determine if prognosis is improved for smaller renal masses with sarcomatoid changes.

**Material and Methods:** A retrospective database inquiry of prospectively collected laparoscopic data identified 22 patients who underwent either laparoscopic partial (4) or laparoscopic radical nephrectomy (18) and had sarcomatoid transformation noted on final pathology. We sought to examine perioperative and long-term follow up data.

**Results:** Twelve patients (55%) presented with metastasis preoperatively with 8 patients having multiple metastases (lung = 7, liver = 2, adrenal = 2, bone = 8, lymph node = 4). The mean age of patients was 57.1 years (range, 32-82 years), and the male-to-female ratio was 3.7:1. The mean tumor size was 6.6 cm (range 2 – 11.5 cm). Mean body mass index (BMI) was 29.6 kg/m². Mean operative time was 206 minutes (range, 120-330 minutes) and mean estimated blood loss was 260 ml. Intraoperative complications included a splenic capsular tear which required no further intervention. Two patients required postoperative blood transfusions for blood loss anemia. Mean length of stay was 65 hours (range, 23-109 hours). Follow up was available on all patients. Eighteen patients (82%) died of disease and had a median survival of 9.75 months. Kaplan-Meier survival analysis demonstrated that survival was significantly impacted by the presence of metastatic disease (p= 0.0046), but not by tumor size (p = 0.06).

**Conclusion:** No preclinical determinants of sarcomatoid transformation in renal cancer exist. Laparoscopic surgery can be safely performed in these patients without increased operative risk. Our dataset with smaller tumors yielded poor overall survival rate similar to larger tumors reported in the literature. This poor outcome may warrant consideration of adjuvant systemic treatment in these patients.
Factors Affecting Renal Function after Laparoscopic Partial Nephrectomy
Kazumi Kamoi, Monish Aron, Burak Turna, Inderbir S. Gill

Objective: To determine the factors affecting kidney function after laparoscopic partial nephrectomy (LPN).

Materials and Methods: Between 09/1999 and 09/2007, 739 patients underwent LPN at our institution. A total of 120 patients undergoing unilateral LPN in the setting of bilateral functioning kidneys for a single mass in one kidney were identified with documented paired split renal function with MAG-3 scan. Estimated GFR (eGFR) was calculated to assess global renal function. Multiple factors were assessed using univariate and multivariate analysis to identify risk factors for change in renal function. For sub-analysis, the study population (n=120) was stratified into 3 groups based on warm ischemia time (WIT; <20 min, 20-40 min, >40 min). ROC analysis was performed for the statistically significant continuous variables on multivariate analysis in order to identify a threshold value.

Results: On logistic regression analysis, only WIT was a significant predictor for ≥30% decrease in eGFR at 6 months. Only tumor size on CT was a significant predictor of ≥30% decline in differential renal function at 3 months. Although tumor size was significant in terms of decrease in eGFR on univariate analysis, this was not independent risk factors on multivariate analysis. Likewise, preoperative serum creatinine, presence of hypertension, presence of caliceal entry and intravenous fluid given were significant on univariate but not on multivariate analysis. On ROC analysis, a threshold value for WIT ≥36 minutes was associated with ≥ 30% decrease in eGFR. A cutoff value of ≥ 3.8 cm tumor size was associated with ≥ 30% decrease in the remnant kidney function on MAG-3 scan.

Conclusions: Increasing warm ischemia time and the tumor size on preoperative CT scan are the most important determinants of postoperative remnant function after LPN.

Computer-Aided Differentiation of Solid Renal Mass with CT image using Classification and Regression Trees Model
Kazumi Kamoi, Brian Herts, Nidhi Sharma, Andre Berger, Georges-Pascal Haber, Monish Aron, Inderbir S. Gill

Introduction and Objective: Currently, thin slice renal CT scanning is the standard radiographic technique for evaluating the nature of a renal mass. However, considerable error exists, such that definitive diagnosis of benign versus malignant cannot be made with certainty. Herein, we determined if solid renal cortical tumors can be differentiated on CT images on the basis of their morphologic features and enhancement patterns.

Methods: Between December 2004 and June 2006, 182 consecutive patients with a renal mass underwent preoperative renal CT and laparoscopic partial nephrectomy. We retrospectively reviewed CT records in 131 patients with solid renal mass, size less than 7 cm in diameter, and 1mm slice thickness CT scans available before surgery. Oncocare software (Siemens AG, Erlangen, Germany) was used to obtain volumetric measurements, and assess the various tumor characteristics on unenhanced (NC), parenchymal phase (PP), and vascular phase (VP) of the CT scans. The RECIST (Response Evaluation Criteria in Solid Tumors) diameter, orthogonal WHO diameter, and tumor volume were calculated on VP. Means and standard deviations (SD) of attenuation in the entire tumor were calculated on all phases. We employed classification and regression trees (CART) model to generate a binary recursive-partitioning scheme and correlated with final pathology reports.

Results: The 131 tumors (median size, 2.8 cm; 0.9-6.7 cm) included 70 (53%) clear cell RCCs, 26 (20%) papillary, and 13 (10%) chromophobe type RCCs; 12 (9%) lipid-poor angiomylipomas and 10 (8%) oncocytomas. Partition tree analysis showed that hierarchical divisions by mean and SD of attenuation in the entire tumor on PP and NC correctly predicted malignancy in 76% of solid tumors with 93% sensitivity and 36% specificity. Pathological subtype analysis showed that hierarchy of divisions by mean and SD of attenuation on PP, VP and NC correctly identified 75% of these five subtypes of renal tumor with high agreement (kappa = 0.62).

Conclusions: Certain imaging features and the degree of enhancement may be helpful in differentiating subtypes of renal cortical tumors. Such computer-aided measurements may provide useful information for differentiating malignant from benign renal tumor preoperatively.

continued
Evolving Management of Renal Cell Carcinoma with Coexistent Renal Artery Disease

Kefer JC, Hafez K, Novick AC, Campbell SC

Introduction: Coexistent renal cell carcinoma (RCC) and renal artery disease (RAD) offers several management challenges. RAD can attenuate renal function, and oncologic efficacy must be tempered by preservation of renal parenchyma. Here, we define updated guidelines for the management of these patients and the increasing role of minimally invasive therapies for long-term management.

Methods: From 1969 to 2005, 82 patients presented with masses suspicious for RCC and RAD. Patients were grouped into four categories to facilitate clinical decision-making: 1) solitary kidney with RCC and RAD (n=15), 2) bilateral RCC with RAD (n=11), 3) unilateral RCC and contralateral RAD (n=29), and 4) unilateral RCC and bilateral RAD (n=27). Causes of RAD were atherosclerosis (n=69), medial fibroplasia (n=9), renal artery aneurysm (n=3), and arteriovenous malformation (n=1).

Results: All patients had complete excision of tumor, with partial nephrectomy (PNx) preferentially performed in 75 patients (91%), including 5 laparoscopic PNx. Intervention for RAD was performed selectively (25 patients, 30%) as needed to preserve essential renal function. Pathology revealed RCC in 78 patients, oncocytoma in 3, and benign cyst in 1. Mean follow-up was 67 months. There were no perioperative deaths. Renal function was preserved in 81 patients (98.8%: Postop $\Delta$Cr was $0.56 \pm 0.3$, $0.5 \pm 0.26$, $0.4 \pm 0.18$, $0.67 \pm 0.41$, for groups 1-4, respectively). Five patients (6%) required temporary dialysis, and one patient underwent transplant 2 years after surgery. RCC recurred in 10 patients (12%), and 6 patients (7%) died of metastatic disease. Recurrence-free survival rates were 91% at 5 years and 68% at 10 years after surgery. A shift in treatment paradigms was also observed within this series. From 1969-1998, 13/15 patients (87%) requiring intervention for RAD underwent surgical revascularization. After 1998, 9/10 patients (90%) requiring intervention underwent endovascular treatment, with only one surgical revascularization. Further, 5 patients have undergone laparoscopic PNx since 1998.

Conclusion: Excellent oncologic and functional results can be achieved in this challenging patient population utilizing nephron-sparing surgery whenever possible and selective endovascular intervention for RAD. Treatment protocols have evolved towards minimally invasive approaches in the past decade.
Preliminary Laboratory Experience with Retrograde Intrarenal Surgery using a Novel Robotic Platform

Monish Aron, Mihir Desai, Georges-Pascal Haber, Inderbir S. Gill

Introduction: We report our laboratory evaluation of a prototype flexible robotic system (Hansen Medical, Mountain View, CA) for retrograde intrarenal surgery.

Methods: Using this system we performed flexible ureterorenoscopy in five female pigs (27-51 kg). The specific parameters measured were: a) need for ureteral dilation, b) time to access each calyx, c) reproducibility of access into each calyx, d) ability to fragment intrarenal calculi in 4 kidneys, e) stability of the system, f) reproducibility of the auto-retract mechanism, and f) evidence of tissue trauma and fluid extravasation.

Results: Ureteral dilation was required in 1 animal (weight 27 kg). Of the 85 calyces in the 10 kidneys, each calyx could be inspected. Median time to inspect the entire collecting system was 3 minutes. One lower pole calyx in each kidney of 1 animal (weight 32 kg) could not be entered due to the small ostial size although a 3F basket could be passed into these 2 calyces. Reproducibility of access into each calyx was rated 10/10 on a visual analog scale (VAS). The stability of the system was rated 10/10 and the reproducibility of the auto-retract mechanism 8/10 on a VAS. All calculi could be fragmented with a laser fiber to a size smaller than the diameter of the fiber. There was one ureteral perforation (10%) in the first animal due to a technical error.

Conclusions: This could be a promising robotic platform for flexible endoluminal surgery with enhanced stability, while distancing the surgeon from the radiation source.

Effect of Sunitinib in Patients with Unresectable Primary Renal Cell Carcinoma

Anil Thomas, MD, Brian R Lane, MD, PhD, Brian I Rini, MD, Steven C Campbell, MD

Introduction and Objective: Sunitinib has been shown to produce tumor shrinkage and delayed time to progression in patients with metastatic renal cell carcinoma (RCC). In this preliminary study, we sought to investigate the activity of sunitinib in primary renal tumors in patients with unresectable RCC with or without distant metastases in order to assess tumor shrinkage and conversion to resectable disease.

Methods: Between 2/2006 and 11/2006, 15 patients with unresectable RCC have been treated with sunitinib off-protocol. Tumor was deemed unresectable because of bulky regional lymph nodes (1), vascular invasion (3), invasion into neighboring organs (3), proximity to vital structures/vessels (3), or burden of metastatic disease (5). Sunitinib was given orally as 50 mg on days 1-28 of a 42 day cycle. Tumor was assessed by axial CT or MR imaging prior to treatment and at 8-10 week intervals to determine tumor size and resectability. Patients were treated until the primary tumor was reduced to the point of resectability, disease progression, or unacceptable drug toxicity.

Results: Median age was 54 years (range: 51-78). Initial mean radiographic renal tumor size was 10.9 cm (range: 3-20). Clinical stage was T1 (1), T2 (2), T3 (9), T4 (3); N0 (8), N1 (1), N2 (6); and M0 (3), M1 (12). At most recent follow-up, 6, 8, and 1 patients have received 1, 2, and 3 cycles of sunitinib, respectively. Side effects were observed in 13 patients (87%), including fatigue (8), gastrointestinal (7), mucositis (3), hand-foot syndrome (2), and hypertension (1). However, no patients discontinued treatment due to drug toxicity. Follow-up CT scans were performed in 7 patients; response has yet to be assessed in the remaining 8 patients. Systemic disease progression was evident in 5 patients, 1 patient had stable primary and lymph node involvement, and 1 patient had a partial response in both the primary and metastatic sites. During a median follow-up of 2 months (range 1-5), 1 patient expired and none have undergone nephrectomy to date. Additional data regarding outcomes in all 15 patients will be presented as well.

Conclusions: Administration of sunitinib in patients with unresectable primary RCC is feasible. Treatment is ongoing to determine the effect in reducing primary tumor size to permit subsequent surgical resection.
Surgical Resection of Renal Cell Carcinoma after Targeted Molecular Therapy
Anil A Thomas, Brian R Lane, Brian I Rini, Steven C Campbell

Introduction and Objective: The use of molecular targeted therapy in patients with advanced RCC who may undergo subsequent surgical resection requires careful consideration due to the potential effects of several of these agents on wound healing and vascular integrity. We performed a retrospective review of surgical outcomes of patients with locally advanced or metastatic RCC treated with targeted therapy.

Methods: Between 6/2005 and 9/2007, 13 patients who were treated with targeted molecular therapy underwent resection of locally advanced (6), locally recurrent (5), or metastatic (2) disease. Patients were treated with either sunitinib (8), sorafenib (3), or bevacizumab and IL-2 (2). Targeted therapy was withheld at least 4 weeks prior to surgery.

Results: Median age was 61 years (range: 43-80). Patients were treated with between 2 and 7 cycles of targeted therapy prior to resection. Surgical resection involved open (11) or laparoscopic (2) approaches to extirpate the primary tumor or recurrent disease through nephrectomy (6) or metastasectomy (7). Mean estimated blood loss was 1350cc (range 150 to 4500cc) for 12 patients. One patient had a significant intraoperative hemorrhage and disseminated intravascular coagulopathy from a concomitant liver resection and subsequently died several days postoperatively from multisystem organ failure. An anastomotic bowel leak and abscess were noted postoperatively in another patient who underwent en bloc resection of his primary renal tumor and adjacent colon. No postoperative wound healing complications were identified. Pathological analysis revealed clear cell RCC (76%), sarcomatoid RCC (8%), and unclassified RCC (8%) in 12 specimens, and one patient (8%) was found to have no viable disease upon resection. At most recent follow-up (mean 4; range 0-12 months), 11 (85%) patients were alive, 5 (45%) demonstrated disease progression, and 5 (45%) were continued on targeted therapy.

Conclusions: Treatment with targeted molecular therapy prior to surgical extirpation appears well tolerated with low overall morbidity in the majority of patients. However, 2 patients (16%) experienced significant complications including 1 perioperative hemorrhage and 1 bowel anastomotic leak, raising potential concerns for possible compromise of tissue and vascular integrity associated with this treatment. Careful patient selection and close follow up is warranted in this challenging patient population in order to determine the optimal integration of surgery and molecular targeted therapy in patients with advanced RCC.

Active Surveillance of Small Renal Masses in Elderly Patients
R. Abouassaly, MD, B.R. Lane, MD, A.C. Novick, MD

Introduction and Objectives: Small renal masses are being diagnosed with greater frequency as a result of the increased use of radiographic imaging. Active surveillance (AS) is offered to patients with advanced age and in those with high operative risk. The aim of this study is to identify and report on the large number of patients treated with active surveillance (AS) at our institution.

Material and Methods: We identified 997 patients evaluated in our department for a renal mass and were ≥ 75 years-old between January 2000 and December 2006. One hundred and ten patients with enhancing renal neoplasms (11%) were initially managed with AS, and this group made up the cohort for our study. Medical records were reviewed for clinical and radiological follow-up, and vital status was obtained from the social security death index.

Results: Patients had a median age of 81 years (range 76-95), with a median Charlson comorbidity index of 2 (range 0–7) at the time of diagnosis. Patients had as many as 9 tumors being followed (median of 1), with a median tumor size of 2.5 cm. Chronic renal insufficiency was present in 43 patients (39%). Clinical follow-up was available in 114 patients (median 19 months), and radiographic follow-up in 89 patients (median 18 months). The mean tumor growth rate was 0.26 cm/year, and this was significantly higher for smoker when compared to non-smokers (0.47 cm/year vs. 0.22 cm/year, p = 0.03). Statistically, there was no difference between patients with tumor growth (n = 51), and those with stable disease (n = 38). Four patients (3.6%) were treated as a result of disease progression 12 to 54 months after diagnosis. Thirty-four patients (31%) were deceased at the conclusion of the study. Overall survival did not differ between patients with tumor growth, and those without. To our knowledge, the renal mass did not contribute to the cause of death in any patient.

Conclusions: Active surveillance of incidental renal masses appears to be a viable option in patients with multiple medical comorbidities and a limited life expectancy.
The Impact of Number and Location of Cores on the Diagnostic Accuracy of Renal Mass Biopsy: An Ex Vivo Study

Brian R Lane, Steven C Campbell, Hakan Aydin, Christopher J Weight, Ming Zhou

Introduction and Objective: Renal mass biopsy (RMB) has not been used routinely in the evaluation of renal masses suspicious for malignancy because of reportedly high rates of indeterminate or inaccurate diagnoses. We evaluated whether biopsy location or number affects accuracy of RMB.

Methods: Three 18-gauge biopsy cores (1 targeting the central and 2 targeting the peripheral portion of the tumor) were obtained from each of 36 renal masses before histologic processing immediately after nephrectomy. Each biopsy core was evaluated independently by a single GU pathologist blinded to the final diagnosis in the resection specimen with regard to tumor subtype and Fuhrman grade.

Results: Median tumor size was 4.2 cm (IQR: 3.3-5.8). Final pathology revealed 89% of tumors to be malignant. Histologic subtypes included clear cell RCC (n=25, 71%), papillary RCC (n=4, 11%), chromophobe RCC (n=2, 6%), or oncocytoma (n=4, 11%). Fuhrman nuclear grade was 1, 2, 3, or 4 in 1, 14, 13 and 3 patients with RCC. A comparison of biopsy results with final pathology can be seen in Table 1. The biopsy of the lesion was indeterminate in 44% of individual cores for various reasons including sampling of normal adjacent tissue, scar, necrosis, or insufficient material. Single-core biopsy correctly identified malignancy or suspected malignancy in 59% compared with 82% for 2- and 3-core biopsy. Histologic subtyping was accurate for only 44% of single-core biopsies compared with 66% and 68% for 2- and 3-core biopsy. The diagnosis of 7 lesions (20%) remained indeterminate in spite of at least 1 central and 1 peripheral core.

Conclusions: A single-core RMB results in insufficient diagnostic accuracy and precludes confidence in making treatment decisions. Obtaining 18g biopsies from both the middle and periphery enhances accuracy both for diagnosis of cancer and histologic subtyping. Two- and three-core RMB have similarly improved diagnostic accuracy compared with single-core RMB, but still are unable to accurately diagnose a significant number of renal lesions. We therefore continue to oppose the routine use of RMB with standard histopathologic analyses prior to nephrectomy. If RMB for a suspicious renal mass is to be performed, it should include at least 1 central and 1 peripheral core.

Table 1. Diagnosis according to ex vivo biopsy core number and location

<table>
<thead>
<tr>
<th>Diagnosis category</th>
<th>Any one core (n=105)</th>
<th>Center core (n=35)</th>
<th>Any one lateral core (n=70)</th>
<th>Two lateral cores (n=34)</th>
<th>Center and any one lateral core (n=35)</th>
<th>Center and two lateral cores (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: identical to resection diagnosis, including cancer diagnosis and histological subtyping</td>
<td>46 (44%)</td>
<td>16 (46%)</td>
<td>30 (43%)</td>
<td>22 (65%)</td>
<td>23 (66%)</td>
<td>23 (68%)</td>
</tr>
<tr>
<td>2: similar to resection diagnosis, including cancer diagnosis, but subtyping not possible</td>
<td>7 (6.7%)</td>
<td>2 (5.7%)</td>
<td>5 (7.1%)</td>
<td>3 (8.8%)</td>
<td>3 (8.6%)</td>
<td>3 (8.8%)</td>
</tr>
<tr>
<td>3: suspicious for cancer with a cancer diagnosis in the final resection specimen</td>
<td>9 (8.6%)</td>
<td>4 (11%)</td>
<td>6 (8.6%)</td>
<td>3 (8.8%)</td>
<td>2 (5.7%)</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>4: lesion missed, including sampling of normal adjacent tissue, scar or necrosis, or insufficient material present</td>
<td>43 (41%)</td>
<td>13 (37%)</td>
<td>29 (41%)</td>
<td>6 (18%)</td>
<td>7 (20%)</td>
<td>6 (18%)</td>
</tr>
</tbody>
</table>
Management of Ipsilateral Adrenal Gland during Partial Nephrectomy
Brian R Lane, Christopher J Weight, Ho-Yee Tiong, Benjamin T Larson, Edward Diaz, Andrew C Novick, Inderbir S Gill, Stuart M Flechner

Introduction and Objective: Robson's radical nephrectomy has been replaced over the years with minimally-invasive techniques and partial nephrectomy (PNx). The indications for adrenalectomy (Ax) for patients undergoing PNx are not clearly defined. We analyzed initial management and oncologic outcomes of the ipsilateral adrenal gland after open PNx in a single surgeon series.

Methods: Information regarding all PNx's performed at a single institution was collected in an IRB-approved registry. Data regarding all 805 patients that underwent open PNx by a single surgeon (ACN) between 1999 and 2005 are included. The ipsilateral adrenal gland is routinely resected if a suspicious adrenal nodule is noted on radiographic imaging, or intraoperative findings indicate direct extension or metastasis.

Results: Of 805 open PNx, concomitant Ax was performed in 23 patients (2.8%). Pathologic analysis revealed direct invasion of periadrenal fat by RCC (1), RCC metastasis (1), or benign tissue (21, 91%). During a mean follow-up of 2.0 years, ipsilateral adrenal metastasis was identified in 2 patients (<0.3%). Overall survival at 5 years in patients undergoing open PNx with or without Ax was 74% and 85% (p=0.08).

Conclusions: Over 90% of suspicious adrenal nodules resected at the time of open PNx for presumed renal cell carcinoma are benign. Overall survival comparing patients undergoing PNx with ipsilateral adrenalectomy were similar to PNx alone. These findings support the practice of resecting the ipsilateral adrenal gland only in the presence of a suspicious lesion. Adrenalectomy should not routinely be performed is not mandatory during PNx for the upper pole tumors.

Gene Expression Profiling to Predict Clinical Outcome in Sporadic and Bilateral Conventional Renal Cell Carcinoma
Brian R Lane, J Li, M Zhou, D Babineau, SC Campbell, AC Novick, BRG Williams

Objective: Gene expression profiling has been shown to provide prognostic information regarding patients with a single, sporadic renal cell carcinoma (RCC). In patients with bilateral RCC, there is currently no reliable way using clinical and/or pathologic data to differentiate bilateral primary tumors from synchronous renal metastases. We present data using a custom kidney cancer cDNA array that can add prognostic information in patients with bilateral RCC.

Methods: Fresh frozen tissue from 38 conventional RCC (cRCC) and 5 other renal neoplasms were analyzed using a cDNA array containing 3966 genes relevant to cancer or kidney development. Median follow-up was 4.4 years; 12 (43%) patients had recurred and 11 (39%) patients were deceased at last follow-up.

Results: A set of 44 genes differentiated between aggressive and indolent cRCC. GEP prediction out-performed and improved predictions of recurrence-free survival at 5y based on SSIGN score. In addition, GEP correctly predicted disease progression in 4 patients with metachronous RCC.

Conclusions: Expression data from 44 genes can differentiate between aggressive and indolent cRCC and improve survival prediction by SSIGN. In addition, GEP can provide information to help characterize patients with uncertain clinical stage, including those with bilateral or locally-recurrent tumors.
Using Gene Expression Profiling to Define the Clinical Stage of Patients with Bilateral or Locally-Recurrent Conventional Renal Cell Carcinoma

Brian R. Lane, Jianbo Li, Ming Zhou, Denise Babineau, Pieter Faber, Andrew C. Novick, Bryan R. G. Williams

**Purpose:** Gene expression profiling has been shown to provide prognostic information regarding patients with a single, sporadic renal cell carcinoma (RCC). In patients with bilateral RCC, there is currently no reliable way using clinical and/or pathologic data to differentiate bilateral primary tumors from synchronous renal metastases. We present data using a custom kidney cancer cDNA array that can predict outcomes in patients with unilateral RCC and clarify the likely clinical staging in patients with bilateral or locally-recurrent RCC.

**Methods:** Fresh frozen tissue from 38 conventional RCC (cRCC) and 5 other renal neoplasms were analyzed using a cDNA array containing 4162 genes relevant to cancer or kidney development. Median follow-up was 4.4 years; 12 (43%) patients had recurrent and 11 (39%) patients were deceased at last follow-up.

**Results:** The full gene expression data differentiated the cRCC’s from the other renal neoplasms. A gene expression profile (GEP) containing 60 differentially-expressed genes was then identified using a training dataset of 4 aggressive and 4 non-aggressive cRCC’s. This GEP was able to correctly classify the majority of tumors according to the known clinical behavior. In addition, the GEP from 1 bone metastasis grouped with aggressive cRCC. The GEP classification (aggressive or non) was then used to provide staging information for 8 patients with uncertain clinical staging, including 7 bilateral tumors and 1 patient with a locally recurrent cRCC. Four of 8 tumors were non-aggressive according to GEP and none of these patients has had cancer recurrence. Of the 4 aggressive tumors by GEP, 2 are dead of disease, 1 has had multiple synchronous recurrences, and 1 patient with bilateral synchronous cRCC (pT1b) that had been thought to represent two independent primary tumors is without recurrence during 1 year of follow-up. This last patient is being re-evaluated to rule out other metastatic involvement.

**Conclusions:** A kidney cancer-specific cDNA array can be used to generate GEP’s that differentiate between cRCC’s and other renal neoplasms and that predict the clinical behavior of cRCC’s. In addition, GEP can provide information to help characterize patients with uncertain clinical stage, including those with bilateral or locally-recurrent tumors.

Comparison of Laparoscopic and Open Partial Nephrectomy for a Single Renal Tumor in a Solitary Kidney

Brian R Lane, Amr F Fergany, Jihad H Kaouk, Inderbir S Gill, Andrew C Novick

**Introduction and Objective:** Laparoscopic partial nephrectomy (LPN) is feasible in patients with a solitary kidney, but recent studies suggest that LPN is performed with longer warm ischemia time (WIT) and carries a greater risk of postoperative complications. We therefore compared the postoperative and early renal functional outcomes of patients undergoing LPN or open PN (OPN) for a tumor in a solitary functioning kidney.

**Methods:** Between 1999 and 2006, 189 OPN and 32 LPN have been performed for a single sporadic renal tumor ≤7 cm in size in a solitary functioning kidney. Data was collected and analyzed retrospectively. GFR (in ml/min per 1.73 m²) was estimated by the abbreviated MDRD equation.

**Results:** Patients undergoing OPN and LPN were similar with regard to median age (61 v 62), ASA score (2.9 v 2.7) and BMI (27 v 29). More patients undergoing OPN had symptomatic presentation (33% v 7%) and reduced performance status (16% v 3%). Median tumor size was 3.9 (IQR 2.9-5.0) and 2.8 cm (IQR 2.5-3.9) in the 2 groups, respectively. Median WIT was 21 (IQR 17-27) or 30.5 (19-40) minutes after OPN or LPN. Intraoperative blood loss ≥1000 ml or any transfusion occurred in 8% and 6% of OPN and LPN. Other intraoperative events during OPN included 1 pleural and 2 ureteral injuries, and during LPN included 1 ureteral injury, inability to locate the tumor in 1, and 1 open conversion each for hemorrhage, positive margin, or poor sewing angle. A total of 70 and 26 postoperative complications occurred in 24% and 45% of patients after OPN and LPN, respectively. Urologic complications (12% v 30%), including postoperative hemorrhage (12 v 4), urine leak (9 v 3), and acute renal failure necessitating dialysis (2 v 3), occurred in 10% and 15% of patients. Preoperative serum creatinine was 1.2 ng/ml in both groups and GFR was 63 (IQR 49-77) and 64 (46-78). The highest GFR measured within 3 months of OPN or LPN was 48 (32-64) or 38 (30-60), with a median decrease in GFR of 21% (9%-41%) or 28% (13%-36%), respectively. Chronic renal failure occurred in 4 (2%) or 3 (9%) of patients after OPN or LPN.

**Conclusions:** While LPN is technically feasible for a single tumor in a solitary kidney, WIT is longer and complication rates higher when compared with OPN. In addition, early renal functional outcomes are somewhat poorer, although the exact factors contributing to these early differences are not entirely clear. Therefore, OPN may be the preferred operative approach at this time for these and other patients at high risk for chronic kidney disease.
Factors Predicting Renal Functional Outcome after Partial Nephrectomy

Brian R Lane, Denise Babineau, Inderbir S Gill, Andrew C Novick

Introduction and Objective: When compared to radical nephrectomy, partial nephrectomy (PN) allows for greater preservation of renal parenchyma and function. Although several clinical factors are thought to contribute to the change in renal function after PN, including age, preoperative renal function and comorbidities, the contributions of tumor and surgical factors have not been well studied. We performed multivariable analysis to identify factors predictive of decreased renal function after PN.

Methods: Between 1999 and 2005, 1049 patients underwent PN (595 open and 454 laparoscopic). Data were recorded in an IRB-approved database. The preoperative serum creatinine (sCr) and lowest postoperative sCr measured within 90 days of surgery (nadir) were used in the abbreviated MDRD formula for estimation of GFR (units: ml/min per 1.73 m²). Postoperative GFR (at nadir sCr) was analyzed using a multivariable linear regression model. Covariates in the model included open or laparoscopic approach, clinical tumor size, age, contralateral kidney status, bilateral disease, central vs. peripheral tumor, warm ischemia time (WIT), operative time, and preoperative GFR. Continuous covariates were modeled using restricted cubic splines. A robust covariance matrix was also used to account for heteroscedasticity among patient responses.

Results: Mean age was 60.3 and 66% were male. Median preoperative sCr and GFR were 1.0 ng/ml and 75.9 ml/min. Median tumor size was 3 cm and 47% abutted the collecting system (central). Median operative time was 232 minutes and WIT was 25 minutes (20 for open PN and 32 for laparoscopic PN). Median postoperative sCr and eGFR were 1.1 ng/ml and 65.3 ml/min, respectively. Multivariable analysis showed that GFR was lower in patients undergoing PN for a tumor in a solitary kidney (8.1 ml/min; 95% CI: 4.7-11.5; p<0.0001) or with bilateral disease (2.9 ml/min; 95% CI: 0.2-5.7; p=0.035). GFR was also significantly decreased with increasing tumor size (p=0.0381), increasing age at surgery (p=0.0018), increasing WIT (p<0.0001), and decreasing pre-operative eGFR (p<0.0001). Surgical approach (open vs. lap, p=0.8), tumor depth (central vs. peripheral, p=0.5), and OR time (p=0.9) were not found to have any statistically significant effect on GFR.

Conclusions: The strongest predictors of postoperative GFR were preoperative GFR, PN for tumor in a solitary kidney, and WIT. WIT is therefore the strongest modifiable risk factor for decreased renal function after PN, and efforts to limit WIT should be pursued in both open and laparoscopic PN.

Uniformly Benign Clinical Behavior of Classical, Atypical, and Epithelioid Angiomyolipoma in 197 Patients

Brian R Lane, Teresa L Danforth, Ming Zhou, Inderbir S Gill, Andrew C Novick, Steven C Campbell

Introduction and Objective: Classical angiomyolipoma (AML) is a benign renal neoplasm that presents as a fat-containing lesion on CT or MR imaging. Fat poor AML fail to demonstrate fat on imaging. Pathologically-confirmed AML uniformly follow a benign course, but the far more rare epithelioid variants of AML have been reported to recur and metastasize. We investigated the pathologic and long-term oncologic characteristics of pathologically-atypical and epithelioid variants of AML in comparison with classical AML.

Methods: Clinical, radiographic, and pathologic data were recorded for 197 patients treated for 207 pathologically diagnosed renal AML between 1981 and 2006. The suspected radiographic diagnosis of AML or renal cell carcinoma (RCC) was determined based on the presence or absence of fat on CT or MR imaging. The histopathology of atypical cases were reviewed by a single pathologist and immunohistochemical stains (HMB45, SMA, melan-A) were used in selected cases.

Results: Median age was 51 years (14-89) and 77% were female. AML was diagnosed pathologically after partial nephrectomy (141), radical nephrectomy (59), or cryoablation/biopsy (7) for suspected AML (45%) or fat poor AML (55%). Atypical pathologic features of AML necessitating additional stains were present in 26% of all AML, including 10 with epithelioid features (5%). Although 65% of atypical or epithelioid AML were fat poor AML, 50% of AML with typical pathologic features were also fat poor AML. While 112 patients (57%) had a single AML, 85 patients (43%) had multiple AML, including 12 patients (6%) with a definite diagnosis of tuberous sclerosis (TS). Median clinical size was 3.2, 4.9, and 10 cm in patients with a single AML, multiple AML, and TS, respectively. In these 3 groups, 45%, 56%, and 76% of patients had symptomatic presentation, respectively. Twenty-five (12%) patients with AML had concomitant RCC, including 20 with ipsilateral RCC; a single local recurrence of RCC was treated with RFA. Concomitant RCC was present in 12% vs. 11% of patients with classical vs. atypical/epithelioid AML. No classical, atypical, or epithelioid AML recurred during a mean follow-up of 3.3 years (0-23.7).

Conclusions: Although fat poor AML were more commonly found to have atypical pathologic features than classical AML (32% vs. 20%), these pathologic variants of AML were not associated with a higher likelihood of concomitant RCC or disease progression. In this series of 207 tumors, no AML with classical, atypical, or epithelioid features exhibited malignant behavior.
A Preoperative Prognostic Nomogram for Solid Enhancing Renal Tumors ≤7 cm Amenable to Partial Nephrectomy

Brian R Lane, Denise Babineau, Michael W Kattan, Andrew C Novick, Inderbir S Gill, Ming Zhou, Christopher J Weight, Steven C Campbell

Introduction and Objective: Small renal masses (SRM) are increasing in incidence. The majority of tumors ≤7cm in size are treated with radical or partial nephrectomy (PNx), but clinicians are increasingly relying on ablative therapies and observation for some SRM. We present novel nomograms that predict the likelihood of benign, likely indolent, or potentially-aggressive pathology based solely on readily identifiable preoperative factors.

Methods: Information regarding all PNx's performed at a single institution was collected in an IRB-approved registry. Using retrospectively-collected data for all 862 patients that underwent PNx for a single, solid, enhancing, clinical T1 (≤7cm) tumor between 1999 and 2005, tumors were classified as benign or malignant, and grade 3 clear cell renal cell carcinoma (RCC), grade 4 RCC of any type, and any RCC with vascular, fat, or collecting system invasion were regarded as potentially-aggressive. The likelihood of benign, likely indolent, or potentially-aggressive pathology was modeled using multivariable logistic regression models based on age, gender, radiographic tumor size, symptoms at presentation, and smoking history.

Results: Of 862 tumors, 80% were malignant, including 30% with potentially-aggressive cancers. All 11 patients with systemic symptoms had cancer, 4 of which were potentially-aggressive. The remaining 851 patients underwent further analysis. Factors that were most strongly associated with the likelihood of benign pathology were age, gender, tumor size, and smoking history, and a nomogram constructed to predict benign histology proved to be relatively accurate and discriminating (bootstrap corrected concordance-index (CI) = 0.644) and calibrated. SRM in older men and younger women were more likely to be benign. With regard to differentiating indolent from potentially-aggressive cancers, only advanced age (p<0.005) was independently significant in multivariable analysis. The nomogram for this outcome performed with limited ability (CI = 0.557).

Conclusions: Clinical factors provide substantial predictive ability to predict benign vs. malignant pathology for SRM amenable to PNx. However, our ability to predict potentially-aggressive cancer in this population remains limited.

Cystic Nephroma and Mixed Epithelial and Stromal Tumor of the Kidney: Clinical, Radiographic and Pathologic Characteristics

Brian R Lane, Ming Zhou, Erick M Remer, Amr F Fergany, Stephen B Williams, Andrew C Novick, Christopher J Weight, Cristina Magi-Galluzzi, Steven C Campbell

Introduction and Objective: Cystic nephroma (CN) and mixed epithelial and stromal tumor (MEST) are benign renal tumors readily distinguished from cystic renal cell carcinoma (RCC) and other malignant variants based on histopathology. Clinical and radiographic data regarding these lesions are sparse, especially with respect to factors providing clinical suspicion for CN or MEST.

Methods: Pathology of 22 CN (21 patients) and 10 MEST (9 patients) treated between 1987 and 2005 was re-reviewed according to 2004 WHO classification. Data were recorded in an IRB-approved registry.

Results: Nineteen CN patients (90%) and 9 MEST patients (100%) were female and median ages were 55.3 and 51.6 years, respectively. Twenty-two patients (73%) presented symptomatically. CN were commonly Bosniak III lesions (77%), while 70% of MEST had solid enhancing components. An intraluminal component was present in 5 CN (23%) and no MEST. Preoperative radiologic suspicion was documented in 36% of CN, but in only 1 patient with MEST. Nephron-sparing surgery was performed for 16 tumors (50%), including 5 suspected preoperatively and 3 ≥7cm. There was one case each of bilateral CN and MEST. Two patients with CN had concomitant RCC. One patient with MEST had sarcomatous component. At mean follow-up of 4.4 years (0.4-18), no patient has developed novel or recurrent tumors.

Conclusions: CN and MEST typically present symptomatically in perimenopausal women. Pedunculation of a multiloculated cystic lesion may allow for preoperative suspicion of these lesions in the proper clinical setting. Nephron-sparing surgery is the preferred treatment even for large and/or central lesions, if amenable.

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>CN</th>
<th>MEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>55 (39 - 79)</td>
<td>52 (39 - 67)</td>
</tr>
<tr>
<td>Female:Male (% female)</td>
<td>19.2 (91%)</td>
<td>9.0 (100%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>16/21 (76%)</td>
<td>6/9 (67%)</td>
</tr>
<tr>
<td>Mean follow-up, years (range)</td>
<td>4.9 (0.7 - 18)</td>
<td>3.4 (0.4 - 12)</td>
</tr>
</tbody>
</table>

continued
Comparison of 1800 Laparoscopic and Open Partial Nephrectomies for Single Renal Tumors

Brian R Lane, Inderbir S Gill, Michael L Blute, Denise Babineau, Jose R Colombo, Igor Frank, Sompol Permpongkosol, Christopher J Weight, Michael W Kattan, Andrew C Novick

Introduction and Objective: Laparoscopic partial nephrectomy (LPN) is an increasingly performed minimally-invasive alternative to open partial nephrectomy (OPN). We compared the early postoperative outcomes for 1800 patients undergoing OPN by experienced surgeons with the initial experience of LPN in patients with a single renal tumor ≤7 cm.

Methods: Data regarding 1800 consecutive OPN or LPN were collected prospectively or retrospectively in tumor registries at 3 large referral centers. Demographic, intraoperative, postoperative, and follow-up data were compared between the two groups.

Results: Compared to the LPN group (n=771), patients undergoing OPN (n=1029) comprised a higher-risk group, with a greater percentage of patients presenting symptomatically, with reduced performance status, impaired renal function, and tumor in a solitary functioning kidney (p<0.0001). More tumors in the OPN group were >4 cm and centrally located (p<0.0001) and more proved to be malignant (p=0.0003). Based on multivariable analysis, LPN was associated with shorter operative time (p<0.0001), reduced operative blood loss (p<0.0001), and shorter hospital stay (p<0.0001). The chance of intraoperative complications was comparable for both groups. However, LPN was associated with longer ischemia time (p<0.0001), more postoperative complications, particularly urologic (p<0.0001), and increased number of subsequent procedures (p<0.0001). Renal functional outcomes were similar 3 months after LPN and OPN, with 97.9% and 99.6% of renal units retaining function. Three-year cancer-specific survival for patients with a single cT1N0M0 RCC was 99.3% and 99.2% after LPN and OPN, respectively.

Conclusions: Early experience with LPN is promising. LPN offered the advantages of less operative time, reduced operative blood loss, and a shorter hospital stay. When applied to patients with a single renal tumor ≤7 cm, LPN was associated with additional postoperative morbidity compared to OPN; however, equivalent functional and early oncologic outcomes were achieved.
CD3+ Lymphocyte Apoptosis and Ganglioside GM2 Positivity: Potential Novel Prognostic Biomarkers for RCC

Matthew N. Simmons, Amy Richmond, Soumika Biswas, Steven C. Campbell, Andrew C. Novick, James H. Finke

Introduction: Renal cell carcinoma (RCC) tumor cells secrete ganglioside GM2, a glycosphingolipid that induces apoptosis and inhibits activation of CD3+ T cells [Cancer Research (2006) 66: 6816-6825]. We hypothesized that T cell apoptosis and GM2 positivity would be increased in peripheral circulating CD3+ lymphocytes in patients with localized and metastatic RCC.

Methods: Venous peripheral blood samples were collected according to an IRB-approved protocol from January 2005 to October 2007 from age-matched normal volunteers (n=10), and patients with pathologically and radiologically-verified localized (n=7) and metastatic (n=25) RCC. Live CD3+ cells were purified by antibody bead-based negative selection, and labeled with anti-CD3 and anti-GM2 antibodies, fluorescent annexin-V, and 7-AAD. Labeled cells were then analyzed by flow cytometry.

Results: The percent of apoptotic CD3+ cells was 5.2% in normal controls compared to 24.9% (p=0.014) and 27.3% (p<0.001) in patients with localized and metastatic RCC, respectively. The percent of GM2-positive CD3+ cells was 1% in normal controls compared to 4.5% (p=0.02) and 20.8% (p=0.02) in patients with localized and metastatic RCC, respectively. The mean fluorescence intensity (MFI) of GM2 staining was 12.9 units in normal controls compared to 41.8 (p=0.004) and 222.2 units (p<0.001) in patients with localized and metastatic disease, respectively. GM2 MFI was significantly higher in patients with metastatic vs. localized disease (p=0.004). GM2-positivity and MFI significantly correlated with tumor size, tumor stage, and Fuhrman grade. Apoptosis and GM2 positivity did not correlate independently with age, gender, or nodal status.

Conclusions: Patients with RCC have an increased percentage of apoptotic and GM2-positive T cells in circulation. The data suggests that CD3+ T cell apoptosis and GM2 positivity may serve as potential prognostic biomarkers for RCC. Prospective outcomes studies are ongoing.

Effect of Surgical Approach (Laparoscopic or Open) on Overall Survival after Nephroureterectomy for Urothelial Carcinoma of the Upper Urinary Tract

Benjamin T Larson, Brian R Lane, Christopher J Weight, Inderbir S Gill, Andrew C Novick, Michael Gong

Introduction and Objective: Open nephroureterectomy (OUN) has long been considered the gold standard treatment for urothelial carcinoma of the upper urinary tract (UC-UUT). However, in the last decade, laparoscopic nephroureterectomy (LNU) has emerged as a potential viable alternative for management of the kidney during NU. Several groups have analyzed the various approaches for management of the bladder cuff during NU. In this report, we compare the overall survival of patients treated by LNU and ONU in order to evaluate the effectiveness of LNU for the treatment of UC-UUT.

Methods: Using the Glickman Urologic and Kidney Institute’s Kidney Cancer Database, 303 consecutive patients were identified who were treated for UC-UUT between 1/1992 and 11/2007. Of those patients, 162 were treated with LNU and 141 were treated with ONU. Data was collected prospectively and retrospectively when missing. Survival was determined from clinical follow up and the social security death index. Data was analyzed for overall survival.

Results: The median age at the time of surgery was 70 years (IQR 61-78) and 68 years (IQR 58-76) for LNU and ONU groups respectively (p=0.08). Median follow up was 16 months (IQR 10-38) and 34 months (IQR 14-95) for LNU and ONU groups respectively (p<0.001). Kaplan-Meier estimate (see below) revealed no significant difference in overall survival (log-rank p=0.34). Five-year overall survival rates were 57.5% and 53.0% for LNU and ONU groups.

Conclusions: In this single center experience, the surgical approach for nephroureterectomy for urothelial carcinoma of the upper tract does not appear to affect overall survival. Given the decrease morbidity profile and the equivalent overall survival, we routinely recommend LNU for the treatment of UC-UUT.
Section 8

Kidney Transplant
Renal Allograft Outcomes in Combined Liver and Kidney Transplantation

HoYee Tiong, Alvin Wee and Venkatesh Krishnamurthi

**Aim:** This study evaluated the outcomes of renal allografts in patients with combined liver and kidney transplantation (CLKT) at a single institution.

**Methods:** Between 2004 and 2007, a total of 18 CLKT was performed. The main indications for CLKT were liver cirrhosis with renal damage secondary to hepatorenal syndrome. Demographic and clinical outcome data was collected retrospectively. 72% of the recipients were male with a mean age of recipients was 54.8. Mean MELD score was 27.4 and 61% of patients were dialysis dependent.

**Results:** All CLKTs were performed from the same donor. All patients received whole liver grafts. All patients received induction immuosuppression with either Simulect or Thymoglobulin and were maintained on Prograf, Cellsept and prednisone. Mean liver and kidney cold ischemia times were 453 and 787 minutes respectively. After a median follow-up of 9 months (range 2 to 42 months), the overall patient survival rate was 89% (n=16). Perioperative complications included bilary leak in 1 cases, liver graft failure from infarction in 1 case, pancreatitis in 1 case and peri-renal hematoma requiring washouts in 2 patients, urinary tract infection in 2 patients. There were 2 cases of delayed renal function, requiring temporary hemodialysis with progressive graft improvement in 1 case. All surviving patients during the follow up period had a functioning kidney allograft. No cases of acute rejection were noted in the all of the kidney allografts. Serum creatinine levels at 1 month and 1 year post transplant was a mean of 1.24 and 1.20 mg/dL respectively.

**Conclusions:** Although there are significant perioperative comorbidity associated with combined liver, kidney transplantation, outcome of kidney allografts after combined transplantation are good with an evident immunological advantage.
Reduction in Posttransplant Lymphoceles Using Closed Suction Drains for De Novo Sirolimus Treated Kidney Recipients

Ho Yee Tiong, Alvin Wee, Brian Lane, Lingmei Zhou, Charles Modlin, David Goldfarb, Andrew C Novick, Stuart Flechner

Introduction: Post-transplant lymphocele formation is reported with greater frequency in kidney recipients given de novo sirolimus; especially those with a BMI >32 kg/m². We report a program to reduce lymphoceles and wound problems based on the use of closed suction drains.

Methods and Materials: Consecutive series of adult kidney-only recipients given de novo sirolimus, mycophenolate mofetil, and steroids for immunosuppression were compared. Group 1—204 patients were transplanted with no drains. Group 2—95 patients were transplanted with retroperitoneal closed suction drains placed at surgery (Jackson-Pratt or Blake). All available records and imaging studies were reviewed for peritransplant fluid collections greater than 2.5 cm after removal of the drains. Demographic characteristics and the risk factors for lymphocele were compared in these 299 recipients using univariate and multivariate analysis.

Results: There was no significant difference in recipient demographics between Group 1 and 2 groups, including mean age (48.4 vs. 47.7), mean BMI (26.5 vs. 26), proportion of male recipients (68.6% vs. 62.1%), of white recipients (78.9% vs. 68.4%), of deceased donor source (50% vs. 50.5%), and of diabetic patients (27.9% vs. 28.4%) (p=NS). The overall incidence of lymphocele formation was 118 of 299 cases (39.4%) and the overall incidence of treated lymphoceles was 55 of 299 (18.4%). The incidence in patients with and without drains was 24.2% (n=23) and 46.6% (n=95) respectively. These differences were significantly different (p<0.001). The odds of patients without drains developing lymphoceles was 1.9 compared to patients with drains. Similarly the incidence of treated lymphoceles was 5.3% (n=5) and 24.5% (n=50) respectively (p<0.001). In addition, Surgical drainage (open or laparoscopic) was required in a greater proportion of patients in Group 1 compared to Group 2 (14.2% vs. 2.2% P=0.01).

Conclusions: Intraoperative drain placement should be considered for kidney transplant patients starting de novo on Sirolimus based immunosuppression as it significantly reduces the incidence of lymphoceles.

An Effective Tool to Promote/Increase Organ Donor Registry Registration Rates: A Culturally Competent Educational Outreach Program in the Minority Community: Using the Venues of Community Bureau of Motor Vehicles (BMV)

Carlumandarlo E.B. Zaramo, M.Sc., CLsp (MB), Toni Morton, DD, MBA, Ji Won Yoo, M.D. Gordon R. Bowen, M.S., and Dr. Charles S. Modlin, M.D., FACS

Background: The multiplicity of the United States’ population is one of society’s greatest assets, but the richness of this feature is many times overshadowed by the disproportionate burden of disease and illness that exists in some of America’s racial and ethnic minority populations. Compelling evidence of the disparate health status minority populations is documented in the form of shorter life expectancies, higher rates of cancer, birth defects, infant mortality, asthma, diabetes, and cardiovascular disease, as well as a plethora of other diseases that necessitate organ transplantation. These circumstances however can be alleviated with the public disclosure to the necessary lifesaving awareness and practice of organ transplantation. In this particular research circumstance we have concentrated our focus on improving some of the particular limitations of organ transplantation. The development of a very “unique” collaborative outreach curriculum that increases organ donation awareness, education, willingness, and most notably “on site registries/issuance” have occurred at specific Ohio Bureau of Motor Vehicles Deputy Registrar License Agencies ® (BMV or DVM).

Methodology/Interventions: We have used a practical outreach approach with selective aspects of cultural competency which in this analysis indicates “how well minority’s culture has the ability to strongly influence the amount and type of culturally sensitive communication between individuals and attitudes” (i.e. a physician and patient a doctor-patient relationship). This outreach contest was strategically targeted towards twenty-eight (n=28) Northeastern Ohio’s BMVs between March 1st 2007 to June 30th, 2007 to promote, encourage and assist in an outreach educational programs regarding organ donation and registry issuance.

Results: The overall consequence of the “OutReach Organ Donation Registry Contest” and collaborative has resulted in a mean increase of 3.425 % in all the functional BMVs. One particular BMV, being a predominantly minority attended BMV, won 1st place for the number of donations registries: (* 6.425% (*p<0.05) Wade Park in Cleveland, Ohio © 2007).
Conclusion: To maintain these organ donor registry increases in awareness, education, promotion and issuance, we will continue in the construction of these vital programs of outreach along with proper incentive for encouragements (i.e. “BMV contest”). In addition to this, it is practical to maintain and elaborate on as many culturally sensitive programs as possible, to assist health care providers, medical facilitators, physicians, nurses, community personnel, and students in the promotional donor programs that reach such a suitable population at the nation’s Bureau of Motor Vehicles. © 2007
Avagard™ Hand Antisepsis vs. Traditional Scrub in 1800 Pediatric Urologic Procedures

Christopher J. Weight, MD and Jeffrey S. Palmer, MD

Objectives: Avagard™ is a waterless, scrubless, and brushless hand antiseptic approved by the Food and Drug Administration (FDA) as a replacement for traditional pre-surgical brush hand scrubbing. We evaluated the use of Avagard™ compared to hand brush scrub preparation for inpatient and outpatient pediatric urological operations.

Methods: We evaluated the first 900 patients for whom we used Avagard™ as a preoperative hand antiseptic and compared them with the last 900 consecutive patients that we performed traditional antiseptic-impregnated hand-brush scrubbing. All patients underwent a variety of inpatient and outpatient open, endoscopic and laparoscopic pediatric urologic procedures. Patients were monitored postoperatively for wound infection, and patients and surgeon were monitored for side effects. A cost analysis was performed.

Results: The incidence of wound infection was 1/900 (0.11%) in the Avagard™ group and 2/900 (0.22%) in the hand-scrub group (p>.99 Fisher's exact test). All wound infections were successfully treated with a single course of oral antibiotics. No side effects for the patients or surgeon were noted, including skin irritations or allergic reactions in either group. The traditional hand scrub is nearly two times more expensive per application than Avagard™.

Conclusions: The incidence of wound infections in pediatric urologic procedures is low (0.17%). We observe that Avagard™ provides comparable hand antisepsis to the traditional surgical scrub in a variety of pediatric urologic procedures. Avagard™ is superior to the surgical hand scrub in cost effectiveness and time efficiency. Urologist should consider using Avagard™ for hand antisepsis before surgery.
Horizontal Urethral Duplication

Christina Ching, MD and Jeffrey S. Palmer, MD

Urethral duplication is a rare anomaly. Most urethral duplications occur in the same sagittal plane, but those in the same horizontal plane are even rarer. We present a case of horizontal plane incomplete urethral duplication with communication of the duplicated urethra to the normal midline urethra just proximal to the external urinary sphincter.

An 8 month-old male presented with two glanular openings – one midline and the other left of midline. The patient voids through his midline opening. There is no history of urinary tract infections. A renal ultrasonogram and VCUG were both normal without a duplicated urethra noted. At 20 months of age, the patient underwent cystourethroscopy, which demonstrated a normal caliber midline urethra with a smaller caliber lateral urethra. The lateral urethra narrowed to a pin-point opening just proximal to the external urinary sphincter.

Therefore, this case demonstrates an uncommon variation of urethral duplication.

Ungated ESWL in Pediatric Population: Safe and Effective

Jeffrey S. Palmer, MD

Objectives: Ungated extracorporeal shock wave lithotripsy (ESWL) is unsynchronized to the patient’s electrocardiogram. Although ungated ESWL in adults has been associated with arrhythmias, its safety in children is not well established. We report on the safety and efficacy of ungated ESWL of renal calculi in children.

Methods: We evaluated all children less than 18 years of age undergoing ungated ESWL of renal calculi. All patients underwent lithotripsy with gradual incremental energy increase. All patients were monitored intraoperatively and postoperatively for arrhythmias and vital signs.

Results: Twenty consecutive children between 3.5 and 17 years of age (8 boys and 12 girls) underwent 28 ungated ESWL procedures for renal calculi ranging in size between 5 mm to 19 mm. No patient had the procedure terminated prematurely or required conversion to gated ESWL. No cardiac arrhythmias or other cardiac complications occurred intraoperatively or postoperatively. The overall stone-free rate was 92% based on abdominal radiograph and renal/bladder ultrasonography.

Conclusions: This series suggest that ungated ESWL of renal calculi in children less than 18 years of age is safe and efficacious. The arrhythmias associated with ungated ESWL in adults do no appear to occur in children. Additional studies are warranted to further evaluate the use of ungated ESWL in children.
The Proper JJ Stent Length in the Pediatric Patient: Age + 10 is a Simple and Reliable Formula

Jeffrey S. Palmer and Lane S. Palmer

Objectives: The proper length of a double J (JJ) stent inserted in the pediatric population is determined empirically by the urologist rather than by a mathematical formula. Is there an accurate and easy to recall mathematical relationship between JJ stent length and another parameter, such as age? We evaluated if such a relationship exists between appropriate JJ stent length and the age of the child.

Methods: We reviewed the ages and JJ stent length inserted in all children over the past 6 years. The proper stent length was defined as a gentle curve of the distal coil within the bladder (direct vision) and the proximal coil within the renal pelvis (fluoroscopically or ultrasound). The data were stratified according to gender and laterality. Regression analyses were then performed between patient age and stent length.

Results: There were 207 patients, age range 2 months to 17.9 years, who were stented during this time period. The surgeries for which a stent was used included stone disease, ureteral reimplantation, and renal surgery. The regression analyses demonstrated consistent and reliable ($r^2$) relationships between patient age and JJ stent length irrespective of gender or laterality. The general relationship determined between stent length and age is: STENT LENGTH = PATIENT AGE (years) + 10.

Conclusions: This study demonstrates that simply adding 10 to the patient’s age is an accurate and reliable “rule of thumb” to determine proper length of JJ stent in children irrespective of gender or laterality.

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Single-Port Laparoscopic Varicocelectomy in the Pediatric Population: Initial Experience

Jihad H. Kaouk, MD and Jeffrey S. Palmer, MD

Introduction: Laparoscopic varicocelectomy is traditionally performed through 3 ports. To further minimize abdominal incisions, we adopted a new approach in which the entire procedure is performed through the umbilicus. After accumulating initial experience in adults, we report the initial experience with single port transumbilical laparoscopic varicocelectomy in children.

Methods: Since October 2007, we performed 3 consecutive cases of left varicocelectomies using single-port laparoscopic (SPL) surgery. Initial abdominal access was achieved through a 1.5cm semicircular incision in the inferior aspect of the umbilicus. The rectus fascia was incised and a novel laparoscopic port with multiple working channels was inserted under direct vision into the umbilical incision. Special curved laparoscopic instruments were used to circumferentially dissect the left gonadal vessels that was then clipped and cut.

Results: SPL was completed as an outpatient procedure in all 3 children without additional ports added or conversion to an open technique. Mean age was 14.7 years (range: 13-16 years) with a mean follow-up of 5 weeks (range: 3-6 weeks). Indications for surgery included grade 3 left varicocele noted on physical examination. Operative time was less than 1 hour for each procedure. No intraoperative or postoperative complications occurred. All patients on follow-up have demonstrated a good cosmetic result without varicocele recurrence or hydrocele formation.

Conclusion: SPL is feasible and safe for simple pediatric procedures. Further experience and evolution of both instruments and surgical techniques are required to further minimize port incisions for more complex laparoscopic procedures in the pediatric population.
Robotic-Assisted Laparoscopic Pyeloplasty in Children: Techniques to Improve Efficacy

Jeffrey S. Palmer, Jason Hafron, Lynn Woo, and Jihad Kaouk

**Introduction:** Robotic-assisted laparoscopic pyeloplasty (RALP) is a safe and established technique in the pediatric population for the treatment of ureteropelvic junction (UPJ) obstruction. We present operative techniques to facilitate RALP in children.

**Methods:** In this video we describe and highlight various techniques to improve the efficacy of a RALP. Specifically, we describe our technique of ureteral transposition for a high ureteral insertion, transmesenteric approach for the severely dilated renal pelvis, and mobilization of the renal pelvis and ureter with an anterior crossing vessel. We illustrate each point with video images.

**Results:** Utilizing a 3-port technique all patients underwent a dismembered pyeloplasty (Anderson-Hynes) with the da Vinci surgical system. All techniques were successfully completed without conversion to laparoscopy or to open pyeloplasty. There were no intraoperative or postoperative complications related to these techniques.

**Conclusions:** The technique for RALP is continues to evolve. Further refinements in technique and longer term follow-up are required to objectively assess the advantages of a RALP in the pediatric population.

Retrograde Proximal Semirigid Ureteroscopy: Safe and Effective in Prepubertal Children

Jeffrey S. Palmer, MD

**Objectives:** Semirigid ureteroscopy in adults and children is traditionally reserved only for distal ureteral procedures due to the risk of injury associated with proximal ureteroscopy. However, the safety of proximal semirigid ureteroscopy in prepubertal children has not been established. The potential advantages of the use of semirigid compared to flexible ureteroscopes include enhanced optics and larger working channels.

**Methods:** We evaluated all children 12 years of age and younger who underwent attempted semirigid proximal ureteroscopy. All patients were evaluated postoperatively with renal and bladder ultrasonography and abdominal radiography if the stone was visible prior to treatment.

**Results:** Twenty-seven consecutive children (range 3.4 to 12 years) underwent attempted semirigid proximal ureteroscopic procedures. Twenty-three children of the 27 (85%) successfully underwent 23 semirigid procedures. Only 4 children of the 27 (15%) were converted from semirigid to flexible ureteroscopy in order to successfully perform 4 ureteroscopic procedures. The indications for ureteroscopy were treatment of ureteral and/or renal pelvic calculi (25 patients) and evaluation of hematuria (2 patients). The range of follow-up was 0.6 to 3.6 years (median of 1.6 years) for the semirigid ureteroscopic patients. No stones of the affected system were noted ureteroscopically at the end of procedures. No complications occurred during any of the procedures.

**Conclusions:** Proximal semirigid ureteroscopy can be successfully and safely performed in a high percentage of prepubertal children. This technique can be safely used in this population to treat proximal ureteral and renal pelvis calculi as well as to perform diagnostic ureteroscopy.
Passive Dilation by Ureteral Stenting Prior to Ureteroscopy in the Pediatric Population: Active Dilation Eliminated

Jeffrey S. Palmer, MD

Objectives: Active dilation of the ureteral orifice is commonly performed to access the ureteral orifice prior to ureteroscopy. Our study evaluated the use of passive dilation by ureteral stenting of inaccessible ureteral orifices at initial cystoscopic evaluation in children prior to a ureteroscopic procedure.

Methods: We evaluated all children less than 18 years of age scheduled to undergo a ureteroscopic procedure that were not able to have the ureteral orifice endoscopically accessed by a ureteroscope. All children then underwent double J stent insertion rather than being actively dilated and then returned at parental convenience for attempted ureteroscopy.

Results: A total of 40 children (22 boys and 18 girls) between 7.3 and 14.1 years of age (median 11.2 years) underwent 43 passive dilations of initially inaccessible ureters. Stents remained in place from 2 to 8 weeks (median 3 weeks). All patients then underwent successful flexible and/or semirigid ureteroscopy after preoperative stent placement. Active dilation of the ureteral orifice was not required in any patient. There were no complications from the ureteroscopic procedures or stent placement. No patient required a urinary tract infection.

Conclusions: Our study demonstrates that passive dilation of the inaccessible ureteral orifice in preparation for ureteroscopy is a straightforward, successful, and beneficial technique in children.

Extravesical Ureteral Reimplantation: An Outpatient Procedure

Jeffrey S. Palmer, MD

Objectives: Extravesical ureteral reimplantation is believed to have less morbidity than the intravesical approach. A critical pathway and modification of surgical technique were developed to determine if extravesical ureteral reimplantation can be consistently performed as an outpatient procedure without increased morbidity.

Material and Methods: We evaluated all children undergoing extravesical ureteral reimplantation using a modified technique which limits ureteral dissection, ureteral mobilization, and detrusor dissection to as distally as possible so that a 5:1 ratio of tunnel length to ureteral diameter can be accomplished. No surgical dissection occurs in proximity to the obliterated umbilical artery nor is the artery ligated. Patients follow a strict postoperative critical pathway, and parents receive extensive preoperative and postoperative education. A child is required to fulfill 5 strict criteria in order to be discharged including urinating several times.

Results: Forty-three children (35 girls and 8 boys) between 0.9 to 10.5 years of age (mean of 5.5 years) were evaluated. Twenty unilateral and 23 bilateral procedures were performed. Overall, 37 children (86%) were discharged home the same day while only 6 children (14%) went home the next day. All patients who underwent a unilateral procedure and 74% a bilateral procedure were outpatient. However, when evaluating the last 23 consecutive patients (10 unilateral and 13 bilateral procedures), all patients (100%) were discharged home the day of surgery without increased morbidity or requiring additional analgesics. None of the children had urinary retention, acute urinary tract infections, or required hospitalization after discharge. All patients had radiographic resolution of the vesicoureteral reflux on postoperative voiding cystourethrogram.

Conclusions: In our experience, unilateral extravesical ureteral reimplantation can be consistently performed as an outpatient procedure without increased morbidity. Most recently, bilateral procedures have resulted in similar results.
Use of KISS Catheter in Robotic-Assisted Laparoscopic Pyeloplasty in Children

Jeffrey S. Palmer, Jason Hafron, and Jihad Kaouk

Objectives: Kidney Internal Splint/Stent (KISS), a percutaneous nephroureteral catheter, is commonly used postoperatively after open pyeloplasty in children in order to bridge the anastomosis and permit renal drainage. One advantage of this catheter in children over the double J stent is that the former can be removed in the office without sedation or anesthesia. Also, the KISS catheter can be cut to the appropriate size so as to only bridge the anastomosis without entering the bladder, thereby preventing urinary reflux across the anastomosis and bladder spasms. We report on the first case using the KISS catheter in a laparoscopic pyeloplasty.

Methods: A 7 year-old boy with left ureteropelvic junction obstruction underwent a robotic-assisted dismembered pyeloplasty. A 4-French KISS catheter was brought into the operative field through a working port, inserted into the renal pelvis/ureter defect, brought through a small pyelotomy proximal to the anastomosis, and the pelvoureteral anastomosis was performed. The catheter was then brought through and sutured to the skin, and then connected to a small collection bag. A perinephric Penrose drain was also left in place.

Results: A renal ultrasonogram performed 1 week postoperatively did not demonstrate perinephric fluid collections and the KISS catheter was removed in the office. The patient did not have any complications including urinary leak, urinary tract infection, or wound infection.

Conclusions: This case demonstrates that a KISS catheter can be utilized for robotic-assisted laparoscopic pyeloplasty in children. Additional patients are warranted to further evaluate the use of KISS catheters for this procedure.

Horseshoe Kidney with Proximal Ureteral Obstruction Presenting with Prenatal Hydronephrosis

Pravin K. Rao, MD and Jeffrey S. Palmer, MD

Ureteropelvic junction (UPJ) obstruction is a well-documented associated condition of horseshoe kidneys. We present a case of prenatal hydronephrosis of a horseshoe kidney with proximal ureteral obstruction distal to the UPJ and not associated with the renal isthmus.

A newborn presented with left prenatal hydronephrosis. Postnataally a horseshoe kidney with left-sided hydronephrosis was identified on ultrasonography and no vesicoureteral reflux noted on VCUG. A diuretic MAG3 renal scan demonstrated relatively equal differential function and poor drainage of the left kidney.

A retrograde pyelogram confirmed proximal without distal ureteral obstruction. Intraoperatively, proximal ureteral obstruction was identified distal to the UPJ and not associated with the renal isthmus. The obstructed ureteral segment was excised and a spatulated ureteral anastomosis was performed. Postnataally, the patient has had marked reduction of the hydronephrosis.

Therefore, this case demonstrates that prenatal hydronephrosis of a horseshoe kidney may be associated with proximal ureteral obstruction distal to the UPJ and not associated with the renal isthmus.
Double-Layered Ventral Dartos Flip-Flap to Cover the Neourethra after Urethroplasty

Jeffrey S. Palmer, MD

Objectives: The use of a rotated subcutaneous tissue pedicle dissected from the dorsal prepuce is commonly interposed between the neourethra and skin after urethroplasty to reduce urethrocutaneous fistula formation. An alternative technique is described which involves placement of a well-vascularized dartos flap mobilized from the ventral aspect of the penis, which is flipped over the neourethra twice to give a double-layered support.

Methods: We reviewed our experience of all boys with hypospadias who underwent Thiersch-Duplay urethroplasty and a double-layered vascularized pedicle of dartos tissue mobilized from the ventral aspect of the penis. The technique is as follows. The vascular supply to the dartos flap is based on the distal side of the rectangle located either proximal to the original meatus or lateral to the neourethra depending on hypospadias location. This results in the first layer of coverage of the neourethra with redundancy of the flap on one side of the neourethra. The redundant flap is then folded back over the neourethra and secured laterally to the contralateral side of the neourethra resulting in a double-layered dartos flap. Hypospadias location was classified as anterior (glanular and subcoronal), middle (distal penile, midshaft, and proximal penile), and posterior (penoscrotal, scrotal, and perineal). Patients were evaluated postoperatively for urethrocutaneous fistula, urethral diverticulum, meatal stenosis, chordee, and penile torsion.

Results: Ninety-one consecutive boys between the ages of 4.8 months and 9.7 years (median of 10.8 months) underwent this technique. The positions of the hypospadias were 31 anterior, 55 middle, and 4 posterior (including 1 hypospadias cripple). The median follow-up was 8.4 months (range of 3.6 months to 2.4 years). Postoperative complications included only 1 urethrocutaneous fistula (1.1%), 1 urethral diverticulum (1.1%), and 2 meatal stenoses (2.2%) developed, which have all been successfully repaired. Penile chordee and torsion were not noted postoperatively.

Conclusions: The double-layered dartos flip-flap is a simple and highly successful technique to interpose tissue between the neourethra and skin after urethroplasty for all degrees of hypospadias.

Distal Granular Epispadias Presenting with Urinary Stream Deviation

Jeffrey S. Palmer, MD

Objectives: Epispadias, a rare penile anomaly, is most commonly the penopubic variety with associated penile chordee and complete urinary incontinence. We describe a very distal form of granular epispadias with a small urethral meatus and without penile chordee. The different types of clinical presentation are also discussed.

Methods: We reviewed our experience of all boys with mild distal granular epispadias. Children were evaluated for the age and reason for presentation to the pediatric urologist, and associated penile chordee. Surgical repair involved a meato-plasty using the following technique. A fine straight clamp is used to clamp the bridge of tissue between the dorsal meatus and the tip of the penis. The thinned avascular tissue is divided and excised, creating a V-shaped defect without creating a hypospadias. The granular channel is then gently and atraumatically calibrated to 12 French without any difficulty. Then interrupted 7-0 Chromic sutures are used to approximate the edges of the V. This provides a meatus at the tip of the glans without stenosis. Meatal stenosis was defined as a meatus that could not be catheterized with a 5-French catheter.

Results: 10 boys between the ages of 6 months and 5.0 years (median of 3.3 years) presented with mild distal granular epispadias. No associated penile chordee or other penile anomalies were noted. The reasons for presentation were dorsally-directed urinary stream deviation (n=9) and epispadias (n=1). All patients underwent meato-plasty at the time of surgery. All patients were noted intraoperatively to have meatal stenosis. Postoperatively all children voided with a non-deviating urinary stream. No complications were noted postoperatively.

Conclusions: We describe a very distal form of granular epispadias with a small urethral meatus and without penile chordee. Ninety percent of children presented to the pediatric urologist with urinary stream deviation and only 10% with epispadias.
The More Complicated Ureteral Reimplantation can be Performed Extravesically

Jeffrey S. Palmer, MD

Objective: Ureteral reimplantation with ureteral tapering and paraureteral diverticulectomy has traditionally been performed intravesically. We present an extravesical surgical approach to perform both of these more complicated ureteral reimplantations.

Methods: We evaluated all patients who underwent extravesical ureteral reimplantation with ureteral tapering and/or paraureteral diverticulectomy. The surgical technique first involves a detrusorrhaphy and development of detrusor flaps. The ureter is then transected at the ureterovesical junction. The ureter is then tapered around an 8-French catheter and/or the diverticulum is then resected with reapproximation of the bladder mucosa to treat a megaureter and large paraureteral diverticulum, respectively. The distal ureter is placed within the detrusor trough and the edges of the detrusor flaps are then closed over the ureter, thereby sandwiching the ureter between the detrusor and the bladder mucosa. A final 5:1 ratio of tunnel length to ureteral diameter is accomplished. A Foley catheter was left postoperatively. Patients underwent postoperative renal ultrasonography and voiding cystourethrogram postoperatively.

Results: Eight children (7 males and 1 female) underwent 6 extravesical tapered ureteral reimplantations and 7 diverticulectomies. The age of patients treated ranged from 2.8 to 12.5 years (median 6.0 years). Follow-up was from 0.9 to 2.1 years (median 1.2 years). There have not been any surgical complications. All patients had radiographic resolution of the vesicoureteral reflux and diverticuli on postoperative voiding cystourethrogram. No evidence of postoperative ureteral obstruction was noted on ultrasonography.

Conclusions: Our initial series demonstrate that ureteral reimplantation with ureteral tapering and paraureteral diverticulectomy can be managed safely and effectively using an extravesical approach. A larger series of patients is necessary to further evaluate this surgical approach.

Circumcision Revisions with Asymmetric Redundant Skin: A Straight-Forward Technique with Minimal Suture Lines

Jeffrey S. Palmer, MD

Objectives: The circumcised penis with asymmetric redundant penile skin requiring circumcision revision can result in multiple sutures lines. The technique that we describe allows for reconstruction of the penile skin such that there is a symmetric, circumferential mucosal collar, uniform penile skin, and suture lines only around the mucosal collar and the median raphe. This results in a cosmetically acceptable penis with minimal suture lines.

Materials and Methods: We reviewed our experience of all children who underwent circumcision revision using the following technique. A circumferential incision is made around the distal penile shaft along the mucosal collar resulting in a symmetrical mucosal collar. An incision is then made along the median raphe and the penis is degloved. The redundant dorsal penile skin is then incised along the midline creating Byar’s flaps and then sutured to the mucosal collar. Then the flaps of penile skin are then rotated around the penis ventrally allowing uniformity of the penile skin and excision of redundant non-uniform skin. The penile shaft skin is sutured to the mucosal collar circumferentially. The excessive ventral skin is the excised with suturing of the flaps ventrally with recreation of the median raphe. The penis is then wrapped circumferentially with a sterile dressing.

Results: Ninety-three consecutive boys between the ages of 0.5 and 16.1 years (median of 1.6 years) underwent circumcision revision using this technique. All patients tolerated the procedure well and had a cosmetically acceptable penis with a symmetric, circumferential mucosal collar, uniform penile skin, and suture lines only around the mucosal collar and the median raphe. There were no postoperative complications including hemorrhage, infection, or excessive penile foreskin.

Conclusions: This straight-forward technique for circumcision revision allows for a penis with reproducible results of symmetric skin, minimal suture lines, and a penis that looks similar to a well-performed circumcision.
Efficacy of Caudal Analgesia for Urologic Procedures with Flank Incisions
Katherine C. Hubert, Jack S. Elder, Mireya Diaz-Insua, Paul A. Tripi, and Jeffrey S. Palmer

**Background:** Traditionally, caudal blocks have not been utilized for flank procedures for they are believed not to be efficacious. We evaluated the efficacy of caudal analgesia for intraoperative and postoperative pain management in children undergoing diverse urologic procedures with flank incisions.

**Methods:** We retrospectively evaluated all children less than 18 years old who underwent an isolated urologic procedure via a single flank incision during a 4-year period and received either a pre-incision caudal block with 0.125% bupivacaine or a post-procedure intercostal nerve block with 0.125% bupivacaine. Intraoperative outcome measures included an increase in the patient's systolic blood pressure and/or heart rate more than 20% above baseline, and the need for additional intraoperative analgesia after the surgical incision. Postoperative outcome measures included the number of doses of weight-based morphine received, the time to the first dose of morphine, and the need for patient controlled analgesia (PCA). A statistician performed the statistical analysis.

**Results:** Twenty-five patients received a pre-incision caudal block and 25 patients received a post-procedure intercostal nerve block. There were no statistically significant differences between the two analgesic groups with respect to intraoperative and postoperative pain control and analgesic requirements. Children undergoing surgeries other than pyeloplasty had a higher probability of requiring morphine postoperatively at an earlier time (hazard ratio 2.15, p<0.069). No other variable examined had an effect on the probability of requiring morphine.

**Conclusion:** Children who receive caudal analgesia for urologic procedures with flank incisions appear to have similar level of intraoperative and postoperative pain control and postoperative pain medication requirements compared to children who receive intercostal nerve blocks.

3-Point Fixation Repair of the Buried Penis: A Simple Anatomical Technique
Jeffrey S. Palmer, MD

**Objectives:** A straightforward surgical technique is described to repair a lack of both penopubic and penoscrotal junctions resulting in a buried penis.

**Methods:** We reviewed our experience of all boys with buried penis that underwent a 3-point fixation technique. The technique is as follows. The penis is first degloved. Penopubic fixation is then performed with a single absorbable suture between dartos fascia and the superficial aspect of Buck's fascia at the 12 o'clock position of the penile base (dorsum and midline of penis) to the corresponding position of the dermis at the penopubic junction. Penoscrotal fixation is then performed using two interrupted absorbable sutures between dartos fascia and the superficial aspect of Buck's fascia at the 5 o'clock position and at the 7 o'clock position of the penile base (ventral penis) to the corresponding positions of the dermis at the penoscrotal junction. Patients were evaluated postoperatively for resolution of the buried penis (i.e. distinct penopubic and penoscrotal junctions) and complications, including skin dimpling at suture locations, chordee, penile torsion, and urethrocutaneous fistula formation.

**Results:** Sixty-three consecutive boys between the ages of 5 months and 12.8 years (median of 1.1 years) underwent repair using this surgical technique. Patients were distributed based on synchronous procedure as follows: 17 for circumcision, 20 for revision of circumcision, 25 for urethroplasty for hypospadias, and 1 for urethroplasty for epispadias. The median follow-up was 10 months (range of 3 to 18 months). No complications were noted.

**Conclusions:** The 3-point repair is an anatomically-based, simple repair of the buried penis with reproducible cosmetically successful results. This technique can be implemented in children undergoing circumcision, revision of circumcision, or urethroplasty.
Bilateral Extravesical Ureteral Reimplantation in Toilet-Trained Children: A Short-Stay Procedure without Urinary Retention

Jeffrey S. Palmer, MD

Objectives: Bilateral extravesical ureteral reimplantation has been associated with postoperative urinary retention. A critical pathway and modification of surgical technique were developed to determine if the bilateral extravesical procedure could be performed in toilet-trained children with patients discharged after a one-day hospitalization without urinary retention.

Material and Methods: We evaluated all toilet-trained children undergoing bilateral extravesical ureteral reimplantation using a modified technique which limits ureteral dissection, ureteral mobilization, and detrusor dissection to as distally as possible so that a 5:1 ratio of tunnel length to ureteral diameter can be accomplished. No surgical dissection occurs in proximity to the obliterated umbilical artery nor is the artery ligated. Patients follow a strict postoperative critical pathway, and parents receive extensive preoperative and postoperative education. A child is required to fulfill 5 strict criteria in order to be discharged including urinating several times.

Results: Eighty one toilet-trained children (62 girls and 19 boys) between 1.9 to 12.8 years of age (mean of 4.6 years) were evaluated. Seventy eight patients were discharged on the first postoperative day and most recently 3 patients were discharged on the same day as surgery. All patients were able to void postoperatively without any instances of urinary retention. None of the children had acute urinary tract infections or required rehospitalization. All patients had radiographic resolution of the vesicoureteral reflux on postoperative voiding cystourethrogram.

Conclusions: This study demonstrates that bilateral extravesical ureteral reimplantation can be performed in toilet-trained children after a one-day hospitalization without postoperative urinary retention. Most recently, this has been accomplished as an outpatient procedure. The critical pathway and limited dissection extravesical approach were essential for this success.

An Outcome Analysis and Comparison of Two Treatment Regimens for the Treatment of Phimosis with Topical Betamethasone

Amine Karapetian, MD, Lane S. Palmer, MD, and Jeffrey S. Palmer, MD

Objectives: Parents seek non-surgical alternatives for the treatment of phimosis. We evaluated the efficacy of two different topical betamethasone treatment regimens with respect to outcome and untoward effects in phimotic boys.

Methods: Boys with phimosis were treated with topical betamethasone (0.05%) and manual retraction. One author (JSP) prescribed betamethasone BID (twice daily) for 30 days (60 doses) and the other author (LSP) prescribed betamethasone TID (thrice daily) for 21 days (63 doses). All boys had severe phimosis (pre-pu$e unretractable to evaluate meatus) prior to treatment. Phimosis was graded 1 month after treatment as mild (penile adhesions), moderate (retractable to less than 50% glanular exposure), or severe. Treatment failure was defined as persistent severe phimosis.

Results: 150 consecutive patients from each group were included. The median ages were similar with 3.6 years for the BID group and 4.1 years for the TID group. There was an 83.3% response rate (moderate to no phimosis) to the BID regimen and an 86% response rate to the TID regimen (p=NS). Only 1 child had an untoward effect (candidal dermatitis). Three patients were diagnosed with congenital urethral malformations (2 hypospadias and epispadias) after treatment.

Conclusions: Topical betamethasone with manual retraction is a highly efficacious, well-tolerated, and safe treatment of phimosis. The 21-day TID and 30-day BID regimens are equally efficacious. Either treatment regimen can be offered to parents requesting non-surgical management of phimosis.
Avagard™ in Pediatric Urological Surgery: Safe, Effective and Time Efficient

Jeffrey S. Palmer, MD

Introduction: Avagard™, chlorhexidine gluconate 1% solution and ethyl alcohol 61% w/w is a waterless, scrubless, and brushless hand antiseptic indicated as a replacement for traditional pre-surgical brush hand scrubbing. We compared Avagard to hand brush scrub preparation by the urologist in preparation for outpatient and inpatient pediatric urological operations.

Methods: We evaluated the first 900 patients that we used Avagard as a preoperative hand antiseptic and compared them to the last 900 consecutive patients that we performed traditional antiseptic-impregnated hand brush scrubbing. A pediatric urological procedure was performed on each child. Patients and surgeon were monitored for side effects, and patients were monitored postoperatively for signs of wound infection. A cost analysis of the use of Avagard as compared to an antiseptic-impregnated hand brush for preoperative hand preparation was performed.

Results: No side effects for the patient or surgeon were noted including allergic reaction or skin irritation in either group. The incidence of wound infection was 1 in the Avagard group and 2 in the hand-scrub group (not statistically significant). A single course of oral antibiotics successfully treated all wound infections without any long-term sequelae. The use of Avagard was cost effective and more time efficient.

Conclusion: This study demonstrates that Avagard is a fast, easy to apply, effective, and safe surgical hand preparation for pediatric urological surgery. Its use is time efficient as well as cost effective in relation to the traditional surgical scrub.

Horizontal Urethral Duplication

Christina Ching, MD and Jeffrey S. Palmer, MD

Urethral duplication is a rare anomaly. Most urethral duplications occur in the same sagittal plane, but those in the same horizontal plane are even rarer. We present a case of horizontal plane incomplete urethral duplication with communication of the duplicated urethra to the normal midline urethra just proximal to the external urinary sphincter.

An 8 month-old male presented with two glanular openings – one midline and the other left of midline. The patient voids through his midline opening. There is no history of urinary tract infections. A renal ultrasonogram and VCUG were both normal without a duplicated urethra noted. At 20 months of age, the patient underwent cystourethroscopy which demonstrated a normal caliber midline urethra with a smaller caliber lateral urethra. The lateral urethra narrowed to a pin-point opening just proximal to the external urinary sphincter.

Therefore, this case demonstrates an uncommon variation of urethral duplication.
Timing for the Development of Urethrocutaneous Fistulae after Hypospadias Repair

Jonathan Ross, MD

Introduction: Urethrocutaneous fistulae (UCF) are a common complication of hypospadias repair (HR). While many fistulae are detected in the immediate post-operative period, some may present years after initial HR.

Objective: To evaluate timing for the development of UCF after HR and development of recurrent UCF after prior UCF repair.

Methods: Charts of all patients seen with UCF following HR from 1995 – 2005 were reviewed. Age of HR, level of hypospadias, type of HR, time at which parent/patient noted UCF, date/type of UCF repair, time at which recurrent UCF was noted, date/type of secondary repair, date of last follow up were documented.

Results: 26 patients were seen with UCF. 15 patients had at least one prior operation at another institution. Time between HR and initial UCF and time between UCF repair and recurrence are presented in the figure. 58% of patients with UCF following HR and 61% of patients with UCF recurrence following initial repair presented in the immediate post-operative period. 23% of patients with initial UCF presented >2 years after HR repair (up to 17 years later) while only 5.5% of patients with UCF recurrence presented >1 year after UCF repair. Ages of presentation with initial UCF after repair were as follows: 0-12 mos (N=5), 12-24 mos (N=6), 24-36 mos (N=6), 36-48 mos (N=2), >48 mos (N=7). Median follow up was 1.3 mos (0-69 mos).

Conclusion: While many UCF occur immediately following HR, nearly 1/4 UCF present well beyond many urologists’ typical follow-up period. In addition, these complications often present to other urologists. These findings suggest that rates of late UCF development may be underestimated and longer follow-up may be warranted. Late recurrence of UCF is rare (5.5% seen >1 yr), suggesting that more limited follow-up may be appropriate.
Section 10

Basic Science
Long-term Impact of Pubourethral Ligament Disruption on Leak Point Pressure Alterations in the Rat Model of Stress Urinary Incontinence

Kefer JC, Liu G, Daneshgari F

Introduction and Objectives: Mid-urethral slings were invented based on the integral theory of deficiency of pubo-urethral ligament (PUL) in women. We have hypothesized that injury to PUL in female rat would cause stress urinary incontinence as measured by leak point pressures (LPP), and have presented the short term effects of PUL injury on LPP (Kefer et al: J of Urol. Feb 2008-in press). The aim of this study was to examine the long-term effects of PUL deficiency as a potential model for SUI through comparison to an established model of SUI.

Materials and Methods: A total of 20 female age-matched Sprague-Dawley rats were randomly assigned to 1 of 3 groups: PUL transection (PULT) with LPP measured at 28 days, sham-PUL transection with LPP measured at 28 days, and bilateral pudendal nerve transection (PNT) with LPP measured at 28 days post-op. PUL transection was performed according to our previously described method (Kefer et al: J of Urol. Feb 2008-in press). LPP was measured 28 days later via an implanted suprapubic catheter. Following LPP, all animals were sacrificed with intracardiac perfusion of PBS and their suprapubic area was harvested including the urethra, vagina, and pubic arch for histological examination. Wilcoxon rank sum tests were used to evaluate differences in LPP between the experimental groups.

Results: Twenty eight days after PULT, LPP was significantly decreased in true PULT compared to sham group (15.7 cm ± 6.46 vs. 42.6 cm ± 12 cm H2O, p<0.001) and no different from PNT group (15.7 cm ± 6.46 vs. 15.09 ± 4.98, p<0.76), indicating durability of effects of PULT on inducing SUI in female rat. Histological examination of the en-block suprapubic areas shows absence of PUL in PULT group, but not in sham PUL or PNT groups.

Conclusion: Our results demonstrate that deficiency of the PUL in the female rat induces SUI that is comparable to the established SUI model via PNT. Our novel rat model could be used for investigation of mechanisms of SUI in female including the role of urethral hypermobility and potential therapeutic interventions of SUI.
Introduction and Objectives: Mice lacking the protein, lysyl oxidase-like 1 (LOXL1 KO) develop pelvic organ prolapse (POP) and demonstrate voiding dysfunction after pregnancy and delivery. Further characterization of the LOXL1 KO model is important to determine its relevance to female pelvic floor disorders (FPFD) in humans. The objective of this study was to compare the anatomy and function of the lower urogenital tract (LUT) of LOXL1 KO mice with and without POP.

Methods: 62 LOXL1 KO mice were observed for POP. Degree of POP was quantified using the MOPQ system. LUT anatomy in live anesthetized mice was assessed using a 7 Tesla MRI scanner to produce high resolution T1-weighted, fat-suppressed images. Age and parity-matched LOXL1 KO mice were divided into prolapsed (n=11) and non-prolapsed (n=6) groups. LUT function was evaluated using conscious cystometry (CMG) and leak point pressure (LPP) testing. Quantitative histologic analysis was performed on mid-urethra samples stained with von Gieson (elastin) stain. Kaplan Meier curves were used to describe the development of POP over time with differences determined using chi-square tests. Statistical analysis included: univariate analysis using t-test on normally distributed data, Wilcoxon rank sum test on non-normally distributed data, multivariate analysis using two-way ANOVA, and pairwise multiple comparisons using the Tukey test. P < 0.05 was considered significant.

Results: By 25 weeks of age, 50% of parous LOXL1 KO mice developed POP. Parity significantly affected the age at which POP developed (p=0.016). With each delivery, the age at development of POP decreased by 25%. MRI showed that LOXL1 KO mice with POP had variability in the size and location of the bladder and vagina compared with mice without POP. Multivariate analysis revealed lower LPP in the prolapsed mice compared with non-prolapsed mice when controlled for parity (p=0.02). There was a significant increase in the number of elastin clusters in the external urethral sphincter of LOXL1 KO mice with POP compared with LOXL1 KO mice without POP and C57Bl/6 controls (p=0.002).

Conclusion: LOXL1 KO mice can be studied as a relevant genetic animal model for FPFD. Parity is the significant factor that triggers POP in LOXL1 KO mice. LOXL1 KO mice with POP have variable internal pelvic anatomy. Both parity and POP are associated with a significant decrease in LPP in LOXL1 KO mice. An increase in elastin clusters in the urethra of LOXL1 KO mice with POP suggests that elastin disorganization associated with POP may lead to functional abnormalities.

Purpose: Angiotensin II (Ang II) is increased in diabetic retina. Ang II induces apoptosis in several cell types. The aim of this study was to evaluate Ang II and apoptosis in experimental diabetic retina.

Methods: Diabetes was induced in 10 week old Harlan Sprague-Dawley rats (35 mg/kg streptozotocin-sodium citrate). Blood glucose >250 mg/dL and impaired growth confirmed the diabetic phenotype. Glycohemoglobin was measured to monitor glycemic status. Control rats received citrate buffer. At 9 weeks the rats were anesthetized with urethane (1.2 g/kg, I.P) and perfused in situ with PBS followed by 4% paraformaldehyde. The eyes were enucleated and fixed with 4% paraformaldehyde-PBS. The eyes were then frozen in OCT and stored at -80º C. Ang II was localized by immunohistochemistry and fluorescence imaging using anti-Ang II (Phoenix Pharmaceuticals, 1:200). The immunoreactivity was resolved with anti-rabbit Alexa 488. Slides were mounted in anti-fade medium containing DAPI. Terminal dUTP Nick –End Labeling (TUNEL) was performed using the Apop TAG in situ apoptosis detection kit-fluorescein. Frozen sections (10μm) were analyzed at four to five adjacent locations. For the negative controls 1% BSA was substituted for TdT enzyme. Slides were mounted in anti-fade medium containing DAPI. Sections were examined first with the fluorescein isothiocyanate (green) and systematically scanned for positive red fluorescent cells indicating apoptosis. LEICA DM5000 fluorescent microscope equipped with a QImage Camera and ImagePro Software were used for imaging.

Results: The intensity and extent of Ang II labeling was significantly higher in diabetic retina. Ang II in the Müller cellular processes extends from the nerve fiber layer throughout the entire retina to the photoreceptor layer in the diabetic, whereas Ang II appears to extend up to the outer plexiform layer in the non-diabetic. Ang II in the Müller cellular processes extends from the nerve fiber layer throughout the entire retina to the photoreceptor layer in the diabetic, whereas Ang II in the Müller cellular processes extends from the nerve fiber layer throughout the entire retina to the photoreceptor layer in the diabetic, whereas Ang II in the Müller cellular processes extends from the nerve fiber layer throughout the entire retina to the photoreceptor layer in the diabetic, whereas Ang II in the Müller cellular processes extends from the nerve fiber layer throughout the entire retina to the photoreceptor layer in the diabetic, whereas Ang II in the Müller cellular processes extends from the nerve fiber layer throughout the entire retina to the photoreceptor layer in the diabetic, whereas Ang II in the Müller cellular processes extends from the nerve fiber layer throughout the entire retina to the photoreceptor layer in the diabetic, whereas Ang II in the Müller cellular processes extends from the nerve fiber layer throughout the entire retina to the photoreceptor layer in the diabetic, whereas Ang II in the Müller cellular processes extends from the nerve fiber layer throughout the entire retina to the photoreceptor layer in the diabetic, whereas Ang II in the Müller cellular processes extends from the nerve fiber layer throughout the entire retina to the photoreceptor layer in the diabetic. The intensity and extent of Ang II labeling was significantly higher in diabetic retina. Ang II in the Müller cellular processes extends from the nerve fiber layer throughout the entire retina to the photoreceptor layer in the diabetic, whereas Ang II appears to extend up to the outer plexiform layer in the non-diabetic. TUNEL positive cells were detected in the outer nuclear layer (ONL) of the diabetic, whereas Ang II appears to extend up to the outer plexiform layer in the non-diabetic. TUNEL positive cells were detected in the outer nuclear layer (ONL) of the diabetic, whereas Ang II appears to extend up to the outer plexiform layer in the non-diabetic. TUNEL positive cells were detected in the outer nuclear layer (ONL) of the diabetic, whereas Ang II appears to extend up to the outer plexiform layer in the non-diabetic. TUNEL positive cells were detected in the outer nuclear layer (ONL) of the diabetic, whereas Ang II appears to extend up to the outer plexiform layer in the non-diabetic. TUNEL positive cells were detected in the outer nuclear layer (ONL) of the diabetic, whereas Ang II appears to extend up to the outer plexiform layer in the non-diabetic. TUNEL positive cells were detected in the outer nuclear layer (ONL) of the diabetic. In the diabetic retina TUNEL positive cells were significantly increased throughout the entire ONL and inner nuclear layer.

Summary: Ang II and TUNEL positive cells were significantly increased in diabetic compared to non-diabetic retina. The link between Ang II and TUNEL positive cells in retina remains to be established.
Alpha Melanocyte Stimulating Hormone (α-MSH) Protects Against Acute Renal Failure in a Porcine Renal Ischemia Surgical Model

Simmons, MN, Haber-Pascal, G, Colombo, R, Ukimura, O, Zhou, M, Gill, IS

Introduction: Despite advances within the past 15 years, no intervention to date has significantly improved morbidity or mortality for acute renal failure (ARF). Renal functional preservation is a key consideration in nephron-sparing surgery and transplantation. α-MSH is an endogenous anterior pituitary hormone that has been shown to mitigate ARF in a rodent model of ischemic renal injury (J Clin Invest. 1997 Mar 15;99(6):1165-72). We sought to study if α-MSH exerted a similar renoprotective effect in higher vertebrates.

Methods: The study was conducted as a blinded prospective randomized clinical trial in 12 pigs. Using laparoscopic surgical technique the renal vessels were clamped bilaterally for 2 hours. Upon reperfusion either placebo or α-MSH (175μg/kg) were administered intravenously. Right kidneys were nephrectomized 0 to 6 hours after reperfusion, and tissues were analyzed. All pigs convalesced with a solitary injured left kidney. Post-operative serum electrolytes, BUN, and creatinine were measured at specified intervals. Pigs were sacrificed after 1-16 days, and left kidney tissues were analyzed.

Results: Median serum BUN and creatinine levels were significantly lower in animals that received α-MSH (n=5) versus placebo (n=5) (Mann-Whitney U-test post-op day #1 p=0.05 and p=0.02, respectively). Animals that received α-MSH had a 30-fold lower expression level of IL-8 at 6 hours post-reperfusion as determined by real-time RT-PCR. Pathologic analysis revealed a statistically significant higher degree of cortical tubular injury in control animals (p=0.02). Some subjects in both groups demonstrated functional recovery after 16 days.

Conclusions: Administration of a single dose of α-MSH upon reperfusion correlated with decreased severity of ischemia-induced ARF. Also renal functional recovery was observed in both groups after 2 hours of warm ischemia. Further studies to elucidate optimal α-MSH dose and regimen are underway to prepare for testing of this promising agent in human clinical trials.

Bladder Afferent Specificity of the “Bladder Sensory Test” Device for Assessment of Afferent Sensation of the Bladder

Yasuhiro Yamada, Osamu Ukimura, Guiming Liu, Mei Li, Tsuneharu Miki, and Firouz Daneshgari

Introduction and Objectives: C-fos, an immediate early gene, allows an accurate quantitative evaluation of nociceptive input reaching the spinal cord via afferent fibers from various organs. Previous investigators have demonstrated that noxious (chemical irritation) and non-noxious stimulation (bladder distension) of the rat bladder increased c-fos expression in L6 spinal cord, including the superficial lateral and medial dorsal horn (LDH, MDH, respectively), the dorsal commissure (DCM), and the sacral parasympathetic nucleus (SPN). Noxious stimulation activated greater numbers of c-fos expression in the DCM, whereas non-noxious stimulation induced greater number of expression in the SPN. In this study, we aimed to examine the quantitative expression of the c-fos in response to incremental neuroselective stimulation of C-fibers versus A-delta and A-beta-fibers of the bladder using our newly developed device of Bladder Sensory Test (BST).

Methods: We implanted the BST device in bladder of female rats (n=37). Using the Neurometer®, sine-wave electrical stimulation at 2000 Hz, 250 Hz and 5 Hz (reported to be selective for A-beta, A-delta and C-fibers, respectively) were applied. Spinal cord sections were immunoreacted for fos protein and positive cells were counted in four spinal regions of MDH, LDH, DCM and SPN.

Results: The peak of c-fos expression was located in L6 spinal cord. 250 Hz and 5 Hz stimulation (2.0 mA) significantly increased c-fos expression (81.1 cells/section and 48.8 cells/section, respectively) in L6 spinal cord, compared to control group (29.1 cells/section) (electrode implantation without electrical stimulation), however 2000 Hz stimulation did not significantly induce c-fos expression (31.8 cells/section). 250 Hz stimulation (2.0 mA) induced greater number of c-fos positive cell in SPN (53.7%), whereas 5 Hz stimulation (1.5 and 2.0 mA) activated greater number in DCM (47.7 and 51.2%, respectively) as depicted below.

Conclusions: Using our BST device, neuroselective sine-wave electrical stimulation of C or A-delta fibers of the rat bladder increased the c-fos expression at the spinal cord regions that are similar to patterns caused by intravesical capsaicin or bladder distension. Thus, our BST could be used for examination of the bladder’s afferent pathways that are commonly altered in pathologies such as overactive and neurogenic bladder.

continued
*Achieved statistical significance (p<0.05) between 5 Hz (2.0 mA) and 250 Hz (2.0mA).

**Achieved statistical significance (p<0.05) between 5 Hz (1.5 mA) and 250 Hz (2.0mA).
Emphysematous Cystitis: 
A Review of 135 Cases

Thomas AA, Lane BR, Thomas AZ, Remer EM, Campbell SC, Shoskes DA

Objective: To review recently published data on emphysematous cystitis (EC), a potentially life-threatening condition characterized by air within the bladder wall, and that most typically affects middle-aged diabetic women.

Methods: All articles published in English between 1956 and 2006 were identified using a Medline search for keywords "emphysematous cystitis", and "cystitis emphysematosa." Epidemiological, clinical, diagnostic, pathological and therapeutic data were evaluated, including risk factors such as the presence of diabetes mellitus or other comorbid emphysematous infections of the urinary tract.

Results: In all, 102 published papers, including 135 cases of EC, were reviewed; the median patient age was 66 years, 64% were women and 67% had diabetes mellitus. Most cases were diagnosed using plain films of the abdomen (84%), although more recently, computed tomography was the primary imaging method. Escherichia coli was the most commonly isolated organism. Most patients were treated with medical management alone (90%), while 10% of infections were treated with a combination of medicine and surgery. The overall death rate was 7%.

Conclusions: EC is the most common and typically the least severe gas-forming infection of the urinary tract. Prompt diagnosis and treatment is warranted to prevent the potential morbidity and mortality of this infectious condition.
Assessing Local African American Barbershops and Beauty Salons in the Development of Health Provider’s Cultural Competency

Charles S. Modlin, MD and Carlumandarlo E.B. Zaramo, M. Sc.

Objectives of Program/Intervention: The diversity of the American population is one of our society’s greatest assets, but the richness of this feature is overshadowed by the disproportionate burden of disease and illness borne by America’s racial and ethnic minority populations. Compelling evidence of the disparate health status of America’s racial and ethnic minority populations is documented in the form of shorter life expectancies and higher rates of cancer, birth defects, infant mortality, asthma, diabetes, and cardiovascular disease, as well as a plethora of other diseases and conditions.

African Americans (AA) are three times more likely to develop some form of kidney disease than their Caucasian (C) counterparts, an increased risk that can be partially explained by the higher number of AA who experience diabetes and high blood pressure. Furthermore, AA men are 66% more likely than C men to develop prostate cancer and are more than twice as likely to die from it. Nevertheless, one of the major barriers to eliminating these health disparities is related to the historical distrust that is prevalent in the AA population, which affects their attitudes and healthcare utilization behaviors. This distrust is often a major barrier to AAs undergoing health screenings.

Description of Program/Intervention: An important factor that affects AA health care participation (often overlooked by health care providers) is cultural competency. Cultural competency indicates how culture has the ability to strongly influence the amount and type of communication between the physician and patient in the doctor-patient relationship.

Cultural competency is an important tool for addressing health disparities. It is a strategy, which will allow healthcare providers an increased ability to connect with patients in order to promote health awareness and behavioral changes in minority communities. We have established a unique culturally competent outreach health education AA barbershop initiative to provide health education and screenings for detection of prostate cancer, diabetes, hypertension and renal disease.

Findings to Date: Project Intervention: Men in Cleveland and Northeast Ohio Barbershops were questioned about their attitudes/opinions regarding health screenings, including screening for prostate cancer. Their opinions regarding organ donation were also assessed. Between November 15, 2006 and Jan 31, 2007, 12 area barbershops were visited. Estimates of the number of men encountered in barbershops during this time period is 204 Minority Men, -17 Men per Site. Total exact encounters were 108 (52.9%). Ninety-Six men or 52.9% were signed up to visit the MMHC. There were 60 (55.6%) Were contacted and 36 men were scheduled as patients (Figure 1.) All men during this time period were approached by a trained African American Minority Men’s Health Center Community Outreach Coordinator who identified himself as such, provided the men with health literature, and engaged the gentlemen in dialogue with respect to disease prevention and preventative health screenings. Tables 1. list some of the most common comments posed by men in community barbershops with respect to the subject matter of health screenings, health disparities, barriers to healthcare and attitudes toward healthcare and screenings.

In order to engage in conversation and not disrupt the flow of normal business activities in these barbershops, the format of the discussions in each barbershop was conducted as part of casual conversation; therefore, not every question was asked of every man in each barbershop and special emphasis was placed upon not distracting the shop owners or customers from their schedules.

In addition, written surveys were conducted in many instances; however, at this stage of the program, the goal was first to engage the men in the shops in thought and conversation, rather than in completing surveys.

Findings / Key Lessons: Our intervention facilitates the development of trust between the AA community and healthcare providers. This trust is the single most important prerequisite necessary for healthcare providers to have success in promoting health in the AA communities. This outreach has enabled us to reach over 1000 men between 2004-2007 for screenings and detection of previously unrecognized diseases. To maintain this trust and effectively train culturally competent health providers, medical, nursing, and physician assistant students will be incorporated as supervised members of our outreach team.
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