2007 Research Abstracts

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

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Clinical and basic urology research at Cleveland Clinic Glickman Urological Institute is carried out by our professional staff of 65 physicians and scientists, who offer expertise in every urologic subspecialty area. They contributed 251 scientific publications to peer-reviewed medical journals in 2006, and they are currently conducting 100 prospective clinical research studies and 43 laboratory projects.

We welcome your interest in our urology research and clinical studies. If you would like additional information, please call 216.444.5600 or visit our web site at ccf.org/urology.

Sincerely,

Andrew C. Novick, M.D.
Chairman, Glickman Urological Institute
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Section 1

Prostate Disease
Early Biochemical Recurrence after Radical Prostatectomy for Prostate Cancer: Can We Identify those Patients?


Introduction and Objectives: Early identification of biochemical relapse (BCR) might have an impact on long-term outcomes in patients treated with radical prostatectomy (RP). We examined the rate and the predictors of BCR within 2 years after RP.

Methods: From January 1987 to December 2005, 8620 patients underwent RP for localized PCa in three different centres from Europe and North America. The aim of the study was to identify predictors of BCR within 2 years after RP. Logistic regression models relied on patient age, clinical stage, serum prostate specific antigen (PSA), pathological Gleason sum, extra capsular extension, surgical margin, seminal vesicle invasion and lymphnode invasion. Coefficients were then used to develop a nomogram predicting the probability of BCR within 2 years after RP. The definition for BCR differed in the three centres (rising PSA higher than 0.1 ng/ml, 0.2 ng/ml or 0.4 ng/ml). Data from 2 centres (n= 2911; n= 1614) were used for model development and data from the third centre (n=4095) were used for external validation.

Results: Mean age of the whole cohort was 60.9 years (median: 61.5), mean PSA was 8.4 ng/ml (median: 6.4), surgical margins were positive in 23.7% (n=2046), pathological Gleason sum was 6.8 (median: 7), 30.6% had extra capsular extension (n=2635) and 4.1% had lymphnode invasion (n=353), mean follow up was 3.4 years (median: 2.5, range: 0.1-18.2). Of the whole cohort, 16.7% (n=1436) relapsed during the follow up period. During the first two years 10.0 % (n=865) relapsed, which represented 58% of all recurrences. All covariates represented significant predictors of BCR within 2 years after RP.
Pathological Gleason sum $\geq 7$, lymphnode invasion and seminal vesicle invasion were the most informative predictors of BCR within 2 years after RP. The nomogram predicting BCR within 2 years after RP was 86.6% accurate in the external validation.

**Conclusion:** Two thirds of all relapses occur within two years after RP. Patients at high risk for early relapse might be candidates for adjuvant therapy options as well as they might require closer follow up. They can accurately be identified with the nomogram. The remaining third could be followed up less intensively, which will result in decreased costs for the public health system.
Age Predicting Pathological Stage after Radical Prostatectomy

Eric A. Klein, Pierre Karakiewicz

Introduction and Objective: The prediction of pathological stage is a key element in the process of PCa treatment decision making. We hypothesized that age at treatment combined with classical predictors may increase the accuracy of pathological stage predictions. To test this hypothesis, we addressed the accuracy of pathological stage predictions according to age at treatment.

Methods: Between 1987 and 2006, 11,975 consecutive PCa patients were treated with radical prostatectomy (RP) at 6 different institutions in America and in Europe. Univariable and multivariable logistic regression analyses were used to predict three separate endpoints: extracapsular extension (ECE), seminal vesicle invasion (SVI) and lymph node invasion (LNI). Age at RP was continuously, categorically and cubic spline coded. PSA, biopsy Gleason sum, clinical stage and year of surgery represented covariates. Predictive accuracy represented the performance benchmark.

Results: For ECE predictions, age at treatment only represented a significant univariable predictor when it was cubic spline coded (p=0.02). In the multivariable analyses, age did not reach independent predictor status (p=0.08). Moreover, predictive accuracy was not increased when age was considered (predictive accuracy = 70). For SVI, age represented a significant univariable predictor (p<0.001) and reached independent predictor status in the multivariable analyses (p<0.001). However, predictive accuracy was not increased in a significant fashion. In LNI predictions, age cubic spline coded reached significance in the multivariate analyses (p=0.05), but did not in the multivariable analyses (p=0.08). The predictive accuracy of the base models predicting LNI were not increased when age at treatment was considered.

Conclusions: Age represents a significant univariable and multivariable predictor for SVI at RP. However, age at treatment did not increase the predictive accuracy to predict any of the pathological stage in a clinically significant fashion.
Number of Cores vs. Significative Upgrading of Gleason Score after Radical Prostatectomy

Eric A. Klein, Pierre Karakiewicz

**Introduction and Objective:** Lack of agreement between biopsy and RP grade is a well known phenomenon. However, no study has compared the yield of biopsy grade according to the number of cores. We compared the rate of significant upgrading between sextant vs. extended biopsy schemes (10 or more cores).

**Methods:** Between 2000 and 2006, 4,581 consecutive PCa patients were treated with radical prostatectomy (RP) at 6 different institutions in America and in Europe. Biopsy Gleason sum and final pathological Gleason sum were available in all patients. Significant pathological upgrade was defined as either a biopsy Gleason sum of 2-6 that results in a 7 or 8-10 at RP, or a biopsy Gleason sum of 7 that results in an 8-10 at RP.

**Results:** In these patients, mean age at treatment was 61 (32-82) and mean PSA was 7.5 (0.1-70.7). At biopsy 3079 (67.2%), 1283 (28.0%) and 219 (4.8%) patients had Gleason sum ≤ 6, 7 and 8-10, respectively. 2270 (47.5%) patients were subjected to sextant biopsy and 2311 (52.5%) to extended biopsy schemes. In the first group of patients, significant upgrading was found in 624 (27.5%) patients. Similarly, in those subjected to extend biopsy schemes, significant upgrade at final pathology was found in 629 (27.2%) patients. Significant upgrade of the Gleason sum in 6 cores or less vs. 10 cores or more was not significantly different (27.5% vs 27.2, Chi-square p=0.8).

**Conclusions:** Extended biopsy schemes do not reduce the rate of significant upgrading between biopsy and RP in contemporary patients.
Introduction and Objective: Patients with clinical T1c can choose a wide range of treatment options, like watchful-waiting or definitive radical prostatectomy (RP). To better assess those patients, Epstein criteria were developed to identify potentially insignificant prostate cancer (IPCa). However, to our knowledge, no study as investigated these criteria in a European population. Therefore, we assessed the Epstein criteria of IPCa in a European cohort.

Methods: Between 1996 and 2006, 366 consecutive PCa patients were treated with radical prostatectomy (RP) at 2 different institutions in Europe. Clinical and pathological data was available in all patients. Patients selection was done using the reviewed Epstein criteria of IPCa, namely: Clinical stage T1c, PSA density <0.15 ng/ml, biopsy Gleason sum ≤ 6, the presence of PCa in fewer than 3 cores and the finding of no more than 50% PCa involvement in any of these cores. Several pathological finding at RP were investigated: organ confined (OC), extra-capsular extension (ECE), seminal vesicle invasion (SVI) and lymph node invasion (LNI). We also looked at surgical margins and pathological Gleason sum.

Results: Organ confined prostate cancer was found in 366 (91.8%) patients, whereas the remaining 30 (8.2%) patients were found to have non-organ confined prostate cancer. Of those who exhibit locally advanced disease, almost all had positive surgical margins at final pathology. Only 1 patient had positive SVI at RP and none had positive LNI. And finally, almost one of four (23.7%) patients had high grade Gleason sum at RP.

Conclusions: Epstein criteria for identifying IPCa remains a useful tools for European men in the treatment-related decisions. However, new criteria should be investigated, since almost one quarter of those initially diagnosed as IPCa will have unfavourable pathological characteristics at RP.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Overall population (n=366)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ confined PCa</td>
<td>336 (91.8%)</td>
</tr>
<tr>
<td>+ SM</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Non organ confined PCa</td>
<td>30 (8.2%)</td>
</tr>
<tr>
<td>-SM, no SVI, no LNI</td>
<td>0</td>
</tr>
<tr>
<td>+SM, no SVI, no LNI</td>
<td>29</td>
</tr>
<tr>
<td>SVI, no LNI</td>
<td>1</td>
</tr>
<tr>
<td>LNI</td>
<td>0</td>
</tr>
<tr>
<td>Gleason sum ≥ 7</td>
<td>87 (23.7%)</td>
</tr>
</tbody>
</table>
Introduction and Objectives: Follow-up after treatment for prostate cancer (PCa) is not risk adjusted according to biochemical recurrence (BCR) likelihood. Therefore, we assessed the yearly risk of BCR after radical prostatectomy (RP) according to preoperative and postoperative characteristics.

Methods: Between January 1987 and December 2005, 8620 patients underwent a RP in three large volume centres. BCR was defined as prostate specific antigen (PSA) levels of 0.1, 0.2 or 0.4 ng/ml and rising. We calculated annual hazard rates (HR) for BCR (Nr. of events ÷ Nr. patients at risk). We defined three risk groups according to BCR HR pattern: low risk: (n=1978; PSA <10 ng/ml and pathological Gleason <7 and clinical stage T1c and negative surgical margins and organ confined tumor); high risk: (n=1073; PSA >20ng/ml or pathological Gleason sum >7 or lymph node invasion or clinical stage T3); intermediate risk (n=3104; all other patients). The follow-up scheme is based on a requirement to detect 1 failure in 20 patients during a certain time period. For example, an annual BCR HR of 0.05 would implement one follow-up visit per year.

Results: Mean age of the whole cohort was 60.9 years (median: 61.5), mean PSA was 8.4 ng/ml (median: 6.4), surgical margins were positive in 23.7% (n=2046), pathological Gleason sum was ≤6 in 39.1% (n= 3373), =7 in 54.3% (n=4677) and >8 in 6.6% (n=570), 30.6% had extra capsular extension (n=2635) and 4.1% had lymph node invasion (n=353). Median follow up was 2.5 years (range: 0.1-18) and 2093 patients had a follow up longer than 5 years. The HR for BCR and the risk adjusted follow-up scheme are shown in Figure 1 stratified to the risk groups.

Conclusion: High risk patients should be followed up closely up to the fifth year and thereafter follow up periods might be widened. Patients with intermediate risk factors need less close but constant follow-up up to the 10th year after RP. Patients with low risk factors have a negligible risk of recurrence already in the first year after RP. Those patients can be reassured concerning their cure from the disease and cost intensive follow-up visits can be spared.
<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Follow-up visits per year after RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative year</td>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15</td>
</tr>
<tr>
<td>High Risk</td>
<td>5 4 3 3 2 2 2 1 1 0 0 1 0 0 1</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>1 1 1 1 1 1 1 1 0 0 1 0 0 1</td>
</tr>
<tr>
<td>Low Risk</td>
<td>Optional for functional outcome</td>
</tr>
</tbody>
</table>
Hypofractionated Intensity Modulated Radiotherapy (70 Gy at 2.5 Gy per Fraction) for Localized Prostate Cancer

Eric A. Klein, Chandana A. Reddy, Arul Mahadevan, Twyla R. Willoughby, Patrick A. Kupelian

Purpose/Objective: To present our observations on relapse-free survival and toxicity on patients with long term follow-up after hypofractionated intensity modulated radiotherapy (HFRT) to a total of 70 Gy delivered at 2.5 Gy per fraction over 5 weeks.

Materials/Methods: The study sample includes all 770 consecutive patients with localized prostate cancer treated with HFRT at the Cleveland Clinic from 1998 to 2005. All patients had available pretreatment PSA levels (iPSA) and biopsy Gleason scores (GS). Treatment consisted of intensity-modulated radiotherapy using 5 static fields (anterior, 2 laterals, and 2 anterior obliques). Delivery was performed with a Dynamic Multi-Leaf Collimator. A total of 70.0 Gy was prescribed for all patients at 2.5 Gy per fraction to be delivered in 28 fractions over 5 weeks. The location of the prostate gland was verified and adjusted daily with the BAT transabdominal ultrasound system. The distribution by D’Amico groups was 34%, 28% and 38% for low, intermediate and high risk disease. Sixty percent of patients received hormonal therapy. The median follow-up was 45 months (maximum 86 months). Acute and late toxicities were measured using RTOG scores. Biochemical failure was the endpoint studied with the ASTRO biochemical failure definition.

Results: For all 770 cases, the five-year biochemical relapse free survival rate was 82% (95%C.I.: 79-85. For patients with low, intermediate and high risk disease, the 5-year A-bRFS rates were 95%, 85% and 68% (Figure 1). The RTOG acute rectal toxicity scores were 0 in 51%, 1 in 40%, and 2 in 9% of patients. The RTOG acute urinary toxicity scores were 0 in 33%, 1 in 48%, 2 in 18% and 3 in 1% of patients. The RTOG late rectal toxicity scores were 0 in 89.6%, 1 in 5.9%, 2 in 3.1%, 3 in 1.3%, and 4 in 0.1% (1 patient). The RTOG late urinary toxicity scores were 0 in 90.5%, 1 in 4.3%, 2 in 5.1%, and 3 in 0.1% (1 patient). The actuarial late RTOG grade ≥2 rectal toxicity rate at five years was 6% (95%C.I.: 4-8%). The actuarial late RTOG grade ≥2 urinary toxicity rate at five years was 7% (95%C.I.: 5-10%).

Conclusions: Biochemical relapse-free survival rates are encouraging at five years after treatment. Long term urinary and rectal toxicity has been limited. High-dose hypofractionation is an alternative method of dose escalation in the treatment of localized prostate cancer.
Blacks Continue to Lag Caucasians in Cure Rates After Radical Prostatectomy Late in the PSA Era Despite PSA-Induced Clinical Stage Migration


Introduction: We evaluated biochemical failure (bF) rates after surgery for localized prostate cancer (PCA) between blacks and whites in the early and late PSA eras. Our hypothesis was that the gap in bF between these groups would lessen in the later PSA era owing to “catch up” awareness/availability of screening and treatment.

Methods: Data were evaluated from a prospectively-maintained database and included 2910 men treated by prostatectomy for PCA from 1987 - 2004. Rates of organ-confined disease (OC) were compared by race using Chi-squared tests. bF for the early (1987-1997) and late (1998-2004) PSA periods was analyzed with regard to race using Kaplan-Meier and Cox regression. bF was defined as a PSA >0.2. Patients with <12 months follow-up were excluded in the bF analysis, leaving 2074 pts for this portion of the analysis.

Results: Median follow-up for the early and late periods was 107 months (range 13-218) and 36 months (range 12-88), respectively. Both groups had a higher rate of OC in the later PSA period (blacks: 54% vs. 76% (p=0.0001); whites 50% vs. 71% (p<0.0001)). Despite similar biopsy Gleason grade, clinical T-stage and initial PSA, blacks had higher rates of OC than whites in 1998-2004 (29% vs 24%, p=0.09). Despite the higher rates of OC in both eras and the fact that blacks had higher OC disease, relapse-free survival for blacks lagged whites by 11% in both eras at 5 years (Figures 1 and 2). Race was also a significant predictor of bF in the multivariate analysis for both eras.

Conclusion: Despite larger gains in rates of OC later in the PSA era, blacks continue to show significantly lower rates of cure after surgery not explained by differences in pre- or post-treatment tumor characteristics. The results suggest factors other than known predictors of outcome are responsible for the persistence of lower cure rates in blacks despite PSA-induced stage migration.
Salvage Cryoablation for Recurrent Localized Prostate Cancer Following Definitive Radioation Therapy: Results from the Cold Registry


Introduction and Objective: There are limited options for patients who have demonstrable recurrent prostate cancer following definitive radiation therapy. Salvage cryoablation has historically been associated with a high incidence of complications. The objective of this study is to report contemporary outcomes of salvage cryoablation at a large number of centers, both academic and community, which have participated in the Cryo On-Line Data (COLD) Registry. To the authors’ knowledge, this is the largest registry data report of salvage cryoablation to date.

Methods: A secure on-line database was developed consisting of case report forms designed to collect relevant pre and post treatment information for patients undergoing cryoablation following pathologically confirmed failed definitive radiation therapy for localized prostate cancer. Kaplan-Meier (KM) analysis was performed with biochemical failure defined according to both the original ASTRO definition (three successive rises in PSA) and the 2006 revised ASTRO definition (nadir+2). Incontinence was defined any leak of urine at 12 months as determined by physician interview and was also stratified according to pad use.

Results: Twelve physicians participated and 277 patients were entered. The average age was 70.0 ± 7.1 years. Pre treatment PSA was 7.6 ± 8.2 ng/ml and the median Gleason sum was 7. Patients were followed for 21.6 ± 24.9 months with 47 having at least five year follow-up. KM analysis demonstrated five-year actuarial biochemical disease free rates of 58.9 ± 5.7% and 54.5 ± 4.9% for the original and revised ASTRO definitions, respectfully. The positive biopsy rate was 6.0%. The rectal fistula rate was 1.2%, and incontinence was 6.4% with 3.8% requiring pad use.

Conclusions: Salvage cryoablation offers a potentially curative option following failed radiation therapy and is associated with a morbidity profile favorable to salvage prostatectomy. In contrast to high historical rates, data from patients in the COLD registry indicate that the occurrence of rectal fistulas and incontinence is much less common than in the past. Efforts to continue to minimize these complications should continue.
Assessing Present and Future Risk of Prostate Cancer in Men Presenting for Laparoscopic Hernia Repair

J. Stephen Jones, Lee Ponsky, Steven Rosenblatt

**Introduction and Objective:** It has been shown that laparoscopic mesh hernia repair complicates, if not contraindicates, future radical prostatectomy. However, since many men undergoing herniorrhaphy are younger than is usually considered for screening, there is the potential for large numbers of men to have mesh placed prior to suspicion of prostate cancer. This decision made without forethought of these consequences will limit treatment options in the future when that cancer becomes clinically evident. We sought to determine the current and future risk of prostate cancer in patients presenting for possible laparoscopic hernia repair and the role for aggressive screening.

**Methods:** All patients of a single surgeon (SR) who sought consultation for hernia repair were recommended to have PSA screening. Based on reports of 5.5 times Relative Risk of future prostate cancer with even minimal increase in PSA (Gann et al, JAMA), we assessed both “abnormal” levels (>2.5 ng/dl) and those with PSA in a range suggesting future risk of PCa (1.0-2.49).

**Results:** Between November 1999 and August 2006, 1096 men sought consultation for hernia repair. PSA was obtained in 624. The most common reason for failure to obtain PSA was patient age <40 or beyond age where screening was deemed appropriate. An abnormal PSA was identified in 161 (25.8%), and a PSA in the range suggested by Gann to yield an increased risk of future prostate cancer diagnosis (>1.0) was found in an additional 211 patients (33.8%). A total of 372 patients (59.6%) had a PSA high enough that it was felt that laparoscopic herniorrhaphy would potentially affect future treatment options, and should be undertaken only with informed consent of this potential risk.

**Conclusions:** We have demonstrated that PCa risk is substantial among men presenting with inguinal hernia, and is higher than traditionally identified by population-based screening programs. The interpretation and significance of this is the subject of further consideration. However, any man undergoing laparoscopic hernia repair should be informed that future radical prostatectomy may be precluded as a treatment option, especially if he is at risk based on family history, race, or has a PSA suggestive of future prostate cancer risk.
Low Pretreatment Total Testosterone Levels are Associated with a Predominance of Pattern 4 Prostate Cancer at Prostatectomy and Risk of Biochemical Recurrence

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

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 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.
How About Lowering The Minimal Pre-Screening Age For Minority Patients at Risk For Prostate Cancer?

Andrew Novick, Charles S. Modlin Jr., David Miller, Carlumandarlo E. B. Zaramo

Introduction and Objective: Prostate cancer relics a foremost cause of demise among Americans, partially African Americans, in spite of advances in early detection and aggressive and inventive treatment. This investigative proposition was to provide a conceptual foundation for investigating the awareness and perceptions of earlier African-American males prostate cancer (PCa) pre-screening age (e.g., 30-45 years old).

This approach is exceptional in that it focuses on a disease, which therefore has been associated with advancing age, but yet those in their late 30’s and 40’s are expected to be knowledgeable about prostate cancer screening guidelines and the etiology of the disease.

Experimental Procedure: We developed a conceptual premise that is preparatory education and health literacy about PCa, which may facilitate the initiation of prostate health maintaining behaviors or regular screening compliance at an earlier recommended age (e.g. 35>). With evidence suggesting cPSA begins to increase as soon as two decades before clinical detection of PCa therein-lower age-boundary recommended for PCa screening provide is a logical step.

Preliminary Results: The results combined evidence from two theoretical models: 1) Cognitive-Social Health Information Processing (C-SHIP), and 2) psychosocial stress. C-SHIP incorporates the cognitive and affective processes through which decisions and actions about health seeking behaviors occur. Psychological stressors led African American men to prioritizing activities by importance. However psychosocial stressors contributed to understanding why younger African American men may not avail earlier for PCa screening and options for much less available information.

Conclusions and Prospective Interventions: The significance of this approach is in identifying the attitudes, beliefs and perceptions that hinder health maintaining and health seeking behaviors in African American men relevant at an earlier preventive age period.
Increased Incidence of Prostate Cancer in Male Breast Cancer

J. Stephen Jones, Una J. Lee

Introduction and Objectives: Synchronous occurrences of both prostate cancer and male breast cancer are rare, but provide insight into their hormonal and genetic biology. In one study of 161 patients with male breast cancer at Dana-Farber Cancer Institute and Massachusetts General Hospital between 1977 and 2000, 10 patients had prostate cancer. Steroid hormones play a role in both male breast cancer and prostate cancer. Prostate cancer is androgen-dependent and androgen-responsive, while male breast cancer is estrogen-dependent and generally hormonally-responsive. Estrogen receptors are positive in more than 85% of cases of male breast cancer, and is likely responsible for the good hormonal response. In combination with androgens, estrogens can induce aberrant growth and malignancy of the prostate gland. The treatment of male breast cancer patients with aromatase inhibitors, which is standard therapy for estrogen receptor positive breast tumors, have been shown to increase testosterone, and may stimulate prostate cancer. We aim to determine the incidence of prostate cancer in male breast cancer patients in the clinical context of widespread PSA screening, and to examine estrogen receptor (ER), progesterone receptor (PR), and HER-2/neu receptor (HR) status in these patients.

Methods: A retrospective review was conducted of male breast cancer patients from 1995-2004. Histopathologic characteristics and hormone receptor expression was obtained.

Results: In 38 patients with male breast cancer, 10 (26%) also had prostate cancer. In these 10 patients, 7 had positive ER status and 3 were unreported. 3 had positive PR status, 3 had negative PR status, and 4 were unreported. 1 had positive HR status, 3 had absent HR status, and 6 were unreported. 8/10 patients had hormonal therapy for breast cancer and 3/10 had hormonal therapy for prostate cancer. All 10 patients are alive; 2 have metastatic breast cancer.

Conclusions: Male breast cancer patients have a 26% incidence of prostate cancer in this cohort. This risk factor has implications for careful prostate cancer screening.
Pelvic Lymph Node Dissection during Radical Prostatectomy in Patients with Low Risk Prostate Cancer is Not Necessary

Eric A. Klein, C.W. Weight, Alwyn M. Reuther

**Objectives:** To compare the long term differences in the actuarial biochemical relapse-free survival rates in 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. A subset of 336 patients with low risk prostate cancer (prostate-specific antigen 10 ng/mL or less, biopsy Gleason score 6 or less, and clinical Stage T1 or T2) who did not receive adjuvant or neoadjuvant therapy were stratified into two groups, those who underwent a PLND (n = 140) or those who did not (n = 196). A Cox proportional hazards model was used to analyze the effect of age, race, family history, initial prostate-specific antigen level, tumor stage, biopsy Gleason score, PLND, extracapsular extension, and seminal vesicle invasion on the likelihood of biochemical failure. Biochemical relapse-free survival for each group was estimated by Kaplan-Meier analysis. The median follow-up time for the entire group was 88.8 months, with a similar follow-up for both cohorts (PLND 94.4 months and no-PLND 88.0 months, p value=0.14). Follow-up information was obtained through an institutional review board-approved prospective patient registry.

**Results:** The long term biochemical relapse-free rate for the entire cohort was high, 86.1% at 10 years, with the PLND group versus no-PLND group measuring 83.8% and 87.9%. On Kaplan-Meier curves, there was no significant difference between PLND and no-PLND out to 10+ years (p = 0.33).

**Conclusions:** Our study results continue demonstrated that the omission of PLND in patients with favorable tumor characteristics does not adversely affect long term biochemical relapse rates. Such patients can be spared the morbidity and cost of PLND without affecting the chance for cure.
Perineural Invasion on Prostate Needle Biopsy Does Not Predict Biochemical Failure Following Brachytherapy for Prostate Cancer

Eric A. Klein, Ming Zhou, Christopher J. Weight, Jay P. Ciezki, Chandana A. Reddy

Purpose: To determine if the presence of perineural invasion (PNI) predicts biochemical recurrence in patients who underwent low-dose-rate brachytherapy for the treatment of localized prostate cancer.

Methods and Materials: A retrospective case control matching study was performed. The records of 651 patients treated with brachytherapy between 1996 and 2003 were reviewed. Sixty-three of these patients developed biochemical failure. These sixty-three patients were then matched in a one-to-one ratio to patients without biochemical failure, controlling for biopsy Gleason score, clinical stage, initial prostate-specific antigen, age, and the use of androgen deprivation. The pathology of the entire cohort was then reviewed for evidence of perineural invasion on initial prostate biopsy specimens. The biochemical relapse free survival rates for these two groups were compared.

Results: Cases and controls were well matched, and there were no significant differences between the two groups in age, Gleason grade, clinical stage, initial prostate-specific antigen, and the use of androgen deprivation. PNI was found in 19 (17%) patients. There was no significant difference in the rates of PNI between cases and controls, 19.6% and 14.3% respectively (p = 0.45). PNI did not correlate with biochemical relapse free survival (p = 0.40).

Conclusion: Perineural invasion is not a significant predictor of biochemical recurrence in patients undergoing brachytherapy for prostate cancer.
Predicting Occult Malignancy in the Prostate Prior to Radical Cystectomy

Eric A. Klein, Steven C. Campbell, John C. Kefer, Louis Liu, Armine Karapetian

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 between 1995-2006 undergoing both staging TURBT and RCx 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 is 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 multifocality (OR=2.28, p<0.02) or BNTI (OR=5.10, p<0.0001) were predictive of PI-TCC. BNTI was also predictive of PI-TCC on multivariate analysis (OR=4.73, p<0.0001). Interestingly, all patients with PI-TCC had one or more of these risk factors, and all 36 patients (21%) 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 170 patients (5%) had no risk factors for PI-TCC or CAP, were without prostatic malignancy, and all were identified by preoperative parameters.

<table>
<thead>
<tr>
<th>Preoperative Risk Factors</th>
<th>Total (n=171)</th>
<th>PI-TCC (+)</th>
<th>PI-TCC (-)</th>
<th>OR (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma in Situ (CIS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>48</td>
<td>20 (42)</td>
<td>28 (58)</td>
<td>1.8 (0.09)</td>
</tr>
<tr>
<td>Absent</td>
<td>123</td>
<td>35 (28)</td>
<td>88 (72)</td>
<td></td>
</tr>
<tr>
<td>Multifocal Disease (MF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>73</td>
<td>31 (42)</td>
<td>42 (58)</td>
<td>2.28 (&lt;0.02)</td>
</tr>
<tr>
<td>Absent</td>
<td>98</td>
<td>24 (24)</td>
<td>74 (76)</td>
<td></td>
</tr>
<tr>
<td>Bladder Neck/ Trigone (BNTI)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>95</td>
<td>44 (46)</td>
<td>51 (54)</td>
<td>5.10 (&lt;0.0001)</td>
</tr>
<tr>
<td>Absent</td>
<td>76</td>
<td>11 (15)</td>
<td>65 (85)</td>
<td></td>
</tr>
</tbody>
</table>

continued
**Conclusion:** Our results validate clinical risk factors for predicting prostatic malignancy, and identify a subset of patients at low risk for occult malignancy who may benefit from prostate sparing. This subset is small, however, and prospective validation will be required.
Primary Prostate Cryoablation: Results from 1198 Patients Tracked with the Cold Registry


Introduction and Objective: The use of cryoablation as an initial treatment for localized prostate cancer has increased. The objective of this study is report the outcomes of modern cryoablation at a large number of centers, both academic and community, which have participated in the Cryo On-Line Data (COLD) Registry. The assembled data on 1198 men presented herein is the largest primary prostate cryoablation series reported to date.

Methods: A secure on-line database was developed consisting of case report forms designed to collect relevant pre and post treatment information for patients undergoing prostate cryoablation. 1198 patients who had undergone primary cryo-therapy were identified and stratified according to risk groups as follows. For low risk patients all of the following were true: PSA < 10, Gleason < 7 and Stage < T2b. If a patient had a PSA > 20, Gleason > 7, or stage T2c or greater they were considered high risk. All other patients were considered moderate risk. Biochemical failure was defined according to both the original ASTRO definition (3 rises) and the 2006 definition (nadir + 2). Biopsy was performed at the physician's discretion, but most commonly if a patient had a rising or suspicious PSA. Incontinence was defined by the use of any absorbent pads. Return to intercourse was defined as the ability to penetrate and complete intercourse.

Results: The average age was 69.8 ± 7.5 years. Pre treatment PSA was 9.6 ± 8.6 ng/ml, median Gleason sum was 7 (range: 4-10) and the median stage was T2a. Patients were followed for 24.4 ± 25.9 months. Actuarial survivals as determined with KM analysis and the number of patients at risk at 5 years are reported in the table. Positive biopsies were observed for 82/354 patients (23.7%) biopsied, or 82/1198 (6.8%) of the total population. The rectal fistula rate was 0.4%, and incontinence was 4.8% with 2.9% of patients using pads. Of those patients potent at the time of therapy 16.8% had returned to intercourse but only 8.8% able to do so without any pharmaceutical or device assistance.

Conclusions: Cryoablation, practiced over a spectrum of users, maintains morbidity with the exception of ED comparable to radiation and surgery and efficacy through five years of follow-up according to both ASTRO definitions of biochemical failure. It is imperative that a cryoablation specific definition of biochemical failure be developed in the near future.

continued
### 5-year Biochemical Survival

<table>
<thead>
<tr>
<th></th>
<th>ASTRO (3 rises)</th>
<th>ASTRO (Nadir + 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=182)</td>
<td>77.1 ± 2.1</td>
<td>72.9 ± 2.1</td>
</tr>
<tr>
<td>Low (n=29)</td>
<td>84.7 ± 4.5</td>
<td>91.1 ± 2.9</td>
</tr>
<tr>
<td>Moderate (n=52)</td>
<td>73.4 ± 4.3</td>
<td>78.5 ± 3.6</td>
</tr>
<tr>
<td>High (n=31)</td>
<td>75.3 ± 3.7</td>
<td>62.2 ± 4.9</td>
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Staging Saturation Biopsy in Patients with Prostate Cancer Treated with Active Surveillance

J. Stephen Jones, Robert Abouassaly

Introduction and Objectives: In the current PSA era, it has become clear that one option for patients with low grade, low volume prostate adenocarcinoma is to delay curative treatment until evidence of disease progression exists. The accurate assessment of extent of disease is necessary to determine what patients would be candidates for active surveillance. There is evidence that saturation prostate biopsy provides more accurate staging than more traditional biopsy protocols.

Methods: We reviewed our institutional review board-approved prostate biopsy database and identified patients diagnosed with prostate cancer treated with active surveillance. Between September 2001 and January 2007 we identified 58 patients initially treated with delayed intervention for low grade, low volume disease.

Results: Patients had a median age of 70 (range 51 – 89), with a median PSA of 5.6 (range 0.3 – 19) at the time of diagnosis. Three patients were clinical stage T2a, two were T1a, and all other patients were T1c. Median number of cores taken at the time of initial prostate cancer diagnosis was 12. The median number of positive cores was 1 with median of 10% of the core involved with disease. All but 7 patients had a Gleason score of 6. Fifty of the patients underwent subsequent staging saturation 20-core biopsy a median of 269 days after the initial biopsy (range of 16 – 269 days). Sixteen patients had an upgrading of their disease as defined by an increase in Gleason score or a doubling in volume of disease, leading to a recommendation of active treatment by the treating urologist.

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. Information obtained from such biopsies helps determine what patients can continue to be watched, and what patients need curative-intent treatment.
Patient-Reported Outcomes after Retropubic, Laparoscopic, or Robot-Assisted Prostatectomy: Results from a Prospective, Multi-Center Study

Eric A. Klein, Andrew Wagner, John Wei, Rodney L. Dunn, Brent Hollenbeck, Gerald Andriole, David Wood, Doug Dahl, Jim C. Hu, Larry Hembroff, Mark S. Litwin, Christopher S. Saigal, Adam Kibel, Louis Pisters, James E. Montie, Martin G. Sanda

Introduction: The comparative performance of retropubic (RP), laparoscopic (LAP), and robot-assisted prostatectomy (RAP) in QOL outcome has not yet been established in prospective, multi-center studies.

Method: 602 prostate cancer patients were enrolled pre-prostatectomy (375 RP, 110 LAP, 117 RAP) at 8 academic centers. QOL was measured by the EPIC at baseline and 2, 6, 12, and 24 months after treatment, along with incision pain and cosmetic appearance. Outcomes data were collected by a third-party survey center not affiliated with any of the clinical sites; interviewers were blinded to surgery type. Univariate and multivariable analyses were conducted by intent-to-treat; endpoints were cosmesis, incisional pain, and sexual and urinary QOL.

Results: Incisional cosmesis was after LAP or RAP than RP (p<0.001). Incisional pain was lower with RAP and LAP groups combined as compared to RP (p=0.01), though differences between each of the three groups were only marginal (p=0.06). Urinary continence recovery was similar across treatment groups in univariate analysis and multivariable models (p=0.50). Univariate analysis among nerve-sparing cases showed benefit of RP as compared to LAP or RAP (Figure):

Sexual Recovery by Type of Nerve-Sparing Prostatectomy

continued
Among nerve-sparing cases, mean EPIC sexual function scores at 1 year was 43 (95%CI 39-46) for RP, 21 (95%CI 15-26) for LP, and 33 (95%CI 26-39) for RAP. After covariate adjustment in multivariable models, the pairwise difference between RP & LAP and the difference between RP & RAP favored RP (p<0.001, p=0.05 respectively). Possible role of a learning curve was evidenced by difference in # of open cases versus laparoscopic cases participating surgeons performed in the year preceding enrollment: mean open/retropubic cases per surgeon in preceding year = 79; mean laparoscopic case = 15

Conclusions: Laparoscopic prostatectomy with or without robotic assistance was associated with better cosmetic result and less incision pain than RP. Although RP was associated with better sexual recovery than LAP and marginally better than RAP, there was also a significant difference in overall surgeon expertise with each procedure at start of study, and learning curves may have influence the outcomes. Continued evaluation of LAP and RAP outcomes is indicated.
Aggressiveness of Prostatic Carcinomas Related to RNASEL R462Q Mutations

Eric A. Klein, Cristina Magi-Galluzzi, Ming Zhou, Benjamin T. Larson, Graham Casey, Robert Silverman

Introduction: Mutations in the RNASEL gene have been associated with increased susceptibility to prostate cancer. Specifically, the R462Q mutation has been hypothesized to decrease the apoptotic and antiviral functions of the RNase L enzyme, leading not only to prostate cancer, but more aggressive tumors. This study assesses tumor aggressiveness at the time of diagnosis and by surgical specimens from a prospective database.

Methods: 232 men treated for prostate cancer by radical prostatectomy were genotyped for the R462Q RNASEL mutation. Tumor aggressiveness was assessed at time of diagnosis by age of disease onset, tumor grade, tumor stage, and PSA levels. Aggressiveness was assessed by tumor volume, extra-capsular extension, seminal vesicle involvement, and lymph node metastases in surgical specimens. A subset of patients with T1c stage tumors was analyzed also.

Results: More aggressive tumors were not seen in any genotype. There were no significant differences noted among the three genotypes in tumor aggressiveness at diagnosis or in surgical specimens. The T1c stage subset demonstrated no significant differences, except significantly more extra-capsular extension in homozygous wild-type tumors.

Conclusions: Our study does not seem to support the current epidemiological literature that associates the R462Q RNASEL mutation with more aggressive tumors.
Impact of Prostate Cancer Patient Treatment Outcome on HRQOL and Satisfaction with Cancer Care among their Spouses

Eric A. Klein, John T. Wei, Laurel Northouse, Rodney L. Dunn, Xihong Lin, Jeff Michalski, Howard M. Sandler, Larry Hembroff, Mark S. Litwin, Christopher S. Saigal, Louis Pisters, Nikhil Shah, Martin G. Sanda

Background: The impact of prostate cancer treatment on spouses of treated patients has not been evaluated in prospective, multi-center studies. We sought to evaluate spouse/partner perspectives regarding patient treatment, to measure how patient HRQOL changes caused problems for spouses, and to assess consequent spouse satisfaction with the patients’ prostate cancer care.

Method: The PROST-QA multi-center, prospective study enrolled 614 spouses or cohabitating partners of patients with newly diagnosed prostate cancer from March 2003 to 2006. Spouse/partner follow-up entailed centralized phone interview that measured problems reported by spouse-partners related to patients’ post-treatment HRQOL changes, and measured spouse satisfaction with outcome of patient prostate cancer treatment. Kruskal Wallis test evaluated association of problems reported by spouses with HRQOL change reported by patients; multivariable GEE evaluated associations of post-treatment patient HRQOL change with spouse report of treatment outcome satisfaction.

Results: Spouses/partners reported moderate or worse problems related to treatment effect on patients’ HRQOL as tabulated. Spouse report of problems related to patient HRQOL change post-treatment were significantly associated with the change in measured patient HRQOL scores in urinary and sexual domains and patient report of domain-specific bother (p<0.05; kappa coefficients 0.12-0.35). Spouse satisfaction with treatment outcome associated significantly with patient HRQOL outcome in sexual (p<0.001) urinary incontinence (p=0.002), hormonal/vitality (p=0.007) and bowel/rectal (p=0.04) domains on univariate analysis; sexual and urinary continence remained significant in multivariate analysis.

Conclusions: Spouses/partners of patients treated for localized prostate cancer are impacted by the treatment effects on patient HRQOL, as reflected by spouses having problems significantly related to changes in patient’s HRQOL and by consequent impact on spouse satisfaction with the patient’s cancer treatment. Among various HRQOL domains, sexual and urinary changes have the greatest impact on patient spouses/partners.
### Percentage of Spouse/Partners Reporting Moderate or Worse Bother Related to Patient HRQOL Domains 12 months after Primary Prostate Cancer Treatment

<table>
<thead>
<tr>
<th>HRQOL Domain</th>
<th>Treatment</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RP</td>
<td>XRT</td>
</tr>
<tr>
<td>Sexual</td>
<td>45%</td>
<td>25%</td>
</tr>
<tr>
<td>Urinary</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Bowel/Rectal</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Vitality/Hormonal</td>
<td>16%</td>
<td>15%</td>
</tr>
</tbody>
</table>
The Effect of Fellowship Training on Outcomes After Radical Prostatectomy


Introduction and Objective: We have shown that biochemical recurrence (BCR) after radical prostatectomy (RP) is associated with surgeon's experience. Surgical oncological fellowship training is associated with improved survival in colorectal and breast cancer patients. In this study we sought to determine the effects of the learning curve on BCR in men treated with RP by fellowship (F) vs non-fellowship (NF) trained surgeons.

Methods: The study included 7,850 prostate cancer patients treated with open RP in four health care centers. For each patient, surgeon experience was coded as total number of RPs conducted by the surgeon prior to the patient's RP. The learning curve for BCR was estimated separately for F vs NF trained surgeons, controlling for case-mix (PSA, pathological stage and grade) and year of surgery. The maximum number of RP by NF surgeons was 119. Thus, we tested the effect of fellowship training on BCR in up to the initial 119 cases of F vs NF treated patients.

Results: There were 73 surgeons in our series. The majority of surgeons (53, 73%) were NF trained. There was a strong correlation between training and surgeon experience: the median number of total cases performed by F trained surgeons was 256, compared to only 26 for NF trained surgeons. Among 2375 patients with surgeon experience <=119, there were 548 recurrences. The median follow-up for patients without BCR was 4.3 years. Fellowship training was significantly associated with lower probabilities of BCR. With adjustment for case mix and year of surgery, the 5-yr probability of BCR for patient 50 was 16% vs 23% if treated by a F vs NF trained surgeon, respectively (p<0.005) In addition, we performed an interaction analysis to determine if the learning curve was different for F vs NF trained surgeons. Our hypothesis was that fellowship trained surgeons learned at a faster rate. The interaction term between fellowship training and surgeon experience was statistically significant (p<0.005) protective of BCR.

Conclusions: Surgeon experience affects BCR after RP. However, this surgeon experience effect is influenced by further training. This study suggests that surgical fellowship training significantly reduces the impact of the learning curve on cancer control outcomes.
Surgeon Experience Independently Predicts Biochemical Recurrence Following Radical Retropubic Prostatectomy for Organ Confined Disease

*Eric A. Klein, John C. Kefer, Alwyn M. Reuther*

**Introduction:** Biochemical recurrence (BR) following open radical retropubic prostatectomy (RP) is an excellent target outcome, as it indicates cancer cure and is not influenced by postoperative factors. Herein we determine if 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. Median PSA followup was 61 months, and all had at least 12 months PSA followup. Surgeon experience was defined as total number of RP performed prior to each case. Low and high surgeon 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 following RP using uni- and multivariate Cox proportional hazard models. Analysis was also repeated in 1,310 patients with organ confined disease.

**Results:** High surgeon experience is predictive of decreased BR (HR 2.04, p<0.0001), and is unaffected by case-mix, or stage migration (HR 1.33, p=0.0147, 95%CI 1.06-1.67). Patients with organ-confined disease showed similar results (low vs high experience HR 1.52, p=0.0238). Kaplan Meier (KM) analysis of BR-free survival for all patients at 10 years is shown below. Patients with organ-confined disease also demonstrate benefit from high experience surgeons in KM analysis (89% vs. 81% at 10 years, p=0.0227).

continued
Conclusion: We demonstrate that surgical experience predicts BR following RP, describing a learning curve for RP with differences in outcomes and oncologic cure. These findings suggest that high volume surgeons use different surgical techniques versus lower volume surgeons. Delineation of the aspects of RP technique associated with highest oncologic cure rates remains a critical area of research.
Positive Surgical Margins Increase the Risk of Biochemical Recurrence in Extremely Favorable and Extremely Unfavorable Patients Subjected to Radical Prostatectomy


Introduction and Objective: Positive surgical margins (+SM) status at radical prostatectomy are a well known prognostic factor for biochemical recurrence after radical prostatectomy (RP). However, the urologic community has questioned the value of +SM in either favorable or unfavorable prostate cancer (PCa) patients. We hypothesized that +SM may have a significant impact on the rate of BCR in all patients, independently from the pathological characteristics.

Methods: Clinical and pathological data were available for 8620 patients from 1 European and 2 North American referral centers, subjected to retropubic RP between 1987 and 2006. Patients were stratified in favorable (PSA ≤10 ng/mL, RP Gleason sum ≤6, no extracapsular extension [ECE], no seminal vesicle invasion [SVI] and no lymph node invasion [LNI]), unfavorable (PSA >20 ng/mL or RP Gleason sum 8-10 and SVI or LNI) and intermediate (all remaining patients). Kaplan-Meier and Cox regression analyses addressed the rate of BCR after RP in each stratum.

Results: At RP, 2474 (28.7%), 5267 (61.1%) and 879 (10.2%) patients were classified as favorable, intermediate and unfavorable PCa patients, respectively. In favorable PCa patients, +SM were associated to a higher rate of BCR (Log rank p<0.001) and to a 4.3 fold increase in the rate risk of BCR (p<0.001, OR 4.31). Similarly, in intermediate PCa patients, +SM were associated to a worst prognosis (Log rank p<0.001) and to an increased risk of BCR (p<0.001, OR 2.33). Finally, even in unfavorable PCa patients, +SM were associated to a higher rate of BCR (Log rank p<0.001) and to an increased risk of BCR (p<0.001, OR 1.47).

Conclusions: Surgical margin status is crucial in all patients subjected to RP. Patients with negative surgical margins may expect a lower rate of BCR than patients with +SM, independently from the biological characteristics of the tumor.
The Role of Community Health Fairs in the Elimination of Prostate Cancer Health Disparities in African American Men

Charles S. Modlin Jr, Carlumandarlo E.B. Zaramo, Oluranti Aladesanmi

Introduction and Objective: Improving access to healthcare for African American (AA) men is an approach to decrease health disparities. Cleveland Clinic Minority Mens Health Center (MMHC) was established in 2004 to address the higher rates of mortality in AA men. At the 2005 & 2006 health fairs, 385 & 370 AA men, respectively, were screened for prostate cancer (PCa).

Methods: A descriptive study conducted at two of our annual health fairs. The center hosted the 3rd Health Fair in 2005 and the 4th Health Fair in 2006. Ads were placed in media targeting AA men in Cleveland. Subjects completed questionnaires including demo information, AUA Prostatic Symptoms Scores. Venipuncture was performed on the participants for cPSA. There were seminars on topics including PCa and Health Literacy. Results were communicated to patients by mail. A follow up was arranged for patients with abnormal results. A database for results of cPSA, and DRE, cases were evaluated.

Results: At the 2005 HealthFair, 34% were in the age range 45-55 yrs., 87% were over 40 yrs, and 2.5 % over 75 yrs. The 2006 health fair, 37% were in the range 45-55 yrs, 83% were over 40 yrs, and 2.6 % over 75 yrs. In 2005, the PSA’s had 385 values with mean 1.40, st. dev. of 5.23, 6.3% (25 men) had a PSA greater than 3.6, the highest 5 values were 12.65, 16.17, 29, 54.38 and 79. In 2006 the PSA distribution had 368 values with mean 1.09, stdv. of 2.25, 4.6% (18 men) had a PSA greater than 3.6, the highest 5 values were 6.78, 7.34, 7.57, 18.69 and 33.24.

Conclusions: The age group 45-55 yrs were the largest utilizers of the 2 yrs, hence age appropriate health maintenance should be provided. The age distribution of our subjects is consistent with Fowke et al (Urol. Onco. 2005) and Gil- ligan et al (Arch Intern Med. 2004), of age related differences in PCa screening patterns. Younger AA men, particularly those younger than age 50, are more likely than whites to have had a current cPSA test or DRE, independent of socio-economic status. In men older than age 65 there was less frequent use of screening compared to whites, and this has been partly attributed to SES and factors other than race. Hence, efforts to enhance participation in PCa screenings will be improved considerably by bringing forth health fairs and the vigorous participation of the community.
Incidence and Significance of Prostatic Stones in Men with Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Daniel A. Shoskes, Chun-Te Lee, Donel Murphy, John C. Kefer, Hadley M. Wood

Introduction: Prostatic calcification is common in asymptomatic elderly men however young men with chronic pelvic pain syndrome (CPPS) often have significantly calcified prostates, implicated in symptoms, inflammation and infections. We wished to study the incidence of prostatic calcification in men with CPPS and correlate this with other disease features.

Methods: Between July ’05 and August ’06, 130 new patients at our prostatitis clinic and diagnosed with CPPS. Forty seven had complete evaluations including a transrectal ultrasound (TRUS). Presence of prostatic calcification was correlated with symptoms (NIH chronic prostatitis symptom score (CPSI)), physical exam and cultures. Parametric continuous variables were compared with the student t test, nonparametric variables by the Wilcoxon unpaired test and category variable by the Chi squared test.

Results: Men who underwent TRUS had identical symptoms scores to those who didn’t but were older (46.1 to 41.6 years, p=0.02) and had a longer symptom duration (median 60 months vs 12 months, p=0.0001). Twenty two of the 47 men had significant calcification on TRUS (47%). There was no differences in symptoms between men with and without calcification, including total CPSI (23.7 vs 23.9), all subdomains, and incidence of urinary frequency, ejaculatory pain or erectile dysfunction. Men with calcification had significantly longer symptom duration (median 84 vs 27 months, p=0.05) but similar age (49 vs 45 year p=0.21) and prostate size (21.7 cc both groups). Men with calcification were much less likely to have pelvic floor tenderness (50% vs 85%, p=0.03) but were more likely to have positive prostate fluid cultures for Gram positive bacteria or uropathogens (p=0.05) and had a higher median WBC count in the prostatic fluid (3.5 vs 0 WBC per high power field, p=0.058).

Conclusions: Prostatic calcification is common in men with symptomatic CPPS and is associated with greater prostatic inflammation, bacterial colonization and symptom duration. Pelvic floor spasm is more commonly seen in CPPS patients without calcification and may point to a separate etiology. This may be an important parameter with which to stratify clinical trials, particularly those for antimicrobial or anti-inflammatory therapy.
RNA Yields and RT-PCR Gene Expression Profiles Obtained from Manual-Microdissected, Fixed-Paraffin-Embedded Tissue (FPET) from Prostate Adenocarcinomas

Eric A. Klein, Cristina Magi-Galluzzi, F. Baehner, D. Dutta, T. Maddala, D. Watson, J.W. Cowens

Background: From prostatic adenocarcinomas we examined the RNA extraction yields and gene expression profiles obtained from whole section (WT), enriched tumor tissue (ET) and non tumor tissue (NT) using a RT-PCR assay designed to quantitate the small fragments of RNA present in FPET. Here we report the differential RNA yields and gene expression profiles obtained from ET, NT and WT.

Design: FPET blocks from 10 radical prostatectomy specimens in patients without metastatic or Stage IV disease were used. Three 10 m unstained FPET WT sections or six 10 m unstained FPET manual-microdissected ET and NT sections were separately analyzed. Extracted RNA yields and the expression levels of 380 cancer-related genes and 4 reference genes were measured from WT, ET and NT using RT-PCR in a 384 well format on the ABI 7900HT real time PCR instrument. Expression for each gene was normalized relative to reference genes. Differences in gene expression from ET and WT, ET and NT, and NT and WT were calculated and paired sample t-tests were used to identify differences in gene expression.

Result: The RNA yield per unit surface area in ET compared to NT was approximately three fold higher (average RNA yield of 61.0 ng/mm$^2$ for ET compared to 20.8 ng/mm$^2$ for NT). Differential gene expression was observed among ET, NT, and WT. Eighty genes were more highly expressed in NT compared to ET tissues (unadjusted p-values <0.05) and 45 genes were more highly expressed in ET compared to NT tissues (unadjusted p-values <0.05). With 384 genes being evaluated the expected number of false discoveries was 19. A number of potentially important prostate cancer biomarkers were highly differentially expressed in ET versus NT (e.g., AMACR1 ALCAM higher in ET; IL6 CDKN1A higher in NT).

Conclusion: ET contains higher RNA yields per unit surface area than NT or WT. Differential gene expression is evident among ET, NT, and WT. Optimal quantification of candidate biomarker gene expression in prostate adenocarcinomas will require manual microdissection.
Section 2

Renal Disease / Laparoscopy
Five Year Outcomes Of Laparoscopic Partial Nephrectomy

Inderbir S. Gill, Brian R. Lane

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 upto 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.

Outcomes at 5 years after LPN

<table>
<thead>
<tr>
<th>Oncologic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence (de novo)</td>
<td>1/37 (2.7%)</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>0/37 (0%)</td>
</tr>
<tr>
<td>Death from RCC</td>
<td>0/37 (0%)</td>
</tr>
<tr>
<td>Death of other cause</td>
<td>8/56 (14%)</td>
</tr>
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Renal Functional

| New onset abnormal renal function (any sCr ≥1.5 - 2.0 mg/dl at least 30 days after LPN) | 2/49 (4.1%) |
| New onset chronic renal insufficiency (any sCr > 2.0 mg/dl at least 30 days after LPN) | 1/49 (2.0%) |
| Loss of kidney                      | 1/56 (1.8%) |
Laparoscopic Radical Nephrectomy with Hilar Lymphadenectomy in Patients with Advanced Renal Cell Carcinoma

Jihad H. Kaouk, Inderbir S. Gill, Amr F. Fergany, Matthew N. Simmons

Objectives: To present our series of laparoscopic radical nephrectomy with regional lymphadenectomy in patients with advanced renal cell carcinoma (RCC). In patients with gross lymphadenopathy, lymphadenectomy at the time of radical nephrectomy may improve accuracy of staging, decrease recurrence rates, and improve survival. This procedure has traditionally been conducted using open surgery, but the use of laparoscopic technique is being more frequently applied. This report comprises the largest number of patients undergoing laparoscopic nephrectomy with pre-operatively planned lymphadenectomy to date.

Methods: An IRB-approved prospectively maintained database was reviewed for patients undergoing laparoscopic nephrectomy with lymphadenectomy between July 1997 and September 2006. Of 700 total laparoscopic nephrectomies, 14 patients (13 male, 1 female) underwent laparoscopic lymphadenectomy of lymph nodes detected on pre-operative CT.

Results: Transperitoneal laparoscopic radical nephrectomy was conducted in 12 (86%) patients. Retroperitoneal radical nephrectomy and partial nephrectomy with lymphadenectomy was conducted in 1 patient each (7%). Lymphadenectomy yielded an average of 2.7 lymph nodes. Median tumor size was 9.5 cm (range: 1.5-13), and median lymph node size was 2.3cm (range: 0.8-11). Local tumor stage was ≥T2 in 9 cases (64%), and distant metastasis were present prior to surgery in 7 patients (50%). Hand-assistance was required in 1 case (7%). Elective open conversion was performed on one case due to local extension. Median estimated blood loss was 250ml (range 100-2100). Median length of hospital stay was 2.5 days (range: 2-5). There was a single complication of prolonged ileus that resolved with conservative management on post-operative day 4.

Conclusions: Patients with advanced or metastatic RCC often require cytoreductive nephrectomy for staging and debulking purposes prior to adjunctive therapy. Removal of nodal disease has been shown to improve outcome in these patients. Lymphadenectomy using laparoscopic technique is both feasible and safe. Furthermore decreased morbidity associated with the laparoscopic approach is particularly important in this patient population with advanced and metastatic disease.
Closure of Central Laparoscopic Partial Nephrectomy Defects with a Gelatin Matrix Thrombin Sealant

Inderbir S. Gill, Christopher J. Weight, Brian R. Lane

Objective: To describe a method to decrease warm ischemic time and simplify laparoscopic partial nephrectomy (LPN) in select patients.

Methods: The LPN defect in 27 patients who underwent surgery for a central (n=23) or peripheral (n=4) kidney mass was closed with a gelatin matrix thrombin sealant, without placement of parenchymal stitches or surgicel bolster. Data regarding perioperative and postoperative outcomes were collected in a prospective fashion and then reviewed retrospectively.

Results: Median age was 57 years (range, 30-83) and clinical tumor size was 2.2 cm (0.5-10). Resection of 23 central tumors (85%) required pelvicaliceal suturing of the LPN defect. Median warm ischemia time was 19.5 minutes (5-44), estimated blood loss was 100 ccs (50-1000), and on average, 80% (45-95%) of the kidney was spared. Only two patients required blood transfusions (7.4%), including one who remained stable after receiving 2 units of blood and one who was re-explored to control surgical bleeding. One patient (3.7%) developed a urine leak.

Conclusions: We have demonstrated that in properly selected patients, the defects of central tumors extending to the collecting system can be closed safely with a running pelvicaliceal stitch and FloSeal. The operation is simplified, the transfusion and hemorrhage rates are comparable to those seen with a conventional closure, and warm ischemia time can be significantly reduced.
Comparison of 1800 Laparoscopic and Open Partial Nephrectomies for Single Renal Tumors

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

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.
Complications of Laparoscopic Surgery for Urological Cancer

Inderbir S. Gill, Jihad H. Kaouk, Mihir M. Desai, Jose R. Colombo Jr, Georges-Pascal Haber, J. Eric Jelovsek, Troy Gianduzzo, Monish Aron, Jason Hafron, Robert Stein, Mike Nguyen

Objectives: To determine the incidence of and risk factors for perioperative complications in patients undergoing laparoscopic surgery for urologic malignancy.

Methods: All patients undergoing laparoscopic surgery for urological malignancy at a tertiary care institution from April 1997 to January 2006 were reviewed. Relevant demographic, historical and perioperative data during and within six weeks of surgery were abstracted from the electronic medical record. Various factors were retrospectively analyzed to estimate risk of developing a perioperative complication, such as the Charlson Comorbidity Index, ASA score, European scoring system for laparoscopic urological operations, and surgeon’s experience were also used. Logistic regression was used to identify independent risk factors for perioperative complications.

Results: A total of 1,867 surgeries including radical nephrectomy, partial nephrectomy, radical prostatectomy, nephroureterectomy, and radical cystectomy were performed for cancer. Perioperative complications occurred in 13.7% (95%CI 12.2 to 15.4) including 4.8% (95%CI 3.9 to 5.9) intraoperatively and 8.9% (95%CI 7.6 to 10.2) postoperatively. Intraoperative (3.6%) and postoperative hemorrhage (2.7%) accounted for over half of all perioperative complications. All-cause perioperative mortality occurred in 8 patients (0.4%). Radical cystectomy (adj.OR 4.9, 95%CI 1.3 to 8.0; p<0.001), partial nephrectomy (adj. OR 2.4, 95%CI 1.5 to 3.8; p<0.001), length of surgery >4 hours (adj.OR 2.5, 95%CI 1.7 to 3.8; p<0.001), and serum creatinine >1.5 mg/dL (adj.OR 2.1, 95%CI 1.0 to 4.3; p=0.04) were independent risk factors for perioperative complications.

Conclusion: Laparoscopic surgery for urological malignancy is safe, with an acceptable perioperative complication rate. Efforts should be made to minimize the risk of perioperative hemorrhage.
Laparoscopic Suturing Using Articulated Needle Drivers and 3-D Vision

Inderbir S. Gill, Jihad H. Kaouk, Georges-Pascal Haber, Yi-Chia Lin, Bruno M.R. Santos, Troy Gianduzzo, Jose R. Colombo Jr, Monish Aron, Kamoi Kazumi, Robert Stein, Jason Hafron, Mike M. Nguyen, Burak Turna, Rodrigo Frota

Introduction and Objective: Limited range of freedom using straight conventional needle drivers (CND) and two-dimensional (2-D) vision are major obstacles for laparoscopic free-hand suturing. A novel articulated needle driver (AND) (Radius Surgical System, Tuebingen Scientific, Germany) with 6 degrees of freedom and a three-dimensional (3-D) vision generator (Viking Systems, San Diego, CA) were evaluated and compared in this study.

Method: Following 20 min of AND practice with and without 3-D vision, 2 specific tasks were performed in a pelvic trainer by 15 urologists divided into 3 groups (expert (n=5), intermediate (n=5) and novice (n=5)) according to their laparoscopic experience. The first task included 1 sagittal, 1 coronal and 1 oblique running suture with knot tying in the horizontal plane. The second test consisted of a running urethro-vesical anastomosis in a rubber model. Both tasks were then repeated with the CND. Total time for each line of suturing, time for knot tying, time to accomplish urethro-vesical anastomosis, precision and accuracy were compared.

Results:

<table>
<thead>
<tr>
<th></th>
<th>CND</th>
<th>AND</th>
<th>AND + 3-D vision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expert</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knot tying (sec)</td>
<td>42.5 ± 9.7</td>
<td>120.5 ± 20.8*</td>
<td>110.4 ± 21.8*</td>
</tr>
<tr>
<td>Suturing time (min)</td>
<td>7.4 ± 3.8</td>
<td>9.0 ± 3.6</td>
<td>8.1 ± 5.2</td>
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<tr>
<td>Anastomosis (min)</td>
<td>25.6 ± 10.8</td>
<td>40.1 ± 16.8*</td>
<td>36.5 ± 12.5*</td>
</tr>
<tr>
<td>Precision (%)</td>
<td>81.3 ± 7.6</td>
<td>88.4 ± 6.2*</td>
<td>86.5 ± 7.5*</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>69.7 ± 5.3</td>
<td>85.8 ± 6.3*</td>
<td>86.0 ± 5.4*</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knot tying (sec)</td>
<td>59.5 ± 10.8</td>
<td>113 ± 22.6*</td>
<td>76.5 ± 24.5*†</td>
</tr>
<tr>
<td>Suturing time (min)</td>
<td>9.7 ± 4.1</td>
<td>10.0 ± 4.0</td>
<td>7.5 ± 3.6*†</td>
</tr>
<tr>
<td>Anastomosis (min)</td>
<td>23.8 ± 14.5</td>
<td>32.5 ± 16.8*</td>
<td>28.5 ± 10.5</td>
</tr>
<tr>
<td>Precision (%)</td>
<td>70.9 ± 16.3</td>
<td>88.6 ± 8.8*</td>
<td>89.5 ± 10.6*</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>59.4 ± 12.6</td>
<td>81.3 ± 16.5*</td>
<td>84.6 ± 17.5*</td>
</tr>
<tr>
<td><strong>Novice</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knot tying (sec)</td>
<td>117.6 ± 18.5</td>
<td>173.0 ± 34.5*</td>
<td>158.8 ± 45.5*</td>
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<tr>
<td>Suturing time (min)</td>
<td>12.1 ± 6.5</td>
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<td>14.8 ± 4.6</td>
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<tr>
<td>Anastomosis (min)</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Precision (%)</td>
<td>55.6 ± 16.8</td>
<td>85.6 ± 9.5*</td>
<td>88.6 ± 12.8*</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>54.3 ± 7.6</td>
<td>77.3 ± 19.5*</td>
<td>78.6 ± 10.6*</td>
</tr>
</tbody>
</table>
All data are presented as Mean ± Standard deviation
*: $p<0.05$, comparing to CND; †: $p<0.05$, comparing to AND
na: data not available due to incomplete task

**Conclusion:** Precision and accuracy was significantly improved in all groups with AND and 3-D vision compared to CND. 3-D vision especially reduced the time to accomplish the tasks in intermediate group. Combination of AND and 3-D vision showed benefits in intermediate and novice groups.
Preliminary Laboratory Experience with Retrograde Intrarenal Surgery Using a Novel Robotic Platform

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

**Introduction and Objective:** Maintaining the working tip of conventional flexible ureteroscopes in desired intrarenal calices relies upon a mechanical lever with suboptimal control and stability. Recently, a new prototype catheter and pull-wire based flexible robotic system has been developed (Hansen Medical, Mountain View, CA), which operates on the master-slave principle. We report our laboratory evaluation of this system for retrograde intrarenal surgery.

**Methods:** The system consists of a flexible scope with a 14F outer sheath, both of which are mounted on a robotic arm, and independently controlled by the surgeon seated at a remote workstation. Using this robotic system we performed flexible ureterorenoscopy in five acute female pigs (27-51 kg, mean 43 kg). The specific parameters measured were: a) need for ureteral dilation, b) ability and time to access each calyx, c) reproducibility of access into each calyx evaluated by being able to access each calyx 3 times, d) ability to fragment intrarenal calculi with a 320 micron holmium laser fiber in 4 kidneys, e) stability of the system evaluated by being able to park the effector tip at a desired location for a 5-minute period, f) reproducibility of the auto-retract mechanism evaluated by being able to retract to the original position at the touch of a button, and f) evidence of tissue trauma and fluid extravasation on autopsy.

**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 the 5th animal (weight 32 kg) could not be entered due to the small ostial size although a 3F nitinol 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 was 8/10 on a VAS. All calculi could be fragmented with a laser fiber to a size smaller than the apparent diameter of the fiber. There was one ureteral perforation (10%) in the first animal due to a technical error. Autopsy revealed fluid extravasation in the retroperitoneum.

**Conclusions:** With refinements in scope design, this could be a promising robotic platform for flexible endoluminal surgery with enhanced stability and reproducibility, while distancing the surgeon from the radiation source.
Preliminary Experience with the Niris™ Optical Coherence Tomography (OCT) System During Laparoscopic and Robotic Prostatectomy

Inderbir S. Gill, Jihad H. Kaouk, Monish Aron, Nicholas J. Hegarty, Jose R. Colombo Jr, Georges-Pascal Haber, Benjamin I. Chung, Margarita Kareta, Nancy Tresser

Introduction: To evaluate the feasibility of high resolution optical coherence tomography (OCT) in the identification of neurovascular bundles (NVB) during laparoscopic and robotic radical prostatectomy (LRP).

Methods: Between 11/05 and 3/06, 24 patients undergoing transperitoneal laparoscopic or robotic radical prostatectomy were enrolled in this study. Once the bladder was taken down and the prostate mobilized, the Niris™ imaging system was deployed. In each patient, in-vivo images were obtained to determine the image characteristics of NVB, adipose tissue, prostate capsule, and endopelvic fascia. The NVB was imaged again in-vivo, after the prostate was excised. Ex-vivo images were obtained from the prostate surface to look for presence or absence of NVB and correlate with the surgeon’s assessment of the adequacy of nerve sparing.

Results: From 24 patients, we obtained more than 300 OCT images of tissue structures including endopelvic fascia, prostate capsule, NVB, fat, lateral pedicles, and lymphatics. These images were found to independently correlate with the surgeon’s impression of the tissue being imaged. Preliminary comparison with parallel histology was performed in 4 patients that suggested that OCT could help to identify the NVB and prostate capsule during LRP.

Conclusions: We report our preliminary experience with the Niris™ OCT system for imaging of the NVB during LRP. OCT was able to image the NVB in all patients. This could potentially enhance surgical precision during nerve sparing and positively impact potency rates after radical prostatectomy. Further research will be needed, including parallel histology and follow up, to validate the findings of OCT imaging.
Complications of Contemporary Laparoscopic Partial Nephrectomy: Use of a Standardized Reporting System

Inderbir S. Gill, Matthew N. Simmons

**Purpose:** To report complications of laparoscopic partial nephrectomy (LPN) in a contemporary cohort of 200 patients using a standardized complication reporting system.

**Materials and Methods:** Two hundred consecutive patients undergoing LPN between September 2003 and November 2005 were reviewed. Mean tumor size was 3cm, and mean parenchymal invasion depth was 1.8cm. There were 97 central tumors (48.5%) and 9 tumors in solitary kidneys (4.5%). Complication severity for each patient was graded using a 5-tiered scale based on NCI-CTC reporting criteria. Statistical analysis was employed to assess risk factors associated with complication events.

**Results:** Thirty-five patients (17.5%) had complications. The overall complication rate was 19%. Of the complications 29% were grade I, 42% were grade II, 26% were grade III, and 2.6% were grade IV. There were no grade V complications. Median blood loss was 234ml. Hemorrhagic and urine leak complications occurred in 9 (4.5%) and 4 (2%) patients, respectively. Conversion to open partial and laparoscopic radical nephrectomy was done electively in 2 (1%) and 1 (0.5%) patients, respectively. Compared to previously reported data for the initial 200 patients in our LPN cohort, this contemporary group of 200 patients had statistically significant decreases in overall (p=0.02), urologic (p=0.04), and hemorrhagic (p=0.04) complication rates despite an increase in tumor complexity.

**Conclusions:** Increased experience with advanced laparoscopic techniques has allowed for a significantly reduced complication rate following contemporary LPN, which now appears comparable to open partial nephrectomy. A standardized complication reporting system is advocated.
Development of an In-Vivo Kidney and Prostate Chronic Tumor-Mimic Model

Inderbir S. Gill, Georges-Pascal Haber, Osamu Ukimura, Jihad H. Kaouk, Jose R. Colombo Jr, Monish Aron, Erick Remer, Charles O’Malley Jr.

**Introduction:** Chronic tumor mimic models are vital for research and training on emerging ablative-probe therapy. Herein we report a novel chronic renal and prostate in-vivo tumor-mimic model, hyperechoic on ultrasound and hyperdense on CT scan.

**Methods:** Our formulation is a significant variation of previously described agarose-based tissue mimic model: 6g of agarose, 12 g of natural fiber, 3 g of iron sand, 14 ml of glycerol, 3cc of contrast media (76%), 2 cc methylene blue (USP 1%) and 40 cc of sterile water. The mixture is heated to just under its boiling point in a microwave oven and then cooled to 60°C before being injected slowly through a 20G needle. This mixture has been injected percutaneously in porcine kidneys and transrectal in dog prostates.

**Results:** The mixture return to a gel consistency at 40°C, the created lesions are ovale, intraparenchymal and/or subcapsular. When injecting 1cc of the mixture the lesion created is 1.5*1 cm at day 0, 2.7*1cm at day 2, 2.5*1cm at day 15 and day 30. The lesion is hyperdense on CT scan and chronically hyperechoic on ultrasound. The cost of the all components is less than 250$ and allow to make more than 500 lesions.

**Conclusion:** This new model is very attractive. It allows the creation of large tumours, hyperdense on CT scan and chronically hyperechoic on ultrasound.
Virtual “V”-poster: Novel Concept in Scientific Conferencing

Inderbir S. Gill, Georges-Pascal Haber, Yi-Chia Lin, Mihir M. Desai, Ralph Clayman

Introduction: We present a novel multimedia enhanced method of poster presentation during scientific meetings and assess its impact on the scientific and logistic aspect. To our knowledge this virtual “V”-poster format is the first ever in scientific conferences.

Methods: We utilized the virtual “V”-poster format for the best 300 poster presentations at the recent World Congress of Endourology (WCE 2006) in Cleveland. Fifty, 42” high definition flat LCD display monitors were mounted on individual upraised trusses along the parameter of 3 walls of a conference ballroom. Each LCD screen was connected individually to a laptop, and all screens were networked to each other. Capability was created to project any “V”-poster image on 2 large (12*10 feet) presentation screens erected along the fourth wall of the ballroom. Each poster was created according to a predetermined template and picture-in-picture inclusion of pertinent videos/animation was strongly encouraged. All “V”-posters were uploaded on a dedicated FTP server at least 2 weeks prior to the Congress. Each submitted “V”-poster was reformatted, backed-up and reversed in Cleveland to ensure standardized fluidness of presentation. An email survey was sent to all attendees to assess its impact.

Results: Of the 300 “V”-posters accepted, 285 (95%) were submitted online as requested. These 285 “V”-posters were presented in 12 separate moderated sessions of 2 hours each, over a period of 3-days. Each “V”-poster consisted of a 2 layer presentation that was automatically cycled every 2 to 4 minutes in a continuous loop. All “V”-posters were displayed on the individual LCD screen for the full 2 hours and projected on the large screens during the 3 minutes presentation. All individual LCD and giant screen presentations were executed without any technical/electronic malfunction and all 12 scientific sessions were completed on time. Survey response was received from 524 attendees. The presenters felt they spent less time, same or more time to prepare a “V”-poster compared to a standard poster in 57.5%, 18.4% and 24.1%, instances respectively. On the survey, 94.1% of the attendees and 100% moderators believe that “V”-poster attracted more people. 94.2% of the moderators felt that it is more efficient to moderator a “V”-poster session. Overall, 97% of responders opined that “V”-poster provides additional information that enhances the scientific presentation, and 85% would like to see all future poster presented in a “V”-poster format.

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<table>
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<tr>
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<th>Virtual-Poster*</th>
<th>Printed-Poster*</th>
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<td>Number of session attended per attendees(n)</td>
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<td>3.5 (1-12)</td>
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<td>Number of Posters viewed (n)</td>
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<tr>
<td>Time spent in each session (min)</td>
<td>38.5 (5-120)</td>
<td>12.4 (5-120)</td>
<td>&lt;0.0005</td>
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</table>

*Rate of Poster session on a scale of 0 to 10 (0 = fair – 10 = excellent)*

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<td>Attendees (n=423)</td>
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<tr>
<td>Presenters (n=85)</td>
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<tr>
<td>Moderators (n=16)</td>
<td>9.82</td>
<td>3.29</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

*All data presented as mean (range)

**Conclusion:** Our survey indicated that our novel Virtual “V”-posters presentation were strongly attended and enhance scientific communication. It is likely that this electronic formatted poster will be the method of choice of poster presentation in future.
Section 3

Female
Urology/Voiding Dysfunction
Post Operative Outcomes after Urethral Diverticulum Repair

Sandip P. Vasavada, Howard B. Goldman, Firouz Daneshgari, Raymond R. Rackley, Una J. Lee

Introduction and Objective: The most recognized complications after urethral diverticulum (UD) repair are urethrovaginal fistula, urethral diverticula recurrence, and urinary incontinence. Our goal was to determine the rate of these outcomes after UD repair.

Methods: A retrospective review was conducted of female patients who had undergone UD repair without a simultaneous anti-incontinence procedure between Jan 2000 and July 2005. While 50 of the 66 patients identified met criteria for this study, 16 were excluded because 14 had undergone a simultaneous anti-incontinence procedure, and 2 had undergone simultaneous urethrolysis. To determine the rate of urethrovaginal fistula, diverticula recurrence, and preoperative stress urinary incontinence (SUI) status, we conducted a retrospective chart review. To determine the post-op rate of urinary complaints including SUI, we examined the responses to domain 3 of the urogenital distress inventory-short form (UDI-6), as well as the rate of subsequent procedures for the treatment of SUI.

Results: Of the 50 patients who underwent UD repair, the median age was 44 (range 24 to 73). 34 (68%) were Caucasian and 16 (32%) were African-American. 29 (58%) had a simple diverticulum, 19 (38%) had a saddlebag or “horseshoe” diverticulum, and 2 (4%) patients had a circumferential diverticulum. Postoperatively, 6 (12%) had recurrent urethral diverticula and none had an urethrovaginal fistula.

Preoperatively, 13 patients reported SUI, 18 patients reported no SUI and 19 patients were unknown. Median follow up was 23 months (range 3 to 67 months). Of the 18 patients who did not have SUI preop, none had a postoperative sling procedure and 15 had postop UDI-6 results as follows: 10 reported no SUI, 3 reported “a little bit,” 2 reported “moderate,” and 0 reported being “greatly” bothered by SUI. Of the 13 patients with known preop SUI, 3 patients had a sling procedure post operatively, and 8 had completed UDI-6 as follows: 3 had no SUI, 2 had “a little bit,” 2 had “moderate,” and 1 reported being “greatly” bothered. There was a trend toward more significant SUI in patients with more proximally located and more extensive or saddlebag diverticula.

Conclusions: UD repair has a low incidence of complications. Patients without preoperative SUI have a low rate of de novo SUI postoperatively. Patients with known preop SUI have a higher rate of postop SUI and more frequently require a secondary sling procedure. Patients undergoing urethral diverticulectomy who have preoperative SUI should be considered for a concomitant sling.
Dorsal Genital Nerve Stimulation for the Treatment of Refractory Overactive Bladder Symptoms

Howard B. Goldman, Jeffrey M. Mangel, Cindy L. Amundsen

Introduction and Objectives: The dorsal genital nerve, a component of the pudendal nerve, carries afferent sensory information to the sacral spinal roots. Previous studies indicate that electrical stimulation of this nerve can abolish hyper-reflexive bladder contractions in patients with an overactive bladder. The purpose of this study was to evaluate the acute effects of electrical stimulation on cystometric parameters and the pudendal anal (PA) reflex and to determine if electrodes could be properly placed and be effective and tolerated by subjects during a 1-week home use testing period.

Methods: This was a prospective, multicenter study. The primary diagnosis was urge incontinence in the recruited subjects. Baseline data including demographics, a 3 day bladder diary, and a 24 hour pad test were obtained. Subjects underwent percutaneous placement of a coiled fine-wire electrode using local anesthetic in the clinic procedure room. Cystometry was conducted with and without application of electrical stimulation and pudendal anal reflex activity was observed. A 7 day testing period with the electrode connected to an external pulse generator was performed as well as a 3 day post treatment period. Bladder diaries, 24 hr pad tests and adverse events queries were obtained during these periods.

Results: 21 females were enrolled with an average age of 52.7 years. Average duration of incontinence was 6 years. Electrode placement was well tolerated requiring 5 to 10 minutes to achieve correct placement. There were no relationships between the effect of stimulation on cystometry and the clinical results during the home use testing period. In addition, the PA reflex was not a reliable indicator for placement. Pad weight was reduced by 50% or greater in 13 of 17 subjects (77%), 47% of subjects reported 50% or greater reduction in leaks and 81% of subjects who reported severe urgency at baseline experienced a 50% or greater improvement. Eight patients were completely dry at the end of the week of stimulation.

Conclusions: This study confirmed that electrodes can be placed near the dorsal genital nerves using a minimally invasive pre-pubic approach which is well tolerated by the subject. Cystometry and PA reflex information did not predict response during the testing period. Results from home use testing suggest that dorsal genital nerve stimulation may reduce overactive bladder symptoms.
Short-Term Complications of the Prolift Transvaginal Mesh Procedure for Correction of Pelvic Organ Prolapse

Howard B. Goldman, Courtenay Moore, Sarah McAchran, Humphrey Atiemo

**Introduction and Objectives:** Since 1996, prosthetic meshes have become increasingly popular for the transvaginal surgical cure of pelvic organ prolapse. In 2004, the TVM group from France presented their technique for pelvic floor reconstruction using the Gynecare Prolift pre-cut mesh and kit. The goal of the study was to analyze the short-term complications of this procedure, a minimally invasive alternative for treating patients with pelvic organ prolapse.

**Methods:** We present a retrospective analysis of patients who underwent a total vaginal mesh procedure by a single surgeon to repair pelvic organ prolapse between June, 2005 and August, 2006. Office and hospital charts were reviewed and short-term complications were noted. Complications were then divided into two categories: major and minor. Major complications were those requiring hospital re-admission or surgical intervention. Minor complications were those with minimal patient morbidity.

**Results:** A total of 40 consecutive vaginal mesh procedures were performed using the Gynecare Prolift kit (Ethicon, Sommerville, NJ, USA). Patient ages ranged from 35 to 86 years, with a mean age of 66.8 years. Two patients had concomitant vaginal hysterectomies and one had a concomitant parathyroidectomy. Twenty-three had concomitant tension-free vaginal tape procedures. Thirty-five out of 40 (87.5%) were discharged to home on post-operative day number 1. There were two (5%) major complications: one lower extremity DVT requiring anticoagulation and one delayed bleed requiring transfusion and angio-embolization. The patient with the delayed bleed had a concomitant transvaginal hysterectomy and presented on post-operative day #11 with bleeding from the vaginal cuff. There were 10 (25%) minor complications: 5 symptomatic urinary tract infections, 1 episode of transient urinary retention, 2 intraoperative bladder lacerations, and 2 vaginal mesh extrusions. The urinary tract infections were all treated successfully with oral antibiotics. The bladder lacerations were noted intra-operatively, repaired primarily, and managed successfully with Foley catheter decompression for 10 days. Healing was confirmed with a cystogram at the time of catheter removal. There were only 2 (5%) short-term complications related to the mesh itself, both vaginal extrusions. Both were treated non-operatively. One healed with the addition of topical estrogen cream. The second patient, whose mesh extruded at the vaginal cuff, was the same patient whose post-operative course was complicated by delayed bleeding. This was treated by simple excision in the office.

continued
Conclusions: The Prolift total vaginal mesh procedure is a reportedly highly effective and minimally invasive method for treating pelvic organ prolapse. The major and minor complication rates are comparable to those reported for laparoscopic and abdominal mesh procedures for pelvic organ prolapse, with the notable lack of any bowel-related complications such as ileus or small bowel obstruction. The majority of patients can be discharged from the hospital on post-operative day one.
Robotic Abdominal Sacrocolpopexy Repair of Advanced Female Pelvic Organ Prolapse: Utilizing Pop-Q Based Staging and Outcomes

Jihad H. Kaouk, Firouz Daneshgari, John C. Kefer

Introduction: Surgical repair of the pelvic organ prolapse (POP) has historically been performed through abdominal or vaginal approaches, but abdominal sacrocolpopexy (ASC) is the gold standard operation for advanced POP. Robotic-assisted surgery allows a minimally-invasive technique when performing ASC. Robotic ASC combines the efficacy of open sacrocolpopexy with advantages of minimally invasive surgery for management of women with advanced POP. Here, we assess management of advanced POP with robotic-assisted abdominal sacrocolpopexy (RASC) and evaluate outcomes using the pelvic organ prolapse quantification (POPQ) scale.

Methods: Women with symptomatic stages III and IV FPOP were evaluated at our institution. After complete clinical assessment, including POPQ-based physical examination and urodynamic studies, the patients underwent RASC with or without an anti-incontinence surgery in the presence (sacrouteropexy) or absence of uterus (sacrocolpopexy). The follow up exam at 3 months included POP-Q based examination and patient perception of improved quality of life questionnaire (QOLQ).

Results: Twelve women were consented for RASC; nine women underwent successful RASC, one patient required conversion to laparoscopic ASC, one to open ASC, and one to transvaginal anterior colporrhaphy due to extensive bowel adhesions involving the bladder. Mean patient age was 64 (50-79). Mean preoperative POP-Q stage was 3.1 (3-4). Mean preoperative POP-Q values were Aa: +0.9, Ba: +2, C: -1.0, Ap: -1.0, and Bp: -1.0. Mean postoperative values were Aa: -2.7, Ba: -4.7, C: -8.28, Ap: -2.29, and Bp: -4.14. Mean postoperative POP-Q stage was 0. Mean intraoperative EBL was 81cc (50-150). Mean hospital stay was 2.4 days (1-7 d). Five patients underwent concurrent placement of a TOT sling and one patient underwent concurrent Burch culposuspension for occult SUI. The patient perception of QOLQ improved significantly.

Conclusions: Our results demonstrate that RASC is safe and efficacious, and its outcomes compare favorably to the reported results for open or laparoscopic abdominal sacrocolpopexy.
Introduction: Sacral neuromodulation (SNM) has been shown to be an effective treatment for voiding dysfunction (VD). Fecal incontinence may co-exist in 40% of VD cases and represents another aspect of pelvic floor dysfunction with few effective therapies outside of diverting colostomy. This pilot study aims to identify the efficacy of SNM in the treatment of fecal incontinence in patients presenting with concomitant VD.

Methods: A cohort of 281 female patients with VD undergoing SNM therapy was identified from a single center, multi-physician database. Females with VD +/- fecal incontinence were identified as cases and controls respectively. Relative risk for Stage I SNM success and Stage II explantation in the fecal incontinence group was calculated using multivariate analysis for a retrospective cohort study. Patient Global Assessment Scores for severity and improvement (PGII, PGIS) of symptoms were obtained.

Results: Twenty-six individuals with voiding dysfunction and fecal incontinence were identified. A statistical difference in parity was identified between the two cohorts (Table 1a). Stage I success rates and Stage II explant rates for the fecal incontinence groups were 88% and 9.5% respectively (Table 1b). When compared to controls, no statistical difference was identified. Using a multivariate model, a history of fecal incontinence was not a predictive factor or SNM explantation. At a 50% percent survey response rate, eight out of 12 patients (66%) reported and improvement in fecal incontinence symptoms. Seven of 12 patients (58%) reported either mild to normal status in terms of fecal incontinence severity. One patient with failure of SNM proceeded to have an end colostomy.

Conclusion: Similar efficacy is achieved with SNM in VD patients with concomitant fecal incontinence as compared with controls. Significant patient satisfaction indicates that SNM appears to provide another therapeutic option for patients with complex pelvic floor dysfunction. Replication of this data and prospective trials comparing SNM in the setting of other pelvic health conditions that include fecal incontinence will better determine the role of SNM in the treatment of this disorder.
### Table 1a. Demographics for all patients split up by fecal incontinence status (N=281)

<table>
<thead>
<tr>
<th></th>
<th>Fecal incontinence</th>
<th>No fecal incontinence</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=24)</td>
<td>(N=257)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Mean (s.e.)</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Median (range) / N (proportion)</td>
<td>Median (range) / Proportion</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>24</td>
<td>56 (2.6)</td>
<td>257</td>
</tr>
<tr>
<td></td>
<td>55 (41, 83)</td>
<td>50 (18, 87)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>19</td>
<td>3.5 (0.7)</td>
<td>196</td>
</tr>
<tr>
<td></td>
<td>3.0 (0, 11)</td>
<td>2.0 (0, 10)</td>
<td></td>
</tr>
<tr>
<td>Parity greater than 2</td>
<td>19</td>
<td>11/19 = 58%</td>
<td>196</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>23</td>
<td>15/23 = 65%</td>
<td>250</td>
</tr>
<tr>
<td>Other pelvic surgery</td>
<td>24</td>
<td>8/24 = 33%</td>
<td>257</td>
</tr>
<tr>
<td>Overactive bladder</td>
<td>24</td>
<td>22/24 = 91.7%</td>
<td>257</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>24</td>
<td>3/24 = 13%</td>
<td>255</td>
</tr>
<tr>
<td>Retention</td>
<td>24</td>
<td>2/24 = 8%</td>
<td>257</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24</td>
<td>5/24 = 21%</td>
<td>257</td>
</tr>
</tbody>
</table>

### Table 1b. Outcomes split up by fecal incontinence status (N=281)

<table>
<thead>
<tr>
<th></th>
<th>Fecal incontinence</th>
<th>No fecal incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=24)</td>
<td>(N=257)</td>
</tr>
<tr>
<td>Stage II implantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Stage I success)</td>
<td>21</td>
<td>21/24 = 88%</td>
</tr>
<tr>
<td>Stage II interstim explanted</td>
<td>21</td>
<td>2/21 = 9.5%</td>
</tr>
</tbody>
</table>
Simple Sling Incision for the Treatment of Latrogenic Urethral Obstruction

Howard B. Goldman, Courtenay K. Moore

Introduction: Bladder outlet obstruction (BOO) is reported to occur in 5-20% of women after anti-incontinence surgery. BOO after pubovaginal slings results excessive ventral tension on the urethra. In the past urethral obstruction from pubovaginal slings was treated with urethrolysis. However, urethrolysis is not without morbidity, including significant bleeding and urethral injury. Sling incision offers an effective, simple and safe alternative for women with iatrogenic bladder outlet obstruction after a pubovaginal sling.

Methods: Two patients, one with a synthetic mid-urethral sling, and one with a biologics bladder neck sling, underwent simple sling incision for the treatment of iatrogenic urethral obstruction. The patient is placed in dorsal lithotomy position with steep Trendelenburg. A foley catheter is placed to drain the bladder. The anterior vaginal wall is infiltrated with a mixture of lidocaine and epinephrine. For synthetic mid-urethral slings the incision in the anterior vaginal wall incision is made 2cm from the urethra meatus. In a biologic bladder neck sling the incision is made more proximal overlying the bladder neck. In both cases the sling is identified using careful sharp and blunt dissection. A right angel clamp is then used to create a plane between the sling and urethra and gently spread. The sling is then incised. The vaginal wall is then closed.

Results: Simple sling incision is an effective and less morbid treatment for iatrogenic urethral obstruction than urethrolysis. 70-90% of women undergoing simple sling incision for the treatment of iatrogenic urethral obstruction due to a sling will have significant improvement in their obstructive voiding symptoms. Recurrent stress urinary incontinence is seen in approximately 20% of women after sling incision.

Conclusion: Simple sling incision is an effective, simple, and safe treatment for women with iatrogenic urethral obstruction after placement of a pubovaginal sling and should be used as a first-line treatment.
Urinary Incontinence in a Population Based Study of Women With and Without Breast Cancer

Firouz Daneshgari, Peter B. Imrey, Betsy Risendal, Andrea Dwyer, Matthew D. Barber, Tim Byers

**Introduction:** Most US epidemiological studies of urinary incontinence (UI) have used convenience samples of non-Hispanic White women. UI has seen little study in Hispanic White women and breast cancer survivors, two groups with substantially different distributions of UI risk factors (e.g., adiposity, parity) than such convenience samples. Nor have breast cancer hormonal and chemotherapy treatments been examined for possible effects on FPFD.

**Objective:** The aims of this report were to examine, in a population-based sample of Colorado breast cancer cases and controls, whether UI prevalence differs between Hispanic and non-Hispanic White women, and/or is associated with prior breast cancer and its chemotherapeutic and adjuvant hormone therapies.

**Methods:** UI prevalence, defined as Sandvik severity score ≥3, was studied in relation to ethnicity, breast cancer, and adjuvant therapies, among 379 breast cancer cases and 362 controls, including 250 Hispanic and 491 non-Hispanic White women.

**Results:** Hispanic women reported more stress UI (OR=1.7, p=.005) and mixed UI (OR=1.8, p=.005) than non-Hispanic Whites. These elevations were greatly attenuated by adjustment for known UI risk factors. Cancer cases did not substantially differ from controls in reported UI prevalence. After adjustment for UI risk factors, stress UI prevalence was significantly elevated among prior chemotherapy recipients relative to breast cancer and population controls separately and in a pooled comparison using both control groups (OR=1.7, two sided P=.02 for the latter). Among prior recipients of hormonal therapy, prevalence of any UI and stress UI were each significantly elevated in the pooled comparison (OR=1.6 for both, P=.03 and .02, respectively). In models incorporating both therapies, chemotherapy retained significance (OR=1.7, p=.05), while chemo and hormonal therapies did not significantly modify each others’ effects.

**Conclusions:** UI prevalence was elevated in these Hispanic women, but this was largely explainable by their levels of parity, adiposity, and diabetes. UI prevalence was similar among breast cancer cases and controls. However, after adjustment for UI risk factors, women treated with breast cancer chemotherapy and/or hormonal therapy later reported stress UI more commonly than women who did not receive these therapies.
Section 4

Infertility
Introduction and Objective: Sperm chromatin integrity is important for mammalian fertilization. The sperm chromatin structure assay (SCSA) is one of the most reported methods for the assessment of fragmented sperm DNA. Toluidine blue (TB) assay is an easy alternate test for sperm chromatin assessment. The objective of our study was to evaluate the Toluidine blue test and SCSA for the assessment of sperm chromatin damage in proven & unproven donors.

Methods: Semen samples were collected from 10 unproven donors and 8 proven fertile donors who had initiated a successful pregnancy in the last 2 years. Following liquefaction, seminal ejaculates were evaluated for chromatin abnormalities using Toluidine blue test. In this assay, spermatozoa with abnormal chromatin conformation/DNA integrity) stain dark violet (DV) and those with normal chromatin conformation stain light blue (LB). An aliquot was also examined by the SCSA assay for percentage of spermatozoa with immature nuclear development (high DNA stainability index, %HDS).

Results: Using the Toluidine blue test, proven fertile males showed lower but non significant incidence of spermatozoa with abnormal DNA compared to unproven fertile men (mean ± SE 20.9 ± 4.4 vs. 27.2 ± 4.9; P = 0.09). Similarly, the proven fertile men showed higher incidence of spermatozoa with normal DNA compared to the unproven semen samples (65.9 ± 5.2 vs. 52.7 ± 6.3; P = 0.4). Proven fertile males had lower but non significant %HDS compared with unproven males (5.1 ± 1.9 vs. 7.2 ± 2.7). In unproven fertile males %HDS showed a significant positive correlation with the number of DV stained spermatozoa (r = 0.85, P = 0.002). %HDS was also negatively correlated with the number of LB sperm (r = -0.79, P = 0.002).

Conclusions: Testing of sperm immaturity is important in fertility potential evaluation. While SCSA and Toluidine blue are equally effective as a marker in fertile men, Toluidine blue can be used to identify nuclear immaturity as well as abnormal chromatin in unproven donors.
A New Test to Assess Total Genomic Damage in Sperm

Ashok Agarwal, Reda Z. Mahfouz, Mona A Elsahfei, Samia H Kandil, Sobhy E. Hassab El-Nabi, Rakesh Sharma

Introduction and Objectives: Many tests have been developed to evaluate sperm DNA damage in clinical practice. Our objective was to apply the total genomic damage (TGD) test to detect characteristics of sperm chromatin damage in different semenograms.

Methods: Routine semen analysis was done on 20 men and samples were divided based on the spermiograms. Sperm pellets were prepared for TGD. DNA extraction and detection of apoptosis was tested according to “salting out extraction method”. Briefly, sperm pellets (3 x 10^4 cells) were treated by Lysing Buffer. Electrophoresis was performed for 2 hours at 50 volt. Gel photos were analyzed qualitatively & quantitatively by Gel Pro Analyzer software version 3.1 Media Cybernetics, USA. Both the software and reagents/instruments are easily available and the test can be performed even in a low technology laboratory setting.

Results: Intact and damaged DNA for different semenograms is shown in the Table. Intact DNA was seen in the semen samples of normozoospermic men; however, they were absent in azoospermic samples. Oligoasthenoteratozoospermic samples showed low intact DNA bands with increasing DNA damage (apoptotic bands at multipliers of 200bp). Necrozoospermic samples (low vitality) showed very low intact DNA bands and increasing DNA damage.

Conclusion: Compared to other tests that involve expensive instrumentation and software, assessment of Total Genomic Damage in sperm is simple & cost effective. The results are easy to interpret and related to sperm concentration and morphology. More studies are needed to establish its clinical value.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Intact DNA^a</th>
<th>Damaged DNA^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>500-1000bp</td>
</tr>
<tr>
<td>Normozoospermic (n = 7)</td>
<td>44.9/111.9</td>
<td>15.19/17.46</td>
</tr>
<tr>
<td>Azoospermic (n = 3)</td>
<td>12.5/24.93</td>
<td>5.04 / 11.64</td>
</tr>
<tr>
<td>OAT (n = 7)</td>
<td>17.67 / 66.92</td>
<td>7.58 / 38.12</td>
</tr>
<tr>
<td>Necrozoospermic (n = 3)</td>
<td>16.2 / 76.93</td>
<td>0.39 / 3.8</td>
</tr>
</tbody>
</table>

Results for all groups are expressed according to DNA fragment characteristics; ^aDNA quantity in band (ng)/max Optical density of the band; OAT = Oligoasthenoteratozoospermic.
Association of Fertility Potential with Total Genome Damage in Spermatozoa

Ashok Agarwal, Reda Z. Mahfouz, Mona A. Elsahfei, Samia H. Kandil, Sobhy E. Hassab El-Nabi, Rakesh Sharma

**Introduction and Objectives:** Evaluation of sperm DNA damage is crucial in clinical practice as it impacts on reproductive outcomes. Detection of Total genome damage (DNA fragments) is based on a method introduced by Aljanabi and Martinez 1997. Our objective was to examine sperm total genome damage in proven fertile & infertile men.

**Methods:** Routine semen analysis was done for proven fertile men (n = 7) and infertile men (n = 13). Briefly, sperm pellets (3 X 10^4 cells) were treated for salt-ing out DNA extraction & purification. Gel electrophoresis was performed for 2 hours at 50 volt. Gel photos were analyzed by Gel Pro Analyzer software version 3.1 Media Cybernetics, USA.

**Results:** Significant differences were seen in the maximum optical density (max OD) between fertile and infertile group in terms of the intact and damaged DNA (≤500bp) (P = 0.004 and 0.025 respectively). Max OD of the damaged DNA (500-1000bp) was comparable between the two groups.

**Conclusion:** Total Genome damage test can differentiate between fertile and infertile men. Infertile men show higher incidence of short DNA fragments in their semen.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Intact DNA</th>
<th>Damaged DNA (500-1000bp)</th>
<th>Damaged DNA (≤500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven Fertile (n = 7)</td>
<td>148.03±14.93</td>
<td>6.4±6.2</td>
<td>4.8±4.8</td>
</tr>
<tr>
<td>Infertile patients (n = 13)</td>
<td>75.07±14.29</td>
<td>18.2±9.9</td>
<td>105.69±29.8</td>
</tr>
<tr>
<td>P value</td>
<td>0.004</td>
<td>0.4</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Results expressed as mean ± SEM, P <0.05 was considered significant using Mann Whitney test.
Evaluation of Semen Quality Using Sperm DNA Cytometry Assay

Ashok Agarwal, Reda Z. Mahfouz, Mona A. Elsahfei, Amr A. Fathi, Rakesh Sharma, Samia H. Kandil

Introduction & Objectives: Sperm DNA is being reported to be useful in selecting fertility treatment options and predict outcome. Analysis of sperm chromatin content can differentiate sperm subpopulations into: condensed sperm chromatin (CSC; mature), non-condensed sperm chromatin of haploid spermatid (non-CSC; immature), diploid cell and sub-haploid sperm with low DNA content. Our objective was to investigate the DNA content of the various sperm cells in proven fertile donors and infertile patients.

Methods: Semen samples were collected from 10 proven donors and 42 infertile men. These men underwent routine semen analysis. Sperm DNA content was tested using the cell cycle/ DNA content kit by the flow cytometry.

Results: Proven fertile men had significantly higher level of DNA content in CSC cells vs. infertile men and significantly lower levels in subhaploid sperm cells (p = 0.001, p < 0.001 respectively). No significant differences were seen between proven fertile and infertile men in non-CSC or diploid cells (p = 0.09, p = 0.77 respectively). The infertile men showed a significant negative correlation between subhaploid cells with CSC, non-CSC sperm cells and diploid cells (r = -0.9, -0.6, -0.3). On the other hand, proven fertile men showed significant negative correlation between subhaploid cells with CSC, non-CSC sperm cells and diploid cells (r = -0.97, -0.3).

Conclusion: Sperm DNA cytometry can be used to evaluate semen quality & assessment of male fertility potential. Sperm cells (subhaploid cells) with DNA fragmentation is negatively related to sperm condensation and sperm immaturity indicating a decline in sperm DNA repair capabilities with maturation.

<table>
<thead>
<tr>
<th>DNA content cell subpopulations</th>
<th>Proven fertile</th>
<th>Infertile group</th>
</tr>
</thead>
<tbody>
<tr>
<td>condensed sperm chromatin (CSC)</td>
<td>61.2 ± 2.2</td>
<td>32.7 ± 3.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Haploid non-condensed (non-CSC)</td>
<td>12.4 ± 0.5</td>
<td>8.6 ± 1.1</td>
</tr>
<tr>
<td>Sub-haploid cells</td>
<td>23.5 ± 2.2</td>
<td>55.2 ± 4.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diploid cells</td>
<td>2.7 ± 0.2</td>
<td>3.2 ± 0.9</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± standard error of mean; <sup>a</sup>significant difference between proven fertile and infertile groups.
Association of Sperm DNA Cytometry with ICSI Outcome

Ashok Agarwal, Reda Z. Mahfouz, Mona A. Elsahfei, Amr A. Fathi, Rakesh Sharma, Medhat K. Amer

Introduction and Objectives: Fertilization and subsequent development depends in part on the inherent integrity of the sperm DNA. Analysis of Sperm DNA content can be done by flow cytometry. It can classify sperm subpopulations into: condensed sperm chromatin (CSC), non-condensed sperm chromatin of haploid spermatid (non-CSC), diploid cell and sub-haploid sperm with low DNA content. Our objective was to investigate the DNA content of the sperm cells in infertile patients undergoing ICSI.

Methods: Semen samples were collected from 42 infertile men. Each sample was divided into 3 aliquots for routine semen analysis, for ICSI preparation, and for flow cytometry analysis. Sperm DNA was tested using the cell cycle/ DNA content assay by the flow cytometry. Patients were divided into two groups according to the pregnancy test: group I: positive pregnancy (n=17) and group 2: negative pregnancy (n=22).

Results: Table shows significant differences in CSC cells, non-CSC cells and sub-haploid sperm cells between the 2 groups (p <0.001, <0.01, <0.001 respectively). Group 2 showed significant negative correlation between sub-haploid cells with CSC, non-CSC sperm cells and diploid cells (r =-0.89, -.67, -0.39). Similarly, pregnancy negative group also showed positive correlation between non-CSC with diploid cells. Group 1 showed significant negative correlation between haploid cells with non-CSC, and diploid cells (r =-0.57, -0.59).

Conclusion: Sperm DNA cytometry can be used to predict ICSI outcome. Sub-haploid cell level may be a predictor of ART outcome.

<table>
<thead>
<tr>
<th>DNA content subpopulations</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSC</td>
<td>54.7 ± 3.9</td>
<td>18.3 ± 2.2a</td>
</tr>
<tr>
<td>Non-CSC cells</td>
<td>5.8 ± 2.0</td>
<td>5.7 ± 1.0a</td>
</tr>
<tr>
<td>Sub-haploid cells</td>
<td>28.2 ± 3.0</td>
<td>73.9 ± 2.8a</td>
</tr>
<tr>
<td>Diploid cells</td>
<td>4.6 ± 2.2</td>
<td>1.9 ± 0.3</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± standard error of mean; a significant difference between positive pregnancy test and negative pregnancy test groups.
Association of Early Apoptosis with the Nuclear Integrity and Maturity in Different Seminal Fractions

Ashok Agarwal, Tamer M. Said, Juris Erenpreiss, Reda Z. Mahfouz, Aleksander Giwercman, Donald Evenson

Objective: The integrity and maturity of the paternal genome is an absolute prerequisite for successful fertilization and a healthy offspring. In human spermatozoa, the relationship between apoptosis and the nuclear status remains unclear. Externalization of phosphatidylserine (PS), to the outer sperm membrane leaflet is considered to mark terminal apoptosis. The objective of our study was to investigate differential expression of PS as a marker for early apoptosis with nuclear integrity and maturity of human sperm.

Design: Prospective-controlled study.

Materials and Methods: Semen samples were collected from 19 healthy donors. The neat semen samples were divided into mature and immature sperm fractions using double density gradient centrifugation (80% and 40% layers). Both fractions as well as an aliquot of the neat sample were evaluated for the incidence of early apoptosis (PS externalization) using the annexin V flow cytometric assay. In addition, the %DFI and %HDS were measured using the SCSA.

Results: The means ± standard errors of the percentages of annexin V as well as the %DFI and % HDS in neat semen, mature and immature fractions are given in the table. Externalization of PS was significantly lower in mature sperm fractions compared to the immature fractions and neat semen samples (p<0.0001 and p=0.007, respectively). Similarly, the mature sperm fractions showed lower % HDS compared to the immature fractions and neat semen samples (p<0.0001 and p=0.001, respectively). The %DFI was comparable between all fractions. Externalization of PS showed a significant positive correction with %HDS (r=0.47, p=0.0004) but not with %DFI.

Conclusion: Mature sperm fractions show lower incidence of apoptosis and higher nuclear maturity. The association of PS externalization with %HDS in human semen samples indicates that early apoptosis is associated with immature nuclear development and subsequently abnormal nuclear chromatin (DNA and protein). Our data also supports the lack of association between early apoptosis and sperm DNA fragmentation.
Evaluation of Seminal Fractions using the Toluidine Blue Test and the Sperm Chromatin Structure Assay (SCSA™)

Ashok Agarwal, Tamer M. Said, Juris Erenpreiss, Reda Z. Mahfouz, Aleksander Giwercman, Donald Evenson

Objective: Over the past decade, several techniques have emerged as potential protocols for evaluating the sperm chromatin integrity. Such integrity is of utmost importance for successful fertilization. Most of the techniques used for sperm chromatin evaluation require extensive instrumentation and special expertise. Toluidine blue (TB) test has been reported as an easily accessible alternative test for sperm chromatin assessment. Spermatozoa may either stain as dark violet (DV, abnormal chromatin conformation/DNA integrity) or light blue (LB, normal chromatin conformation). The sperm chromatin structure assay (SCSA) is one of the most standardized methods for assessment of fragmented sperm DNA and the percentage of sperm with immature nuclear development (high DNA stainability index, HDS). The objective of our study was to evaluate the Toluidine blue test and SCSA for assessment sperm DNA damage in different seminal fraction.

Design: Prospective-controlled study.

Materials and Methods: Semen samples were collected from 19 healthy donors. The neat semen samples were divided into mature and immature sperm fractions using double density gradient centrifugation 80% and 40% layers. Both fractions as well as an aliquot of the neat sample were evaluated using Toluidine blue test. In addition, the %HDS was measured using the SCSA.

Results: The means ± standard errors of the percentages of sperm with normal (light blue) and abnormal dark violet) chromatin in neat semen, mature and immature fractions are given in the table below. Using the Toluidine blue test, mature sperm fractions showed higher incidence of spermatozoa with normal DNA compared to the immature fractions and neat semen samples (p=0.04 and p=0.006, respectively). Similarly, the mature sperm fractions showed lower incidence of spermatozoa with abnormal DNA compared to the immature fractions and neat semen samples (p=0.01 and p<0.0001, respectively). The %HDS showed a significant positive correlation with the number of DV sperm (r=0.51, p=0.0002) and a significant negative correlation with the number LB sperm (r=-0.59, p<0.0001).

Conclusion: Mature sperm fractions show a lower incidence of abnormal DNA as measured by the Toluidine blue test. The association of %HDS with cells that are stained dark violet suggests that Toluidine blue can identify immature nuclear chromatin with abnormal chromatin conformation.
Association of Intermediate Staining Patterns using the Toluidine Blue Test with Late Apoptosis and Necrosis in Human Spermatozoa


Objective: The integrity of the paternal genome chromatin structure plays an important role in determining the outcome of fertilization. Toluidine Blue (TB) test was proposed as a simple test for sperm chromatin assessment. Four different sperm groups are distinguished in TB: 1) dark violet (DV, abnormal chromatin/ DNA integrity); 2) light blue (LB, normal chromatin conformation); and two intermediate groups - light violet (LV) and intense blue (B). While DV and LB stained cells were shown to correspond to spermatozoa with intact and damaged chromatin respectively. The biological background of the intermediate cells (LV and B) remains to be investigated. The objective of our study was to elucidate the association of intermediate stained cells using the Toluidine blue test with late apoptosis and necrosis in human spermatozoa.

Design: Prospective-controlled study.

Materials and Methods: Semen samples were collected from 22 donors. The neat samples were divided into mature and immature sperm fractions using double density gradient centrifugation (80% and 40% layers). Both fractions as well as an aliquot of the neat sample were evaluated using Toluidine blue test and for the incidence of late apoptosis and necrosis using the flow cytometric annexin V/ propidium iodide (PI) assay. Late apoptotic sperm stain positive for annexin and PI, while necrotic sperm stain positive for PI only.

Results: Results of intermediate staining patterns using the Toluidine blue test as well as late apoptotic and necrosis in sperm are shown in the Table. The Toluidine blue test showed comparable scores of LV and B stained cells between the neat, mature and immature fractions. Similarly, the incidence of late apoptotic cells was comparable between the neat, mature and immature fractions. The incidence of necrotic cells (PI-positive) was significantly lower in mature fractions compared to neat samples (p=0.01). In the immature sperm fractions, significant positive correlations were found between the cells stained Blue using the TB test and PI-positive (r=0.46, p 0.035) as well as annexin-positive/PI-positive (r= 0.58, p=0.006). No significant correlations were found between result of the TB test and annexin/PI in neat or mature sperm fractions.

Conclusion: Processing of human seminal fluid decreases the incidence of necrotic but not of late apoptotic sperm. The cells stained blue by Toluidine blue test in predominantly immature sperm fractions correspond to the presence of late apoptosis and necrosis.
Comparison of DNA Contents of Apoptotic Sperm Cells in Neat and Processed Semen

Ashok Agarwal, Reda Z. Mahfouz, Tamer M. Said, Juris Erenpreiss, Aleksander Giwercman, Rakesh K. Sharma

Objective: Semen processing is used during assisted reproductive techniques to eliminate unwanted, damaging cells and debris from semen samples. To date little is known about the sperm DNA content and its relation to apoptosis or DNA fragmentation in neat semen and following density gradient centrifugation. Sperm DNA content can be evaluated by flow cytometry using propidium iodide (PI) stain. Flow cytometric analysis could quantitatively differentiate between intensities of haploid spermatid, spermatozoa with condensed chromatin and sub-haploid with low DNA content. Our objective was to investigate the DNA content of the late apoptotic and necrotic sperm cells in neat and processed semen following density gradient centrifugation.

Design: Prospective-controlled study.

Materials and Methods: Semen samples were collected from 22 donors. The neat samples were divided into mature and sperm immature fractions using double density gradient centrifugation (90% and 47% layers). Both fractions as well as an aliquot of the neat sample were evaluated for the incidence of early apoptosis and necrosis using the annexin V/PI assay using flow cytometry. To evaluate the DNA content, PI-positive cells were gated and subjected to analysis. In addition, the DNA fragmentation index (%DFI) and high DNA stain ability index (%HDS) were measured using the sperm chromatin structure assay.

Results: Mature sperm fractions showed significantly lower abnormal DNA content parameters compared to neat samples: sub-haploid (p=0.003) and spermatid (p=0.03), while the number of sperm with condensed chromatin was comparable (Table). Neat semen and mature fractions showed significantly higher proportion of spermatozoa with condensed chromatin compared with immature fraction (p=0.02 and p=0.01, respectively). There was no significant difference between mature and immature fractions regarding the number of sub-haploid cells. In neat semen, there was a significant negative correlation between haploid apoptotic cells and %HDS (r=-0.48, p=0.04), while positive correlation was found between immature and sub-haploid apoptotic cells with %DFI (r=0.6, p<0.01). In mature and immature fractions there was strong positive correlation between each apoptotic haploid and spermatid with DFI (r=0.5, p<0.01 and r=0.6, p=0.005, respectively).

Conclusion: Mature sperm fractions in processed semen contain more normal DNA content than neat and mature semen. The %DFI in neat semen could be related to immature and low DNA content cells, while %HDS could be related to immature cells.
Efficacy of Varicocelectomy in Improving Semen Parameters: A New Meta-Analytical Approach

Ashok Agarwal, Fnu Deepinder, Marcello Cocuzza, Rishi Agarwal, Robert A. Short, Edmund Sabanegh, Joel L. Marmar

Objectives: To determine the efficacy of varicocelectomy in improving the semen parameters.

Methods: A meta-analysis was performed evaluating both randomized controlled trials and observational studies by using a new scoring system. Out of 136 studies identified through the electronic and hand-search of references, only 17 studies were evaluated based on our inclusion criteria. The study population was infertile males having clinically palpable unilateral or bilateral varicocele with at least one abnormal semen parameter who underwent surgical varicocelectomy (high ligation or inguinal microsurgery). The control groups were composed of infertile males with varicocele who declined to undergo surgical repair of varicocele, were randomized to no treatment or medical treatment or randomized to receive treatment after the follow-up period. Only those studies were included which had at least three semen analyses (sperm count, motility and morphology) per patient, before and after surgical varicocelectomy.

Results: Combined analysis demonstrated that sperm concentration increased by 9.71 X 10^6/mL (95% CI: [7.34, 12.08], P < 0.00001) and motility increased by 9.92% (95% CI: [4.90, 14.95], P = 0.0001) following microsurgical varicocelectomy. Similarly, sperm concentration increased by 12.03 X 10^6/mL (95% CI: [5.71, 18.35], P = 0.0002) and motility increased by 11.72% (95% CI: [4.33, 19.12], P = 0.002) after high ligation varicocelectomy. The improvement in WHO sperm morphology was 3.16% (95% CI: [0.72, 5.60]; P = 0.01) following both microsurgery and high ligation varicocelectomy.

Conclusions: Surgical varicocelectomy significantly improves semen parameters in infertile males with palpable varicocele and abnormal semen parameters.
Section 5

Sexual and Pelvic Health
Male Genital Morphology and Function: An Evolutionary Perspective

J. Stephen Jones, Matthew N. Simmons

**Purpose:** The genitals are at the forefront of evolution. Advantageous features of genital form and function determine which individuals pass their genes to future generations. The male genitalia are primarily for sperm deposition, but additional functions of the penis and its accessory structures are being identified.

**Methods:** The literature regarding genital evolution was reviewed.

**Results:** This review explains key theories regarding the mechanisms of genital evolution. Also discussed are the anatomic and functional adaptations among different species that have evolved to optimize fertilization success. Finally, these evolutionary influences are discussed in the context of clinically-relevant human genital morphology and function.

**Conclusions:** The function of the genitalia extends beyond simple sperm transfer. Genital morphology evolves in order to provide primary and secondary functionality that is critical for successful mating. By considering the form and function of human genital morphology in an evolutionary context we gain not only an appreciation for its design, but also a deeper understanding of our treatment goals.
New Paradigms for Implantable Penile Prosthetic Design

Drogo K. Montague, Matthew N. Simmons

Introduction and Objective: Current inflatable penile prosthetics are suboptimal in several regards. 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 250cm H\textsubscript{2}O. 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.
Prevalence and Significance of Abdomino-Pelvic Tenderness in Men with Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Daniel Shoskes, Richard Berger, Kathleen Propert, Angelo Elmi, Scott Zeitlin

Introduction: Neuromuscular spasm is implicated as an etiology for category III chronic prostatitis/chronic pelvic pain syndrome (CPPS), either secondary to infection/inflammation or as the primary cause. We wished to document tenderness on physical exam in a large multicenter cohort of CPPS patients as well as in asymptomatic controls.

Methods: Data was reviewed from the NIH Chronic Prostatitis Cohort study on 384 men with CPPS and 121 asymptomatic controls who had complete physical exam data, from 7 clinical sites from 10/98-8/01. Physician assessed tenderness for 11 sites covering the prostate, genitals, abdomen and pelvic floor was scored as present or absent along with prostate size and consistency. This data was correlated with results of prostatic fluid cultures and symptoms using the NIH Chronic Prostatitis Symptom Score (CPSI).

Results: Overall, 49% of CPPS patients and 93% of controls had no tenderness. The most common tenderness site was the prostate (41% CPPS, 5% controls) followed by external and internal pelvic floor (13% and 14% CPPS, 0 controls) and suprapubic (9% CPPS, 0 controls). For CPPS, 25% had 1 tenderness site, 11% had 2 and 6% had 3. Only 6% of controls had 1 tenderness site and 1% had 2 sites. Tenderness did not correlate with inflammation or infection in the prostate fluid. Prostate consistency was normal in 79% of CPPS and 95% of controls and did not correlate with symptom severity. Patients with at least 1 tenderness site had significantly higher CPSI scores at baseline and at 1 year (24.1 vs 21.2 and 20.2 vs 17.5, p<0.0001).

Conclusions: Abdominal/pelvic tenderness is present in half of CPPS patients but only 7% of controls. Prostate consistency (“soft/boggy”) is not diagnostic of CPPS. Extraprostatic tenderness may identify a cohort of patients with a neuromuscular source of pain requiring targeted intervention.
Section 6

Bladder Cancer
Laparoscopic Radical Cystectomy with Urinary Diversion: “Pure Laparoscopic” versus “Laparoscopic Assisted”

Inderbir S. Gill, Jihad H. Kaouk, Amr F. Fergany, Steven C. Campbell, Georges-Pascal Haber, Jose R. Colombo Jr., Monish Aron

**Purpose:** Laparoscopic Radical Cystectomy with urinary diversion (LRC) is feasible. The entire procedure can be performed intracorporeally “Pure Laparoscopic” (PL) or “Laparoscopic Assisted” (LA) with a minimal abdominal incision for the reconstructive portion. In this study we compare the outcomes of these 2 techniques.

**Materials and Methods:** Between December 1999 and January 2005, 23 male and 14 female with a mean age of 66 years old underwent 37 LRC, 17 PL and 20 LA. Orthotopic neobladder (ON) and ileal conduit (IC) were performed for urinary diversion. A retrospective comparison, PL vs LA included intra-operative data (OR time, Blood Loss, Transfusion) and post-operative data (Oral Intake, Ambulation, complications).

**Results:** see table

**Conclusion:** The extirpative portion of the LRC is safe. Morbidity is due to the reconstructive portion. The complexity of intracorporeal bowel work results in a more significant number of complications. Bowel work and ureteroileal anastomoses are preferable extracorporeally while waiting for more refined suturing devices.

<table>
<thead>
<tr>
<th>Number</th>
<th>Pure Laparoscopic</th>
<th>Laparoscopic Assisted</th>
<th>Pure Laparoscopic Orthotopic Neobladder</th>
<th>Laparoscopic Assisted Orthotopic Neobladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time (hrs)</td>
<td>9.38</td>
<td>7.35*</td>
<td>8.25</td>
<td>6.5*</td>
</tr>
<tr>
<td>Blood Loss (cc)</td>
<td>788</td>
<td>472*</td>
<td>795</td>
<td>457†</td>
</tr>
<tr>
<td>Transfusion</td>
<td>4</td>
<td>1†</td>
<td>1</td>
<td>1†</td>
</tr>
<tr>
<td>Oral Intake (days)</td>
<td>6</td>
<td>2.8*</td>
<td>4.5</td>
<td>2.8†</td>
</tr>
<tr>
<td>Ambulation (days)</td>
<td>16.8</td>
<td>2.46*</td>
<td>13.6</td>
<td>2†</td>
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<tr>
<td>Major complications</td>
<td>29.4%</td>
<td>5%*</td>
<td>12.5%</td>
<td>0%*</td>
</tr>
<tr>
<td>Late complications</td>
<td>17.6%</td>
<td>20%†</td>
<td>25%</td>
<td>30%†</td>
</tr>
</tbody>
</table>

*p<0.05  † p>0.05
Extended Pelvic Lymph Node Dissection is Associated with Lower Recurrence Rates in Patients after Radical Cystectomy: A Nonrandomized Inter-institutional Comparison

Eric A. Klein, Nivedita Dhar, Alwyn M. Reuther, Urs E. Studer

Introduction: To compare and evaluate the rates of recurrence (local and/or systemic) for patients with stage pT2pN_{0-2} and pT3pN_{0-2} urothelial carcinoma of the bladder with limited pelvic lymph node dissection (PLND) at Cleveland Clinic (CCF) or with an extended PLND at University of Bern (Bern).

Patients and Methods: Two consecutive series of 385 CCF patients (median age 61.9 years, range 30.7-83.8) treated by limited bilateral PLND and radical cystectomy (RC) and 394 Bern patients (median age 66.9 years, range 35.3-89.2) treated by extended bilateral PLND and RC each between 1987 and 2000, with negative surgical margins on final pathology were analyzed. Median follow up for CCF patients was 45.1 months (range 1.1-165.7) and for Bern patients was 58.7 months (range 0.03-229.2). All patients were staged N\textsubscript{0}M\textsubscript{0} before RC, and none received neoadjuvant radiotherapy or chemotherapy. Boundaries of limited PLND were the pelvic side-wall between the genitofemoral and obturator nerves, from the bifurcation of iliac vessels to the circumflex iliac vein. With extended PLND the cephalad dissection is extended to the crossing of the ureters with the common iliac arteries and removal of all tissue along the lateral and medial portion of internal iliac vessels. Pathological characteristics, based on the 1997 Tumor-Nodes-Metastasis system and recurrence patterns were determined.

Results: The incidence of positive nodes was higher with extended PLND for comparable pT stages. In addition, the incidence of local and/or distant recurrence was higher in pts with N\textsubscript{+} disease in the group undergoing limited PLND (Table).

<table>
<thead>
<tr>
<th>Institution</th>
<th>Stage</th>
<th># of patients</th>
<th># with N\textsubscript{+}</th>
<th># N\textsubscript{+} w/recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bern</td>
<td>pT2pN\textsubscript{0-2}</td>
<td>150</td>
<td>24/150 (16%)</td>
<td>14/24 (58%)</td>
</tr>
<tr>
<td>CCF</td>
<td>pT2pN\textsubscript{0-2}</td>
<td>200</td>
<td>15/200 (7.5%)</td>
<td>13/15 (87%)</td>
</tr>
<tr>
<td>Bern</td>
<td>pT3pN\textsubscript{0-2}</td>
<td>172</td>
<td>59/172 (34%)</td>
<td>38/59 (64%)</td>
</tr>
<tr>
<td>CCF</td>
<td>pT3pN\textsubscript{0-2}</td>
<td>136</td>
<td>29/136 (21%)</td>
<td>27/29 (93%)</td>
</tr>
</tbody>
</table>

Conclusion: Recognizing the inherent limitations of a retrospective two institution comparison, the results suggest that the more extended the PLND, the more likely positive nodes are found and if so, a meticulous extended PLND may reduce the probability of local and/or distant recurrence when compared to a limited PLND.
International Registry of Laparoscopic Radical Cystectomy: Report on 492 Patients


Objective: To present the International Registry for Laparoscopic Radical Cystectomy on 492 patients undergoing laparoscopic radical cystectomy (LRC).

Methods: We created a registry database involving 13 international centers with published experience in LRC. A standardized data sheet was created and all data were sent to 1 center where a master data sheet was created and data analyzed.

Results: From December 1999 to March 2006, there were 393 males and 99 females with a mean age of 65 years and mean BMI of 26. Extirpative procedures mainly included cystoprostatectomy (72%) and female anterior pelvic exenteration (13%). The most common types of urinary diversion included orthotopic neobladder (53%) and ileal conduit (35%). The reconstructive part of the procedure was performed extracorporeally in 89% and intracorporeally in 11%. Mean blood loss was 556cc (30-5000). Mean operating room time was 6.2 hours (1.6-13.8). Hospital stay was 13 days (3-90). Complications occurred intraoperatively in 33 (7%) and postoperatively in 139 (28%). Nine (2%) positive surgical margins. The mean number of lymph nodes is 13 (0-36); 80 patients (16%) had nodal involvement. Mean follow-up in 474 patients (96%) was 18 months (0.5-72). The overall and cancer-specific survival was 65% and 80%, respectively. Local recurrences were noted in 27 patients (5%), systemic recurrences in 39 (8%) and no port site recurrences.

Conclusions: Laparoscopic radical cystectomy with urinary diversion is being performed at an increasing number of centers worldwide. This International Registry has been organized with the aim of standardizing the operative technique, postoperative data collection, and meticulous long-term follow-up.
Laparoscopic Radical Cystectomy: 5-year Oncological Outcomes

Inderbir S. Gill, Georges-Pascal Haber

Introduction and Objective: Radical cystectomy is the gold standard for the treatment of muscle invasive bladder cancer. The interest in laparoscopic approach is increasing. Herein we report 5-year oncological outcomes after laparoscopic radical cystectomy (LRC).

Methods: Between December 1999 and January 2005, 37 patients (23 men, 14 women) with mean (range) age of 66 years (37-81) underwent LRC with urinary diversion for invasive bladder cancer. In 26 patients extended pelvic lymphadenectomy was performed. Overall and cancer-specific survival data were obtained from patient charts, radiographic reports, telephone contact and a check of the Social Security Death Index.

Results: There were 32 patients with transitional cell carcinoma, 3 with squamous cell carcinoma, and 2 with adenocarcinoma. Pathological staging was: pT4a-4, pT3b-7, pT3a-7, pT2b-11, pT2a-4 and pT1-6. Most lesions were high grade: grade III-29, grade II-7, grade I-1. 8 patients had concomitant carcinoma in situ. Two patients had positive surgical margins. The median number of lymph nodes in the lymphadenectomy specimen was 14 (1-24). Seven patients had positive nodes. 24 patients (65%) are alive without evidence of disease, 11 (30%) are dead; 2 (18%) from metastasis and 9 (82%) from unrelated causes. 2 (5%) patients are lost to follow-up. The overall and cancer-specific survival was 64% and 94% respectively.

Conclusion: 5-year data suggests that LRC provides oncologic outcomes comparable to contemporary open radical cystectomy series.
Surrogate and Intermediate Oncological Outcomes of Laparoscopic Radical Cystectomy

Inderbir S. Gill, Jihad H. Kaouk, Amr F. Fergany, Steven C. Campbell, Georges-Pascal Haber, Rodrigo Frota, Jose R. Colombo Jr, Monish Aron, Burak Turna

**Introduction and Objective:** Radical cystectomy is the gold standard treatment for muscle invasive bladder cancer. Interest in laparoscopic radical cystectomy (LRC) is increasing at select centers worldwide. Herein, we report surrogate and intermediate terms oncological outcomes after LRC.

**Methods:** Between December 1999 and October 2006, 76 patients (56 men, 20 women) with a mean age (range) of 66.5 years (26-87) underwent LRC and urinary diversion for invasive or high risk superficial bladder cancer. In 65 patients (85.5%) extended pelvic lymphadenectomy was performed. Overall and cancer-specific survival data were obtained from patient charts, telephone contact and a check of the Social Security Death Index.

**Results:** The majority of tumors (n=71, 93%) were transitional cell carcinoma, 2 (3%) were adenocarcinoma, and 3 (4%) were squamous cell. Most lesions were high grade: grade III (n=59; 78%), grade II (n=16; 20%), and grade I (n=1; 2%) and 9 (11.8%) patients had concomitant carcinoma in situ. Pathological staging was: pT1N0 (n=9; 12%), pT2N0 (n=41; 54%), pT3N0 (n=14; 18%), and pTanyN+ (n=12; 16%). Median number of excised lymph nodes for patients with extended lymph node dissection was 17 (10-24). Two (2.6%) patients had a positive surgical margin Follow-up data were available in 67 patients (88.1%) and 10 patients (13.1%) have completed 5 year follow-up. Mean follow-up period was 25 months (1-83 months). At last follow-up 54 patients (71%) were alive without evidence of disease and 13 (29%) were dead: 3 (23%) from metastasis and 10 (77%) from unrelated cause. Three patients (3.9%) are lost to follow-up. Overall and cancer-specific survival was 84.2% and 94.5% at 2 years, and 66.9% and 90.4% at 5 years, respectively.

**Conclusion:** To our knowledge, this is the initial report of intermediate-term follow-up data of LRC in a substantial number of patients. Our data suggest that LRC provides oncological outcomes comparable to contemporary open radical cystectomy series, but a direct randomized trial would be required to evaluate this more fully.
Comparison Between Open and Laparoscopic Assisted Radical Cystectomy for Bladder Cancer

Inderbir S. Gill, Jihad H. Kaouk, Amr F. Fergany, Steven C. Campbell, Georges-Pascal Haber, Jose R. Colombo Jr, Troy Gianduzzo, Monish Aron

Introduction: Open Radical cystectomy (ORC) with extended lymph node dissection is the gold standard treatment of invasive or high-risk superficial bladder cancer. The feasibility and safety of Laparoscopic Radical Cystectomy (LRC) with extracorporeal construction of the urinary diversion as compared to the traditional approach is not well defined. The objective of this study is to retrospectively compare the perioperative outcomes of LRC with a contemporary cohort of ORC.

Materials and Methods: Between 12/1999 and 10/2006, 520 patients underwent ORC and 76 patients underwent LRC. The last consecutive 25 LRC (20 men, 5 women) were selected for this study. All of these patients had the urinary diversion (13 ileal conduit, 12 orthotopic neobladder) performed extracorporeally through a 5-6 cm mini-laparotomy. This group was compared to a contemporary cohort of 25 ORC (19 men, 6 women) with urinary diversion (14 ileal conduit, 11 orthotopic neobladder). Data was reviewed from an electronic prospective database approved by our institutional review board.

Results: There were no significant differences between the LRC and ORC group with respect to mean patient age (65 vs. 71; p=0.09), BMI (27 vs. 26; p=0.23), comorbidities, history of prior abdominal surgery and operative indications. Tumor was organ confined (≤pT2N0), non-organ confined (pT3-4N0), and lymph node positive (pTanyN+) in 73%, 27%, 14% of the LRC patients and 64%, 36%, 8% of the ORC patients, respectively, with no significant differences between the groups (p=0.26).
Conclusion: LRC with extracorporeal construction of the urinary diversion offers the potential for reduced blood loss, less ileus, quicker recovery and more rapid convalescence, without any significant difference in operative time and postoperative complications. Surrogate oncological outcomes are encouraging but long-term assessment will be required.
Female Organ Sparing Laparoscopic Cystectomy

Inderbir S. Gill, Amr F. Fergany, Christopher J. Weight, Ja-Hong Kim

Introduction/Objectives: Radical cystectomy in female patients typically results in total loss of hormonal and reproductive function. This is an undesirable option for a substantial portion of younger or sexually active patients who present with invasive bladder cancer. Three populations of females would greatly benefit from these modifications in appropriately selected cases, one those of reproductive age, secondly those with functioning ovaries and finally those who are sexually active but are post menopausal. Here we present our technique for each of the scenarios.

Materials and Methods: The first patient is the younger woman of reproductive age, who still desires to have children. We demonstrate how to preserve the vascular supply to the reproductive organs while completely removing the bladder, distal ureters and urethra. The second patient no longer desires the ability to have children, but is pre-menopausal and desires to maintain hormonal function. The video demonstrates preservation of the ovaries and its vasculature followed by cystectomy. The final patient is post menopausal but sexually active. Images demonstrate the removal of the reproductive organs, but sparing of the full length of the vagina and its support.

Results: These three patients underwent some modification of female organ sparing radical cystectomy. All three subsequently had an open urinary tract reconstruction through a mini-laparotomy incision. Post-operative course was unremarkable for the three patients with no major complications.

Conclusions: In select female patients in need of a radical cystectomy, reproductive organs can safely be spared according to the patients’ current reproductive and hormonal needs. This video demonstrates how this can be done by laparoscopy with the attendant benefits of minimally invasive surgery.
The Role of Routine Imaging in Monitoring for Pelvic Recurrence after Radical Cystectomy for Transitional Cell Carcinoma of the Bladder

Eric A. Klein, J. Stephen Jones, Nivedita Bhatta Dhar, Robert Dreicer, Alwyn M. Reuther

Introduction: In the past our practice has been to obtain serial CT scans of the abdomen and pelvis for at least 3 years following cystectomy, which encompasses the time frame during which most of these tumors recur. One of the major issues regarding to the utility of CT imaging is whether a delay of finding disease 4-8 weeks earlier by imaging vs. symptomatic complaints impacts on outcome and this issue remains undefined. The objective of this study was to evaluate the role of routine imaging in monitoring for disease recurrence after radical cystectomy (RC) for transitional cell carcinoma (TCC) of the bladder.

Patients and Methods: We reviewed a consecutive series of 130 patients who underwent bilateral pelvic lymph node dissection (PLND) and RC between 1987 and 2000 and who later developed pelvic recurrence (PR). PR was defined as a radiographic soft tissue density of ≥ 2cm below the bifurcation of the aorta.

Results: Median time from RC to PR was 7.3 months (range 1.2 to 55.4). No patients had concomitant distant metastasis. Of the patients, 61.5% were diagnosed with PR because of symptoms and 38.5% by surveillance CT scan. Of the 130 patients, 80 (61.5%) were diagnosed with PR because of symptoms and 50 (38.5%) were diagnosed by surveillance CT scan. Of the 80 patients with symptomatic recurrence, 26 (20.0%) complained of ileus, 26 (20.0%) of edema, 17 (13.1%) of either pelvic, perineal or hip pain, 4 (3.1%) of flank pain and 4 (3.1%) of constipation. Three patients underwent laparotomy for small bowel obstruction and all were found to have a pelvic recurrence intraoperatively. Of the 130 patients, 128 (98.5%) died with a median survival from the time of PR of 4.9 months (range 0.1-129.3). The median survival from the time of recurrence to death was 5.2 months (range 0.1 to 49.0) for PR patients diagnosed with CT scan and 4.4 months (range 1.0 to 129.3) for symptomatic presentations (logrank p=0.08).

Conclusion: The observation that 98.5% of our patients with local recurrence eventually died and the fact that there was no difference in survival according to whether the recurrence was suspected by symptoms or found incidentally on CT scan suggests that routine imaging postoperatively is not helpful in monitoring for disease recurrence. The rationale of post-operative CT imaging is to detect early loco-regional or metastatic disease. Given the natural history of TCC where in essence all disease recurrence is systemic, the ultimate utility of close radiographic monitoring will be associated with the ability to bring to bear effective systemic therapy.
Lidocaine 2% Gel Versus Plain Gel for Efficacy of Pain Reduction During Flexible Cystoscopy – a Meta Analysis of Prospective Randomized Controlled Trials

J. Stephen Jones, Denise Babineau, Amit R. Patel

Introduction and Objectives: To conduct a meta-analysis of randomized controlled trials examining the efficacy of 2% lignocaine versus plain gel in decreasing the amount of pain that male patients incur from a flexible cystoscopy.

Methods: We sought to identify and summarize all randomized controlled trials in which male patients were randomized to receive 2% lignocaine or plain gel prior to flexible cystoscopy. A search of MEDLINE, PubMed, and Scopus between 1966 to September 2006 yielded a total of 46 papers. Search terms included: cystoscopy, pain, flexible, lidocaine gel. Our study selection included randomized controlled trials, flexible cystoscopy, male patients, control group receiving plain gel prior to flexible cystoscopy, and treatment group receiving 2% lignocaine prior to cystoscopy. Data extraction included two reviewers (AP, SJ) who independently reviewed each study using a standardized data collection form. To reduce bias, both reviewers were blinded to the source of the publication and the authors' names. Primary outcome measured was pain incurred by patient throughout entire cystoscopy as measured using a VAS. Heterogeneity of study results were investigated using Cochran's Q-test. A summary treatment effect associated with type of gel used prior to flexible cystoscopy was estimated using a random-effects model with each study weighted according to the inverse of the treatment effect variance. Sensitivity analyses were conducted to investigate the robustness of these results.

Results: Based on inclusion/exclusion criteria, data from 9 trials (number of patients = 817) were included in the meta analysis. Assessment of heterogeneity among study treatment differences using Cochran’s Q test yielded a p-value<0.0001, suggesting the use of a random effects model. Based on this model, the difference between the VAS scores for pain obtained from patients receiving 2% lignocaine and patients receiving plain gel was estimated to be -4.61 with an approximate 95% CI of (-9.6, 0.385), indicating no evidence of a statistically significant difference between the VAS scores for pain obtained from patients receiving 2% lignocaine and patients receiving plain gel. Sensitivity analyses showed similar results.

Conclusions: Based on a meta-analysis of 9 randomized controlled trials, it can be concluded that lidocaine gel provides the same efficacy of pain control as plain gel lubrication in men during flexible cystoscopy.
Section 7

Kidney Cancer
Seven Years After Laparoscopic Radical Nephrectomy: Oncologic and Renal Functional Outcomes

Inderbir S. Gill, Jihad H. Kaouk, Mihir M. Desai, Jose R. Colombo Jr, Georges-Pascal Haber, J. Eric Jelovsek, Brian R. Lane, Troy Gianduzzo, Monish Aron, Jason Hafron, Robert Stein, Mike Nguyen

Objective: To compare long-term oncologic and renal function outcomes in patients undergoing laparoscopic (LRN) versus open radical nephrectomy (ORN).

Materials and Methods: Medical records were reviewed of 116 patients undergoing radical nephrectomy for pathologically-confirmed renal cell carcinoma prior to January 2000. Of these, 63 patients underwent LRN and 53 patients underwent ORN. Follow-up oncologic and functional data were obtained from patient charts, radiographic reports, and direct phone calls to patients or their families.

Results: Median follow-up was 65 months (19 – 92) in the LRN group and 76 months (8 – 105) in the ORN group. LRN was successfully completed in all patients without open conversion. Mean tumor size was 5.4 cm in the LRN group and 6.4 cm in the ORN group (p=0.007). Comparing the LRN and ORN groups, 5-year overall survival (78% vs. 84%; p=0.24), cancer-specific survival (91% vs. 93%; p=0.75), and recurrence-free survival (91% vs. 93%; p=0.75) were similar. Similarly, at 7 years, overall survival (72% vs. 84%; p=0.24), cancer-specific survival (91% vs. 93%; p=0.75) and recurrence-free survival (91% vs. 93%; p=0.75) were also comparable. No port site recurrence was noted in the laparoscopic group. Over the long-term, renal functional outcomes were similar in the LRN and ORN groups, with serum creatinine increasing by 33% and 25%, and estimated creatinine clearance decreasing by 31% and 23% from baseline, respectively. Chronic renal insufficiency developed in 4% of patients in each group.

Conclusions: Laparoscopic and open radical nephrectomy have comparable long-term oncologic and renal functional outcomes.
Renal Angiomyolipoma: Percutaneous Selective Arterial Embolization Versus Laparoscopic Partial Nephrectomy

Inderbir S. Gill, Georges-Pascal Haber, Monish Aron, Alireza Moinzadeh, Laurent Lemaitre, Arnauld Villers

Introduction and Objective: Renal angiomyolipoma (AML) is a benign neoplasm that may be associated with pain, hemorrhage or rupture. Nephron-sparing surgery (NSS) is indicated in patients with AML to preserve renal function. In this study we compare 2 minimally invasive NSS treatment for AML: Percutaneous selective arterial embolization (PSAE) versus laparoscopic partial nephrectomy (LPN).

Methods: A total of 61 procedures were performed on 50 patients with one or more renal AML treated at 2 institutions over 13 years (1991-2004). There were 9 men and 41 women with mean (range) age of 47 (25-82) years. Tuberous sclerosis was evident in 15, while 35 had sporadic AML. PSAE was performed for 27 lesions, 12 for acute hemorrhage and 15 for asymptomatic AML with a tumor size >4 cm and associated macroaneurysms. LPN was performed for 34 lesions, 18 for symptomatic AML and 16 for incidental tumor. Median follow-up is 34 months.

Results: The mean size before PSAE was 6.7+/-.3 cm and after PSAE was 3.8+/-0.8 cm. All tumors decreased in size with a mean decrease of 60% (p=0.002). In the LPN group the mean tumor size was 3.25+/-2.4 cm. The mean blood loss was 270cc (50-1200), mean warm ischemia time was 29.4 (5-60) min, mean operative time was 214 min (90-345).

In the PSAE group the mean serum creatinine was 0.98 mg/dL before the procedure and 1.02 mg/dL after PSAE. In the LPN group serum creatinine was 0.86 mg/dL preoperatively and 1.02 mg/dL postoperatively. Hospital stays averaged 2.3 days after LPN and 5 days after PSAE. Postoperative complications were seen in 4 cases (12%) after LPN (urinoma-1, transfusion-1, fever-1, pneumonia-1), and 14 cases (52%) after PSAE (Post-embolization syndrome-11, aseptic necrosis-3). There were 3 late complications after LPN (wound dehiscence-1, wound infection-1, urinoma-1) and 1 after PSAE (delayed bleeding). 3 patients required re-embolization after PSAE for recurrent symptoms. There were no recurrences after LPN.

Conclusions: LPN and PSAE are effective modalities of treatment for symptomatic and incidental renal AML. Recurrence of symptoms requiring re-treatment is more common after PSAE, but it has the advantage of avoiding a surgical procedure.
Laparoscopic Partial Nephrectomy in Obese Patients

Inderbir S. Gill, Jose R. Colombo Jr, Georges-Pascal Haber, Monish Aron, Meng Xu

Objective: To report the experience with laparoscopic partial nephrectomy (LPN) in obese (body mass index >30) patients, compared with a contemporary cohort of non-obese patients.

Materials and Methods: Between 08/99 and 12/04, 140 obese (group I) and 238 non-obese (group II) patients underwent LPN at the authors’ institution. We compare the demographics, operative data and perioperative complications in these two groups.

Results: Group I had a significantly higher incidence of hypertension and diabetes. In groups I and II respectively, the mean estimated blood loss was 310 mL (50 – 1500) vs. 249 mL (50 – 2500), the mean operating time was 3.4 hours (2.5 – 6) vs. 3.4 hours (1.5 – 6) and mean warm ischemia time was 31 min (15 – 51) vs. 32 min (12 – 60). Intraoperative complications occurred in 8 patients (5.7%) in group I vs. 20 (8%) in group II (p=0.19), with blood transfusion rate of 6% and 3%, respectively (p=0.42). Postoperative complication rate was not statistically different between the two groups (13% vs. 9%, p=0.77). Mean hospital stay was 2.8 days (1 – 8) for group I vs. 3.5 days (1 - 32) for group II. The retroperitoneal access was associated with shorter length of surgery and hospital stay in both groups.

Conclusions: LPN was performed safely in obese patients, with perioperative complication rate similar to non-obese patients. Retroperitoneal approach was associated with shorter operative time and hospitalization in obese and non-obese patients.
Preoperative Prognostic Algorithm Predicting Malignancy for Patients with Enhancing Renal Tumors

Andrew C. Novick, Steven C. Campbell, Brian R. Lane, Denise Babineau, Michael W. Kattan, Christopher J. Weight, Indirbir S. Gill

Objective: Clinicians are increasingly relying on ablative therapies and observation for some small renal tumors. Using retrospectively-collected data on 1248 patients, we compared risk factors in patients with renal lesions <7 cm in order to identify those associated with benign disease or aggressive pathology.

Methods: We collected data for all patients that underwent partial nephrectomy for a single clinical T1 tumor at our institution since 1999.

Results: RCC was noted in 79% of patients, including 82% of males and 73% of females (p<0.001). Gender, tumor size and location were significantly different in patients with RCC or a benign lesion. These differences remained when cancers were separated into indolent and aggressive. For example, median size was 3.2, 3.3, 3.6 cm for benign, indolent, and aggressive tumors (p<0.0001). Using a logistic regression model, a nomogram to predict pathologic outcomes based on only preoperative factors is being constructed.

Conclusions: Patients with benign and malignant renal neoplasms differ with regard to several preoperative factors. A nomogram may be useful for patient counseling, especially when observation or tumor ablation is being considered.
Renal Radiosurgery and Sorafenib as Non-Invasive Nephron-Sparing Treatment of Small Localized Renal Masses

Indirbir S. Gill, Monish Aron, Troy Gianduzzo, R. Ganapathi, Arul Mahadevan, Lee Ponsky

Introduction: Radiosurgery allows precise delivery of high-dose radiation with minimal adjacent tissue toxicity. Sorafenib (BAY 43-9006) has demonstrated efficacy against metastatic renal cell carcinoma (RCC) in phase 2 clinical trials. In-vitro and in-vivo analyses have demonstrated that tyrosine kinase inhibitors potentiate the effects of ionizing radiation. Herein our initial clinical experience of renal radiosurgery and the potential application of sorafenib as a radio-sensitizing agent are described.

Materials and Methods: To date, five patients with small renal masses (<4cm) have been enrolled in a dose-escalation extracorporeal renal radiosurgical irradiation protocol. An initial CT-guided biopsy is performed followed by placement of 1-2 gold fiducial markers. Renal radiosurgery is delivered in 4 fractions over 2 days following a second planning CT. Patients thus far have received 4-6Gy/fraction, while future patients will receive increasing doses to a maximum total of 48Gy. Eight weeks following radiosurgery treatment, radical or partial nephrectomy is performed. To investigate the potential application of sorafenib as a radiosensitizing agent, CAKI-1 (WT VHL) cell lines were irradiated with 200, 400, 600 or 800 rads alone, 10µM sorafenib alone for 24 or 48 hours or 10 µM sorafenib for 24 or 48 hours followed by 400 rads radiation. Cells following treatment with sorafenib and/or radiation were then re-incubated in drug-free medium and cell counts determined after 96 hours.

Results: RCC was confirmed preoperatively in 2 patients. Necrosis was evident in 3 of the 5 excised specimens indicating near-complete cell kill. No radiation-induced toxicity has been observed in any case. Preliminary In vitro analysis demonstrated dose-dependant decrease in cell count following irradiation or treatment with sorafenib. Maximal cell survival was 56% at 400 rads and 26% at 800 rads. 10 µM sorafenib that represents the mid-range steady-state concentration achieved with a dose of 400mg bid, led to 63% and 23% survival following exposure to 10 µM sorafenib for 24 and 48 hours respectively. In contrast, in cells pre-treated with 10µM sorafenib for 24 or 48 hours followed by 400 rads radiation, resulted in survival of 26% and 10% respectively; suggesting a synergistic effect.

Conclusions: Renal radiosurgery may offer an alternative, non-invasive, nephron-sparing approach to the treatment of small, localized renal masses. Preliminary in-vitro data suggests possible synergism between radiation and sorafenib. Ongoing studies are focused on the mechanistic basis of this synergy and confirming this effect in vivo and in the clinical setting.
Clinical and Radiographic Features of Cystic Nephroma and Mixed Epithelial and Stromal Tumor of the Kidney

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

Objective: While recent studies have investigated the pathologic features of cystic nephroma (CN) and mixed epithelial and stromal tumor of the kidney (MEST), clinical and radiographic information about these patients is sparse.

Methods: We reviewed 30 patients with 32 tumors in order to identify factors distinguishing CN (n=22) and MEST (n=10) from renal cell carcinoma (RCC).

Results: While the majority of RCC are detected incidentally and in males, 73% of patients with CN or MEST were symptomatic and 93% are female. On CT, CN were often Bosniak III (82%) and occasionally included a renal pelvic component (23%). 70% of MEST had enhancing components vs. 23% of CN. The diagnosis of CN was suspected preoperatively in 40% and PNx was performed for 50%. Two patients had CN and concomitant RCC. At mean follow-up of 4.7 years (0.5 – 18 years), no patient in this series has developed novel or recurrent tumors.

Conclusions: A multiloculated Bosniak III cyst with a pelvic component in a symptomatic middle-aged female should raise suspicion for CN or MEST. Nephron-sparing surgery is the preferred surgical approach to patients with suspected CN, especially given the association with RCC first described here.
Five Year Outcomes of Laparoscopic Partial Nephrectomy

Brian R. Lane, Inderbir S. Gill

Objective: Outcomes after laparoscopic partial nephrectomy (LPN) for patients with a small renal mass are excellent up to a mean follow-up of 3 years. Herein, we present long-term outcomes in 50 patients, each of whom have now completed a minimum of 5 year follow-up after LPN.

Methods: Of the 540 LPN performed at our institution, 52 initial patients have reached 5 years since surgery. Overall and cancer-specific survival data of 50 evaluable patients were obtained from medical records and patient contact.

Results: Mean tumor size was 3 cm and 10% were symptomatic at presentation. Renal cell carcinoma was confirmed in 32 cases, and pathologic tumor stage was pT1a in 29 patients (91%). Final surgical margin was positive for cancer in 1 patient. Mean serum creatinine (sCr) was 1.1 mg/dl at baseline and 1.4 mg/dl 1.7 years post-operatively. No patient with normal baseline sCr undergoing elective LPN developed chronic renal insufficiency (sCr >2 mg/dl). At median follow-up of 5.2 years (0.24 to 6.4), overall and cancer-specific survival was 84% and 100%, respectively. No patient developed local or distant recurrence.

Conclusions: This is the initial report of oncologic and functional outcomes at 5 years after LPN. Outcomes are excellent and comparable to those with open nephron-sparing surgery.
Laparoscopic Partial Nephrectomy in Patients with Compromised Renal Function

Inderbir S. Gill, Jihad H. Kaouk, Mihir M. Desai, Jose R. Colombo Jr, Georges-Pascal Haber, Monish Aron, Troy Gianduzzo, Jason Hafron, Robert Stein, Mike Nguyen

Objectives: To present outcomes of laparoscopic partial nephrectomy (LPN) for tumor in patients with compromised baseline renal function, defined as serum creatinine $\geq$ 1.5mg/dL (normal 0.7 – 1.4 mg/dL).

Methods: Of 485 patients undergoing LPN between 09/99 and 08/05 at our institution, 48 (10%) had compromised baseline renal function (Group I). Outcomes were compared with 437 patients undergoing LPN who had normal baseline renal function (serum creatinine < 1.5 mg/dL; Group II). Both groups were compared regarding perioperative data, complications, and renal functional and oncologic outcomes.

Results: Group I patients were significantly older (67.6 vs. 58.6 yrs, p<0.001), had higher American Society of Anesthesiologists scores (2.8 vs. 2.4, p<0.001), higher Charlson Comorbidity Index (1.9 vs. 0.7, p<0.001), and larger tumors (3.3 vs. 2.7 cm, p=0.01). Intraoperative data, postoperative outcomes, complications, and pathologic data were similar between groups. At a mean follow-up of 8.1 months, the percent deterioration in serum creatinine and estimated glomerular filtration rate was similar between the groups (p=0.99 and 0.89, respectively). Dialysis, temporary or permanent, was required in 5 patients (10%) in Group I and 3 patients (0.6%) in Group II (p<0.001). Within group I, older patients (>70 years) with prolonged warm ischemia (>30 min) had significantly worse renal functional outcomes. Comparing groups I and II, estimated 5-year overall survival was 78% versus 90% (Log-rank =0.01), and cancer-specific survival was 100% versus 98% (Log-rank=0.65).

Conclusions: Laparoscopic partial nephrectomy with hilar clamping can be performed efficaciously and safely in select patients with compromised renal function.
Cystic Nephroma and Mixed Epithelial and Stromal Tumor of the Kidney: Clinical, Radiographic and Pathologic Characteristics

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

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.

continued
## Clinical Features

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<thead>
<tr>
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<th>CN</th>
<th>MEST</th>
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<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>
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## Radiographic Features

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<tr>
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<th>MEST</th>
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<tbody>
<tr>
<td>Bosniak II Cyst</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Bosniak III Cyst</td>
<td>17 (77%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Bosniak IV Cyst</td>
<td>4 (18%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Solid Enhancing Tumor</td>
<td>0 (0%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Intraluminal extension into pelvis</td>
<td>5/22 (23%)</td>
<td>0/10 (0%)</td>
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## Pathologic Features

<table>
<thead>
<tr>
<th></th>
<th>CN</th>
<th>MEST</th>
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<tbody>
<tr>
<td>Median size, cm (range)</td>
<td>6.8 (1.9 - 18)</td>
<td>4.5 (1.7 - 18)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1/21 (4.8%)</td>
<td>1/9 (11%)</td>
</tr>
<tr>
<td>Concomitant RCC</td>
<td>2/21 (9.5%)</td>
<td>0/9 (0%)</td>
</tr>
<tr>
<td>Malignant transformation</td>
<td>0/22 (0%)</td>
<td>1/10 (10%)</td>
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Differential Expression of Protein Kinase N1 in Clear Cell Renal Cell Carcinoma Identified by Gene Expression Profiling

Andrew C. Novick, Ming Zhou, Brian R. Lane, Denise Babineau, P.W. Faber, J. Barnard, B.R.G. Williams

Objective: Gene expression profiles of renal cell carcinoma (RCC) can provide prognostic information. We performed a pilot study using a custom kidney cancer cDNA array in order to identify novel genes that might predict RCC recurrence.

Methods: Fresh frozen tissue from 28 unilateral clear cell RCC were analyzed using a cancer cDNA array containing 4162 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: Using the UCLA Integrated Staging System (Zisman et al, J Clin Onc 20:4559-4566, 2002), 5 patients with a low risk of recurrence were compared with the remaining 23 patients with intermediate or high-risk tumors. Using two sample t-tests of the log transformed fold changes and procedures to control the false discovery rate, the protein kinase N1 (PKN1) gene was differentially expressed between the two groups (adjusted p-value 0.07).

Conclusions: PKN1 is a novel gene that differentiates between low and high-risk ccRCC. Additional analyses are underway in order to identify additional genes or sets of genes to incorporate into predictive models for RCC.
Endoluminal Real-time Ultrasound Monitoring from Renal Pelvis for Minimally Invasive Nephron Sparing Surgery

Inderbir S. Gill, Jihad H. Kaouk, Mihir M. Desai, Kazumi Kamoi, Osamu Ukimura, Georges-Pascal Haber, Jose R. Colombo Jr, Monish Aron, Benjamin Chung, Nicholas Hegarty, Troy Gianduzzo, Yasuhiro Yamada, Tsuneharu Miki

Objective: Real time monitoring of tumors extending close to the collecting system or renal hilum remains challenge, during minimally invasive nephron sparing surgery (NSS). We hypothetize that trans-renal-pelvic endoluminal ultrasound (US) has the potential to provide detailed real-time visualization of treatment margins close to the collecting system. The aim of this study is to evaluate feasibility of endoluminal US through the renal pelvis.

Methods: Small diameter (2-mm), 12-20MHz wavelength endoluminal ultrasound probe was inserted in the renal pelvis retrogradely. This preliminary study was performed on 9 kidneys, including 8 ex vivo human kidneys with renal cell carcinoma, and one in vivo porcine kidney, with tumor mimic models, treated by percutaneous cryotherapy and LPN.

Results: Endoluminal US, inserted retrogradely, visualized detail anatomy of renal collecting system and tumor, and allowed to measure the tumor size and distance between tumor margin and collecting system as well as renal hilum. Endoluminal ultrasound provided real-time images to place cryoprobe and to monitor iceball formation and extension during cryoablation. Laparoscopic scissors tip was also visualized while performing LPN.

Conclusions: High-frequency trans-renal-pelvic endoluminal US was feasible to demonstrate renal tumor and surgical procedure. This has the potential to provide real-time visualization of treatment margins close to the collecting system and renal hilum, especially for central or hilar renal tumor during minimally invasive nephron sparing surgery.
Evolving Management of Renal Cell Carcinoma with Coexistent Renal Artery Disease

Andrew C. Novick, Steven C. Campbell, John C. Kefer, Khaled Hafez

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=16), 2) bilateral RCC with RAD (n=12), 3) unilateral RCC and contralateral RAD (n=30), 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 ∆Cr was 0.56 ± 0.3, 0.5 ± 0.26, 0.4 ± 0.18, 0.67 ± 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.
Factors Predicting Renal Functional Outcome After Partial Nephrectomy

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

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.
Warm Ischemia >30 minutes and Its Impact on Renal Function after Laparoscopic Partial Nephrectomy

Inderbir S. Gill, Jihad H. Kaouk, Mihir M. Desai, Monish Aron, Georges-Pascal Haber, Jose R. Colombo Jr, Benjamin I. Chung

Objective: To evaluate impact of warm ischemia (WI) > 30 min on renal function following laparoscopic partial nephrectomy (LPN).

Methods: Records of 95 patients who underwent LPN at our center from April 2001 to May 2005, with a WI time >30 min, and had pre-operative and post-operative renal scans, were reviewed. This group was divided into subgroups based on duration of WI (Group I-31-40 min, Group II-41-50 min and Group III->50 min). Overall renal function and split function (evaluated by MAG-3 scan) was assessed in the whole group and in the subgroups.

Results: Mean age in the 95 patients was 61 ± 11.6 years. Mean serum creatinine preoperatively was 1.0 ± 0.4 and postoperatively was 1.3 ± 0.5 mg/dL (p=0.000). Split function of the affected kidney averaged 51.2 ± 10.3% preoperatively and 36 ± 12% postoperatively (p= 0.000). An imperative indication for LPN existed in 47%. Mean WI time in the 3 groups was 34, 43, and 56 minutes respectively. Mean tumor size in the 3 groups was 2.9, 3.5 and 4.7 cm respectively. Mean percentage kidney excised was 23%, 30% and 31%, respectively in the 3 groups. Function of the affected kidney decreased from 52% to 42% in group I, from 50% to 30% in group II, and from 51% to 23% in group III after LPN.

Conclusions: Remnant function worsens as duration of WI increases. Deterioration of function could be attributable to 47% of the contralateral kidneys in the entire group being abnormal and the substantive amount of renal parenchyma (28%) excised.
MRI is Inadequate for Monitoring Renal Tumor Destruction Following Radio Frequency Ablation

Andrew C. Novick, Inderbir S. Gill, Jihad Kaouk, Christopher J. Weight, Nicholas J. Heagerty, Brian R. Lane, Eric Remer

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

Methods: From April 2002 to March 2006, 109 tumors in 88 patients have been ablated with RFA, and from Sept 1997 to Jan 2006, 192 lesions in 176 patients have been treated with cryoablation. Patients were followed with radiographic imaging on post-op day 1, then at 3, 6, and 12 months, and then annually thereafter. Routine post-treatment biopsy was scheduled at 6 months in all healthy, routine cases. Biopsy was not done in those who had other complicating factors such as remnant kidneys, or on anticoagulation.

Results: Radiographic and biopsy follow-up was available in 37 RFA and 97 cryoablation patients at 6 months. Radiographic success was 83.9% and 87.6% for RFA and cryoablation respectively. At six month biopsy, success in RFA dropped to 64.8% while cryoablation was 93.8%. Of those with a positive biopsy after RFA (13) nearly half 6 (46.2%) demonstrated no enhancement on post treatment MRI. In patients treated with cryoablation all positive biopsies demonstrated pre-biopsy enhancement.

Conclusions: MRI is inadequate for determining successful treatment of kidney tumors treated with RFA. We propose that a post treatment biopsy should be added to RFA follow up protocols because a substantial population of patients may have 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, lesions treated with cryotherapy seem to correlate nicely with radiographic findings.
Introduction: We report our experience with anticoagulated (AC) patients undergoing partial nephrectomy (PNx) at our institution, and compare outcomes using a case-matched control group without AC. To our knowledge this is the largest study reporting outcomes for this complex patient population.

Materials and Methods: Since 2000, we performed 30 open and 16 laparoscopic PNx in patients on warfarin, clopidogrel, or cilostazol. Warfarin was held 5 d pre-op with heparin bridging and resumed 8 days post-op. Clopidogrel/cilostazol was held 10 days pre-op and resumed 10 days post-op. Retrospective analysis compared AC patients with 46 controls matched for resection bed size, tumor size, procedure year, surgeon, ischemia time and open or lap PNx. Outcomes were analyzed.

Results: Both groups were well-matched for resection bed size, tumor size, % central tumor, solitary kidney, operative time and warm ischemia time (p ≥0.345 for all). Control patients had significantly higher intraop blood loss (300 versus 200, p<0.05) and postop change in hemoglobin (3.5 versus 2.4, p<0.001) versus AC patients, however, the transfusion rates were similar (7 AC patients, 6 controls, p>0.6). Five AC patients had thrombotic events, versus none in the control group.

Conclusion: AC patients present higher perioperative risks, but with careful perioperative AC management, PNx can be performed safely and effectively.
Laparoscopic Partial Nephrectomy in Solidary Kidney

Inderbir S. Gill, Jihad H. Kaouk, Mihir M. Desai, Jose R. Colombo Jr, Georges-Pascal Haber, Troy Gianduzzo, Monish Aron, Jason Hafron, Robert Stein, Mike Nguyen, Kay Tucker

Purpose: To report our experience with laparoscopic partial nephrectomy (LPN) for tumor in a solitary kidney.

Materials and Methods: Of 430 patients undergoing LPN since February 1999 at our institution, 22 patients (5%) underwent LPN for tumor in a solitary kidney. Our employed laparoscopic technique duplicated open principles, including hilar clamping, “cold-cut” tumor excision, and sutured renal reconstruction.

Results: Mean tumor size was 3.6 cm (1.4 – 8.3; median 3cm), median blood loss 200cc (50 – 500), warm ischemia time 29 min (14 - 55), total operative time 3.3 hrs (2.2 – 4.5), and hospital stay 2.8 days (1.3 – 12). Two patients (9%) were electively converted to open surgery. Pathology confirmed renal cell carcinoma in 16 patients (73%), with negative surgical margins in all LPN cases. Major complications occurred in 3 patients (15%) and minor complications in 7 (32%). Median preoperative and postoperative serum creatinine (1.2 and 1.5mg/dL), and estimated glomerular filtration rate (67.5 and 50 ml/min/1.73m²) reflected a change of 33% and 27%, respectively, which appeared proportionate to the median amount (23%) of kidney parenchyma excised. One patient (4.5%) required temporary hemodialysis. At a median follow-up of 2.5 years (0.5 – 4.5), cancer-specific and overall survival was 100% and 91%, respectively. No LPN patient developed local or port site recurrence, or metastatic disease.

Conclusions: Laparoscopic partial nephrectomy can be performed efficaciously and safely in select patients with tumor in a solitary kidney. Advanced laparoscopic experience and expertise are necessary in this high-risk population.
Percutaneous cryoablation of Kidney Lesions Under Combined Real-Time Ultrasound and 3D CT Scan Navigation

Inderbir S. Gill, Jihad H. Kaouk, Cristina Magi-Galluzzi, Georges-Pascal Haber, Osamu Ukimura, Jose R. Colombo Jr, Erick Remer, Charles O’Malley, Massimiliano Spaliviero

Objective: Accuracy of percutaneous cryoablation for kidney tumors performed under combined real-time ultrasound and 3D CT scan navigation in a porcine model.

Methods: Eleven pigs were divided into an acute group (n=3) and a chronic group (n=8). After injecting 2 tumor mimic lesions in each kidney, a CT scan was performed and digital data was saved in a novel navigation system (RVS®) that allows synchronisation with real-time ultrasound images. The cryoprobe was guided percutaneously into the tumor mimic and the ice ball formation monitored continuously using the RVS® navigation system. Kidneys were sent for macroscopic and histopathologic analysis at day 0 in the acute group, day 15 and day 30 in the chronic group.

Results: Thirty-five renal tumor mimic were treated by percutaneous cryotherapy; tumors locations were: 16 tumors (46%) in the lower pole, 14 (40%) middle pole, and 5 (14%) in the upper pole. Eleven tumors (31%) were intraparenchymal and 24 (69%) subcapsular. The synchronization between the CT scan image reconstruction and real-time ultrasound was successful in all cases. The mean (range) tumor size was 2 cm (1.2 - 4). Mean cryo-necrosis size was 3.3 cm, 3.7 cm, and 2.8 cm at day 0, day 15, and day 30, respectively. Three (8.5%) positive margins were found on the macroscopic and microscopic analysis.

Conclusions: This novel RVS® imaging system synchronizing real-time ultrasound with preoperative CT scan enhance accuracy of probe ablation techniques for kidney tumors. Clinical application is imminent.
A Preoperative Prognostic Nomogram for Solid Enhancing Renal Tumors ≤7 cm Amenable to Partial Nephrectomy

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

Background: 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 most strongly correlated with the likelihood of benign pathology were age, gender, tumor size, and smoking history, and an optimized nomogram constructed to predict benign histology proved to be relatively accurate and discriminating (bootstrap corrected concordance-index (CI) = 0.644). 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 resulting nomogram performed with limited resolution (CI = 0.557).

Conclusion: Clinical factors provide substantial predictive power for benign vs. malignant pathology for SRM amenable to PNx. However, our ability to predict potentially-aggressive cancer in this population remains limited.
Renal Radiosurgery and Sorafenib as Non-Invasive Nephron-Sparing Treatment of Small Localized Renal Masses

Inderbir S. Gill, Monish Aron, Lee Ponsky, Arul Mahadevan, R. Ganapathi, Troy Gianduzzo

Introduction: Radiosurgery allows precise delivery of high-dose radiation with minimal toxicity. The tyrosine kinase inhibitor (TKI) Sorafenib has demonstrated efficacy against metastatic renal cell carcinoma (RCC) in phase 2 trials. In-vitro and in-vivo analyses have demonstrated that TKIs potentiate the effects of ionizing radiation. Herein our initial clinical experience of renal radiosurgery and the potential application of Sorafenib as a radio-sensitizing agent are described.

Materials and Methods: To date, 5 patients with small renal masses (<4cm) have been enrolled in a dose-escalation extracorporeal renal radiosurgery protocol. A CT-guided biopsy is performed followed by placement of 1-2 gold fiducial markers. Renal radiosurgery is delivered in 4 fractions over 2 days following a second planning CT. Patients thus far have received 4-6Gy/fraction, while future patients will receive increasing doses to a maximum total of 48Gy. Radical or partial nephrectomy is performed 8 weeks following radiosurgery treatment.

To assess the application of Sorafenib as a radiosensitizing agent, CAKI-1 (WT VHL) cell lines were irradiated with 200, 400, 600 or 800 rads alone, 10µM Sorafenib alone for 24 or 48 hours or 10 µM Sorafenib for 24 or 48 hours followed by 400 rads radiation. Cells following treatment with Sorafenib and/or radiation were then re-incubated in drug-free medium and cell counts determined after 96 hours.

Results: RCC was confirmed preoperatively in 2 patients. Necrosis was evident in 3 of the 5 excised specimens indicating near-complete cell kill. No radiation-induced toxicity has been observed.

Preliminary in-vitro analysis demonstrated dose-dependant decrease in cell count following irradiation or treatment with Sorafenib. Maximal cell survival was 56% at 400 rads and 26% at 800 rads. 10 µM Sorafenib that represents the mid-range steady-state concentration achieved with a dose of 400mg bid, led to 63% and 23% survival following exposure to 10 µM Sorafenib for 24 and 48 hours respectively. In contrast, in cells pre-treated with 10µM Sorafenib for 24 or 48 hours followed by 400 rads radiation, resulted in survival of 26% and 10% respectively; suggesting a synergistic effect.

Conclusions: Renal radiosurgery may offer an alternative non-invasive approach to the treatment of small localized renal masses. Preliminary in-vitro data suggests possible synergism between radiation and Sorafenib which may enhance the efficacy of renal radiosurgery. Ongoing studies are focused on the mechanistic basis of this synergy and confirming this effect in vivo and in the clinical setting.
Uniformly Benign Clinical Behavior of Classical, Atypical, and Epithelioid Angiomyolipoma in 197 Patients

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

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.
Section 8

Kidney Transplant
Implementing Assessments to Extend the Criterion for Both Deceased and Living Donors of Minority Renal Transplantation Patients

Andrew C. Novick, Charles S. Modlin Jr, Car lumandarlo E. B. Zaramo, Stuart Flech-ner, David Goldfarb, Robert Fairchild

Ideology and Objectives: The use of expanded criteria donors (non-traditional donors) can assist in diminishing the current deficiency of minority kidneys available for transplantation. The use of minority elderly donors has accounted for a great assessment of the increase in the minority organ donation charge; nevertheless, the main considerable issue initiated to impact on minority transplant success negatively conventionally have been revealed to be extremes of donor age and last-hour urine output. Less noteworthy variables affecting minority success rates are typical systolic blood pressure, terminal serum creatinine, and time of hospitalization. With the most suitable collection of minority organs from expanded donors, satisfactory effects can be attained. When minority living donors are selected appropriately, kidneys with anatomic variations devoid of pathologic consequence can be used securely. Kidneys with a sensitive prospective for the advancement of progressive disease should not be transplanted. Efforts to reduce the cold ischemia time by escalating the use of kidneys from expanded minority criterion donors may advance the result of minority transplantation further.

Conclusions: Clinical enhancement in surgical procedures, perpetuation solutions, and processes for expected ultimate long-term renal function in kidneys from expanded minority donors will be vital in permitting exact assortment criterion for kidneys for minority transplantation, consequential in the optimal use of a inadequate and valued source. Pending alternative such as xenotransplantation expand into clinically practical use; the dare will be to recognize which minority donor organs formerly considered sub-advantageous can be used carefully to expand the minority organ donor pool.
Nomogram to Predict Renal Function and Graft Survival in Living Donor Kidney Transplantation Based Upon the UNOS Registry

David A. Goldfarb, Michael W. Kattan, Emilio D. Poggio, Joan M. Alster

Introduction: Living donor kidney transplantation has increased significantly in past 10 years and, when available, it offers improved graft and recipient outcomes. Some recipients are fortunate in having many different potential living donors. In this circumstance clinicians are asked to identify the best suitable donor. Historically this judgement was weighted heavily in favor of HLA matching criteria. Currently, it is appreciated that many variables need to be assessed when determining transplant outcome (donor age, size, kidney size, donor GFR). There are limited tools to quantitatively predict outcomes in living donor transplantation. The purpose of this project is to develop nomograms that predict transplant renal function at 1 year (as defined by 4-variable MDRD equation[eGFR]), and graft survival at variable times following transplant.

Methods: Data regarding living donor transplants was obtained from the UNOS registry for the years 2000 to 2003. Two nomograms were designed – one to predict 1 year eGFR based on information known about donor and recipients before the transplant. A second nomogram was constructed to predict 5 year graft survival based on information known not only prior to the transplant but, additionally on significant events that have occurred during the first 6 months after transplantation (delayed graft function, any episode of rejection and 6 month eGFR). Pre-transplant nomogram predictors for recipients included: age, gender, BSA, BMI, height, weight, race, primary renal disease, induction therapy, use of MMF, rapamycin, and /or calcineurin inhibitors. Pre-transplant donor predictors include: weight, height, BSA, BMI, creatinine, HLA mismatch, age, gender, race, donor/recipient relationship, type of procedure(open v. laparoscopic). For the dynamic prediction of 5-year graft survival additional predictors include delayed graft function, any rejection episode in 6 months and the 6 month eGFR. Nomograms were constructed on the basis of a Cox regression model which was internally validated. The concordance index was used as a discrimination measure, with bootstrapping to correct for optimistic bias. Calibration plots were constructed.

Results: The correlation for the renal function nomogram is an r-squared of 0.169. It worked best for eGFR values between 50-70 ml/min. For the dynamic nomogram predicting 5-year graft survival, the bootstrap-corrected concordance index was 0.769. Calibration appeared adequate. This compares favorably with other published nomograms.

Conclusions: A nomogram was developed to predict 1 year eGFR based on information known prior to transplantation. Additionally a nomogram was developed to predict 5 year graft survival of recipients of living donor kidneys based on information known at the time of transplant and also on several important transplant related events occurring in the first 6 months. These tools will be valuable for transplant professionals counseling living donors and recipients, and could be incorporated into clinical trial design.
Percutaneous Radiofrequency Ablation of a Tumor in a Transplanted Kidney

Andrew C. Novick, Inderbir S. Gill, Jihad H. Kaouk, Monish Aron, Nicholas J. Hegarty, Charles O’Malley, Erick Remer

Introduction: We present the management of a patient who underwent percutaneous radiofrequency ablation (RFA) of a 3.2 cm RCC in a renal allograft.

Methods: A 53-year old female who had undergone a renal transplant in 1993 presented with hematuria in March 2004. A CT scan revealed a 5-cm enhancing mass in the right native kidney and a 3.2-cm enhancing mass in the interpolar region of the allograft kidney. A radical nephrectomy of the native kidney was performed and histopathology confirmed papillary RCC. A CT-guided percutaneous RFA of the allograft tumor was performed in June 2004 using a 25 cm Starburst semi-flexible ablation probe. Percutaneous needle biopsy at the time confirmed papillary RCC.

Results: She was followed up with 3-monthly MRI and needle biopsy at 6-months. The 6-month MRI showed a non enhancing 3.7 x 3.0 cm ablated area, although the needle biopsy at this time revealed fragments of a papillary RCC, grade 2. Repeat CT guided percutaneous RFA was performed in February 2005. MRI at 3, and 6 months revealed no enhancement, and a reduction in size of the mass to 2.1 x 1.9-cm. Percutaneous needle biopsies from this post-RFA lesion at 6-months did not reveal any residual tumor in September 2005. At 1-year follow-up the patient is asymptomatic and serum creatinine is stable at 1.5 mg/dL.

Conclusions: We conclude that percutaneous RFA is a viable nephron-sparing treatment option for RCC in a renal allograft. The follow-up should be diligent and include needle-biopsy confirmation of non-enhancement on imaging.
Section 9

Pediatric
Pre and Post-natal Management of a Unilateral Ureterocele Associated With Bilateral Hydronephrosis and Oligohydramnios

Jonathan H. Ross, Hadley M. Wood, Jack S. Elder

Prenatal hydronephrosis is documented in about 0.2% of high risk pregnancies (1). Ureteroceles are associated with duplicated collecting systems in most cases, and most often associated with the ureter upper pole moiety. About three-quarters of ureteroceles are diagnosed via prenatal ultrasound (US) (2). Often, the fetus is managed expectantly, with incision of the ureterocele or partial nephrectomy of the nonfunctional moiety after birth. When antenatal testing suggests that the condition is causing potentially irreversible damage, fetal decompression of the ureterocele via laser or puncture or placement of a vesicoamniotic shunt has been implemented (3). This case details such a case.

**Prenatal Course:** A 28-week GA fetus was noted to have a large right-sided ureterocele, double right hydroureter, and left sided hydronephrosis on routine US. Although an US 10 days prior revealed normohydramnios, the fetus had progressively become oligo-, then anhydramiotic. The mother, a 32 year-old G1 opted for vesicocentesis. This was done using a method coined the “colander” method, whereby multiple punctures are made in the ureterocele in the fashion of holes in a colander. The procedure was tolerated well and normalization of the amnio-fetal index and flattening of the ureterocele was noted until 37 weeks, at which time the fetus was delivered vaginally without complication (4).

**Perinatal Course:** An US done immediately after delivery demonstrated left lower pole hydronephrosis, a decompressed ureterocele, and right hydronephrosis. The patient was immediately started on Amoxicillin 1.4 cc daily and voided on day of life 0.

**Postnatal Course:** Follow up at 1 week of life included an US, which demonstrated findings similar to one week prior. VCUG demonstrated Grade V reflux on the left and no reflux on the right. By 5 weeks of life, Cr = 0.6 mg/dl and a diuretic renal scan demonstrated left-sided differential function of 28% with a T1/2 = 39.5 minutes. The patient was followed with serum creatinine, renal ultrasounds and VCUGs for the next year and a half. She experienced no breakthrough infections during this period. All studies demonstrated stabilization of the problem during this period. At age 19 months, a VCUG again demonstrated improved grade V reflux but a left kidney that was smaller in size when compared with prior. A diuretic renal scan demonstrated a differential function on the left of 26% with T1/2 of 6.3 and 6.1 minutes on the left and right, respectively. Given the failure of the reflux to improve and the inevitability of this patient’s course, surgery was recommended. At 23 months, the patient underwent cystoscopy with excision of ureterocele and left ureteral reimplantation. Follow up is currently ongoing.
We present a case of prenatally-diagnosed bilateral hydronephrosis and right-sided ureterocele, where the contralateral hydroureteronephrosis persisted despite incision of the ureterocele and remained stable for over a decade, suggesting the etiology of the contralateral hydroureteronephrosis to be congenital megaureter.

**Prenatal Course:** A 15 yo G1P1 demonstrated no abnormalities on routine screening at 17 weeks, however, follow-up ultrasound for preterm labor at 31 weeks demonstrated bilateral hydronephrosis and a ureterocele with normal AFI. The patient was followed closely with serial sonography and mild oligohydramnios was noted beginning at 34 weeks GA (AFI=12.4). All other parameters, including biophysical profiles and fetal measurements, remained normal throughout the remainder of the pregnancy. The ultrasound 2 days prior to delivery demonstrated right renal pelvic dilation measuring 8.0 cm and left renal pelvic dilation measuring 5.1 cm. The patient was managed expectantly until 38 weeks GA, when labor was induced. The child was delivered by Cesarean section secondary to failed progression of labor. Family history was significant for renal agenesis in a paternal aunt.

**Perinatal Course:** Birth weight was 3,200 gm. An ultrasound after birth confirmed bilateral hydroureteronephrosis with right parenchymal atrophy with complete ureteral duplication on the right and a ureterocele in the right bladder. The bladder was catheterized at 24 hours for low urinary output. VCUG revealed Grade V reflux of the right lower system and no contralateral reflux. The VCUG also demonstrated bladder neck hypertrophy and a question of the presence of posterior urethral valves. Renal nuclear scan demonstrated a nonfunctioning right kidney. SCr remained stable from birth at 0.7 mg/dL. Ampicillin prophylaxis was initiated. The patient underwent transurethral incision of right ureterocele on DOL6.

**Postnatal Course:** The patient developed Klebsiella urosepsis at 2 weeks. A VCUG was repeated, which did not demonstrate reflux, despite the presence of right-sided reflux 2 weeks earlier. It was felt that the atrophic right kidney may be contributing some fluid to the ureterocele, thereby obstructing the left ureteral orifice, and contributing to left hydronephrosis. The patient underwent an uncomplicated right nephrectomy at 12 weeks. A 3-month follow-up U/S and VCUG demonstrated persistent hydronephrosis on the left with a tortuous, dilated single left ureter. Nine- and 12-month follow-up ultrasounds demonstrated a decompressed ureterocele and unchanged ureteral dilation. The left kidney ap-
Pediatric

peared to be growing. Consideration was given to whether the ureterocele may be prolapsing into the bladder neck with voiding, contributing to outlet obstruction. A DTPA Lasix scan demonstrated a T1/2 = 10 minutes, consistent with a non-obstructive pattern. The patient was followed at 6-month, then 1-year intervals with serial radiographic studies (ultrasonography, VCUG and nuclear imaging, as appropriate) for the next 10 years. Although the patient demonstrates some voiding dysfunction, hydroureteronephrosis has remained stable, suggesting the presence of congenital megaureter. Serum Cr remains stable at 0.7 mg/dL.

**Discussion:** Bilateral hydronephrosis is detected in __ % of pregnancies who undergo routine prenatal screening with ultrasound. The causes of such hydronephrosis include: bilateral UPJO, bilateral VUR, posterior urethral valves or urethral obstruction, ureterocele with obstruction of the contralateral ureteral. Megaureter is defined as a dilation of the distal ureter greater than 1 cm (Fefer, 2006) and occurs with 3-4-fold greater frequency in boys (Williams, 1970 – in Fefer). Primary megaureter is thought to originate from dysfunction of peristalsis of the distal ureter and is most often unilateral, although does occur bilaterally (references). In a nonobstructive, nonrefluxing system, such as the one described in this case, megaureter can be managed conservatively.
Patients with Prenatally Detected Ureteropelvic Junction Obstruction are More Likely to Undergo Pyeloplasty when there is Associated Vescoureteral Reflux

Jonathan H. Ross, Ibrahim Karnak, Lynn L. Woo, Shetal N. Shah, Arlene Sirajuddin

Introduction/Objective: Ureteropelvic junction obstruction (UPJO) is the most common cause of prenatally-detected hydronephrosis. We reviewed the occurrence of associated anomalies and outcomes in a consecutive series of such patients managed according to a standardized protocol. In reviewing this data, we identified a correlation between the presence of vescoureteral reflux (VUR) and the likelihood of undergoing pyeloplasty. We reviewed these cases in detail to further understand this association.

Methods: We retrospectively reviewed the records of all children diagnosed with UPJO based on prenatally-detected hydronephrosis, including those with and without associated VUR. The results of radiographic studies, clinical parameters and outcomes were assessed for both groups.

Results: Of 143 children with prenatally diagnosed UPJO, VUR was found in 11 patients (8%). Male:female ratio was 2.7. UPJO was more frequently left-sided (n=8), and 2 patients had bilateral lesions. Hydronephrosis was grade 4 in 7 renal units (RU), grade 3 in 5 RU, and grade 2 in 1 RU. It resolved (n=1), improved (n=3) or remained stable (n=1) in 5 cases. Of the 11 patients, VUR was detected in a total of 15 RU (grade I in 10 RU, grade II in 4 RU and grade V in 1 RU). VUR contralateral to the side of UPJO occurred in 7 patients. Pyeloplasty was performed in 6 RU for decreasing renal function (n=3), flank pain (n=1), or parental preference in the presence of prolonged washout on renal scan (n=2). Ureteroneocystostomy was ultimately required in 2 RU. The presence of VUR was not considered an indication for pyeloplasty. 54% of children with associated reflux underwent pyeloplasty compared to 18% of children without reflux (p=0.01).

Conclusion: In this series, children with VUR were more likely to undergo pyeloplasty for prenatally-detected UPJO, although the presence of reflux was not considered an indication for intervention. While this finding might be due to a greater likelihood that parents will elect repair in the face of concomitant reflux, or to a higher probability of symptoms in patients with reflux, it is also possible that the presence of one ureteral anomaly (reflux) increases the likelihood that another (UPJ obstruction) will become clinically significant. Confirmation by larger studies may argue for early pyeloplasty in cases of prenatally-detected ureteropelvic junction obstruction associated with vescoureteral reflux.
Prenatally-diagnosed UPJ Obstruction with Unappreciated Ipsilateral Ectopic Ureter in a Functionally Solitary Kidney

Jonathan H. Ross, Lynn L. Woo, Hadley M. Wood

Introduction: We present a case of prenatally-detected ureteropelvic junction obstruction (UPJO) and an unappreciated ipsilateral ectopic ureter in a solitary functioning dysplastic kidney.

Abstract: Bilateral hydronephrosis was detected on prenatal ultrasound (US) at 17 and 21 weeks in a 30 year old primagravida.

A male infant weighing 2898 g was delivered at 37.5 weeks gestation by vaginal delivery. US on day 6 demonstrated severe left hydronephrosis consistent with UPJO along with bilateral renal dysplasia - worse on the right. VCUG was normal. Significant renal impairment with hyperkalemia and acidosis was observed shortly after birth, and left pyeloplasty was performed on day 10. A 4 cm segment of the proximal left ureter was found to be nearly obliterated and was resected at the time of pyeloplasty. Resistance was encountered with attempted passage of the stent into the bladder. A ureteral stent was placed across the anastamosis, and a percutaneous nephrostomy tube was left in place. Improvements were seen in serum creatinine (SCr), electrolytes, and acidosis, however renal function was not fully restored.

Post-operative nephrostogram demonstrated good result from the pyeloplasty and a previously unappreciated ectopic left ureter inserting into the bulbous urethra. Renal scan demonstrated 83% of total renal function coming from the left kidney and poor clearance of contrast from the left kidney. However the quality of the study was limited by poor renal function. The patient tolerated nephrostomy tube clamping without change in SCr or hydronephrosis, and the tube was removed. At one year of age, the patient underwent left ureteral reimplantation. He did well post-operatively but, due to dysplasia, renal function deteriorated and the patient ultimately underwent a living related kidney transplant.

Discussion: While ureterography is not routinely obtained in the evaluation of hydronephrosis, it should be considered in patients with renal dysplasia and an apparent UPJ obstruction.
Timing for the Development of Urethrocutaneous Fistulae after Hypospadias Repair

Jonathan H. Ross, Robert Kay, Hadley M. Wood

Urethrocutaneous fistulae (UCF) commonly occur following hypospadias repair (HR). While many UCF are detected immediately post-operatively, some may present years after HR.

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

Methods: This study is a retrospective review of all pts seen with UCF following HR from 1995 - 2005. The following information was collected: age at HR, level of hypospadas, type of HR, time at which UCF was noted, date/type of UCF repair, time at which recurrent UCF was noted, date/type of 2° repair, date of last follow up (F/U).

Results: Of 26 pts, 15 had ≥1 operation at another institution. 14/26 pts developed 2° UCF and 6 developed 3° UCF. Level of hypospadas was: unknown in 6, proximal in 8, midshaft in 4, and distal in 8. Time between HR and 1° UCF and time between UCF repair and recurrence are presented in Tables 1&2. After HR, 58% of pts with UCF presented at <1 mo, while 61% of pts with recurrent UCF presented <1 mo after 1° UCF repair. However, 23% of the pts who developed UCF presented >2 years after initial HR. Only 5.5% of 2° UCF occurred >12 mos after UCF repair. 12/26 pts had HR at <1 yr and 5/26 at ≥2 yrs of age. Age of presentation with 1° UCF was: 0-1 yr (N=5), 1-2 yr (N=6), 2-3 yr (N=6), 3-4 yr (N=2), >4 yr (N=7). Mean F/U was 5.5 mos (0-69 mos).

Conclusion: While many UCF occur immediately after HR, 23% of UCF were observed >2 yrs after HR suggesting that that rates of late UCF may be underestimated and longer F/U may be warranted.
Results of a Conservative Protocol for the Management of Prenatally-Diagnosed Hydronephrosis Secondary to Ureteropelvic Junction Obstruction

Jonathan H. Ross, Lynn L. Woo, Ibrahim Karnak, Shetal N. Shah, Arlene Sirajuddin

Introduction and Objective: Several algorithms for the management of prenatally-diagnosed hydronephrosis due to ureteropelvic junction obstruction (UPJO) have been previously reported. We utilize a conservative protocol with an emphasis on surveillance and less frequent use of renal flow scans (RFS). We sought to determine the outcomes of children with congenital UPJO, managed according to this approach at our institution.

Methods: The records of 143 children with prenatally-detected UPJO managed at our institution were reviewed. Radiographic and clinical data, treatment, and outcomes were examined. Patients were evaluated initially in the neonatal period with ultrasound (US), voiding cystourethrogram (VCUG), and RFS. The follow-up protocol entailed interval US with repeat RFS reserved only for patients with worsening hydronephrosis or non-improving hydronephrosis on US after 1 year.

Results: 143 children with a total of 198 renal units (RU) were followed in this study. Male:female ratio was 2.7. UPJO was unilateral in 61%, occurring more frequently on the left (68%). Initial US grade of hydronephrosis was grade 1 in 44% RU, grade 2 in 13%, grade 3 in 20%, and grade 4 in 23%. 178 RU were followed conservatively, while pyeloplasty was the initial therapeutic approach in 20 RU. Mean age at the time of surgery was 16±14 weeks. Operative indications included decreasing renal function (12 RU) or lack of tracer clearance (2 RU) on RFS, parental preference (n=3), and acute renal failure (n=3). Postoperative course was uneventful during 33.43±33.53 months (range: 2-120) with favorable US and RFS results. In conservatively-managed patients, mean follow-up time was 14.94±14.35 months (range: 1.5-142). Spontaneous resolution of hydronephrosis was observed in 49% RU, while 6% eventually required surgery for worsening appearance on US and/or function on RFS (n=8), pain or infection (n=3), and/or parental preference due to persistently prolonged T1/2 (n=4). 40% of RU remain under continued surveillance with improvement or stable HN in 94%. 5% of RU were lost to follow-up.

Conclusions: The majority of children with UPJO can be successfully managed with conservative surveillance. Spontaneous resolution of hydronephrosis and/or favorable prognosis were encountered in 87% of conservatively-followed RU. The use of a standardized grading system for hydronephrosis on interval US, selective utilization of repeat RFS, and parental compliance are important factors in the successful management of prenatally-detected UPJO.
Prenatally-Detected Uretero Pelvic Junction Obstruction: Clinical Features and Associated Urologic Abnormalities

Jonathan H. Ross, Lynn L. Woo, Ibrahim Karnak, Shetal N. Shah, Arlene Sirajuddin

Introduction/Objective: Urologic congenital anomalies associated with ureteropelvic obstruction (UPJO) have been previously characterized, however little data are available regarding these associations in a prenatally-diagnosed population. A retrospective study was conducted to evaluate significant clinical features and urological anomalies associated with prenatally-diagnosed UPJO.

Methods: The records of 143 children with prenatally diagnosed hydronephrosis secondary to UPJO were retrospectively reviewed. The gender, side of obstruction, degree of hydronephrosis, associated clinical features and urological anomalies were noted.

Results: 143 children (M/F=2.7) with a total of 198 affected renal units (RU) presenting with unilateral (61%) or bilateral (39%) UPJO were enrolled. In cases of unilateral obstruction, the left side was affected in 60 children (68%). The grade of hydronephrosis was Grade 1 in 56 RU (28%), Grade 2 in 51 RU (26%), Grade 3 in 50 RU (25%) and Grade 4 in 41 RU (21%). Associated clinical features included prematurity (n=7, 4.9%), twinning (n=5, 3.5%) and presentation with renal failure (RF) (n=2). Excluding contralateral UPJO, other urologic anomalies were encountered in 29 patients (20.3%). Associated vesicoureteral reflux (VUR) was encountered in 11 patients (7.7%, M/F=2.7). Pyeloplasty was required more often in children with associated VUR (54.5% vs. 18.2%) (p=0.01). Contralateral multicystic dysplastic kidney (MCDK) was encountered in 6 patients (M/F=2), one of whom presented with renal failure (RF). One child carried the diagnosis of Schinzel-Giedion syndrome (SGS), demonstrating severe developmental and neurological disorders and bilateral hydronephrosis.

Conclusions: The more frequent occurrence of UPJO in males with predominantly left-sided location, association with VUR and MCDK, and increased frequency of bilaterality in our prenatally-diagnosed patients were similar to historical reports. In addition, prematurity and twinning were independently associated with UPJO. The higher rate of pyeloplasty in patients with associated reflux warrants further investigation.
Section 10
Reconstructive Surgery
Technical Modifications of the Laparoscopic Boari Flap

Inderbir S. Gill, Jihad H. Kaouk, Mihir M. Desai, Amr F. Fergany, Matthew N. Simmons

Objective: To describe technical modifications to the laparoscopic Boari flap ureteroneocystostomy procedure.

Materials and Methods: Laparoscopic Boari flap operations conducted at our institution were retrospectively reviewed. Technical modifications were identified. Surgical illustrations and photographs were prepared to illustrate aspects of the operation aimed at improvement of outcome.

Results: An improved scenario for anastomotic healing is facilitated by adhering to specific dimensional ratios during excision of the flap. A modification to the Boari flap mucosa facilitates fashioning of a widely patent anastomosis, and adds an additional means to fortify the suture line and promote healing. A 2 mm port is helpful for intra-operative placement of ureteral stents. Furthermore, removal of ureteral stents prior to surgery can improve ureteral tissue quality.

Conclusions: Laparoscopic Boari flap ureteroneocystostomy is becoming a main-stay treatment of distal ureteral stricture disease, and its efficacy rivals that of open surgery. These modifications contribute to the future success of this procedure.
Laparoscopic Ureteral Reconstruction for Benign Disease

Inderbir S. Gill, Jihad H. Kaouk, Mihir M. Desai, Amr F. Fergany, Matthew N. Simmons

Objective: To describe our experience with laparoscopic ureteroureterostomy, Boari flap, and ureteroneocystostomy in the adult patient with benign ureteral disease.

Materials and Methods: We retrospectively compared adult patients undergoing laparoscopic and open ureteral reconstruction over a 6-year period (January 1999 to November 2005). All patients underwent surgery with the primary intent of alleviating chronic obstruction. Demographic, operative, complication, and outcome data were analyzed and compared.

Results: Patient demographics, and ureteral stricture location and length were equivalent between the open and laparoscopic groups. Etiology of stricture disease was similar in both groups. The open surgical group had higher operative blood loss (258 ml vs. 86 ml; p=0.002) and longer hospital stay (median 5 days vs. 3 days; p<0.001). Complications were categorized using a standardized 5-tiered grading system. Overall complication rates in open and laparoscopic groups were 15% and 8%, respectively (p=0.225). Patency success was equivalent in both groups with one restructure event in the open group and none in the laparoscopic group. The mean follow-up intervals were 34 months for the open group and 23 months for the laparoscopic group (p=0.563).

Conclusions: Laparoscopic ureteroureterostomy and ureteroneocystostomy is technically feasible and efficacious in treating benign ureteral obstructive disease. This technique can be utilized in an adult patient population, and provides several advantages over open surgery.
Percutaneous Nephrostolithotomy in Patients on Anticoagulation Therapy

Mihir M. Desai, John C. Kefer, Stevan B. Streem, Nicholas Hegarty

**Introduction:** We report our results from 15 anticoagulated (AC) patients undergoing PCNL and compare them to a contemporary matched cohort of patients undergoing PCNL without any anticoagulation.

**Methods:** Since 2002, we performed PCNL on 15 patients with large volume calculus disease on AC therapy (Coumadin, Plavix) for various indications. Coumadin was stopped 5 days preoperatively and resumed at regular dose 5 days postoperatively with Lovenox bridging in the interim. Plavix was stopped 10 days preoperatively and resumed 5 days postoperatively. The groups were matched for procedure year, stone burden, and number of access tracts. Both groups were compared for change in hemoglobin (Hb), hematocrit, creatinine, and complications.

**Results:** Mean stone burden for AC and controls was 12.4 (1.7-49)cm$^2$ and 11.9 (3.2-49)cm$^2$, respectively. Mean Hb drop was 1.7(0-4.1) g/dL and 1.6(0.4-2.9) g/dL and increase in Cr was ± 0.28(.1-.4), and ± 0.21(.1-.7), respectively. In the AC group there were no bleeding complications and no patient required transfusion. Two control patients required transfusion postoperatively.

**Conclusion:** With careful perioperative regulation of anticoagulation therapy and clotting parameters, PCNL can be performed safely and efficiently in patients on anticoagulation therapy.
Laparoscopic Versus Open Dismembered Pyeloplasty in a Solitary Kidney

Inderbir S. Gill, Jihad H. Kaouk, Mihir M. Desai, Hadley M. Wood, Justin Albani, Stevan B. Streem

Objectives: To present our experience with laparoscopic pyeloplasty (LP) in a solitary kidney and compare outcome data with open pyeloplasty (OP) in a solitary kidney.

Methods: From 2000-2005, we have performed LP on 145 patients. Of these 9 (6.2%) involved a solitary kidney. One patient was excluded because she expired shortly after surgery of an unrelated cause. All OPs and endopylottomies conducted since 1989 were reviewed (N=250). Of these, 6 (2.5%) involved a solitary kidney and were managed by OP. Peri-operative factors, including operative blood loss (EBL), duration of surgery, use of narcotics, length of hospital stay (LOS), and need for transfusion. Post-operative outcomes in pain, creatinine clearance, and post-operative imaging were also evaluated. Success was strictly defined as symptomatic improvement, stabilization of Cr and improvement of drainage on postoperative imaging.

Results: LP was technically successful in all 9 patients without need for open conversion. Mean in-hospital narcotic analgesic requirement for LP patients was 172 mg IV morphine equivalents (34.5-639.5). Epidural analgesia was employed with most of the OP patients, making a comparison of narcotic use difficult. Summary data for the two groups are presented in the table below. Comparisons were made using a two-tailed t-test. Complications for LP included: 1 pt received a 2 unit blood transfusion on POD1, 1 pt was seen in the ER for pain control 3 days after discharge, 1 pt had an umbilical incisional hernia repaired 18 months after surgery. In the LP vs OP groups, preoperative CrCl (82 vs 55 mL/min) (p=0.17) and postoperative CrCl (70 vs 62 mL/min) were similar (p=0.58).

<table>
<thead>
<tr>
<th></th>
<th>LP (N=8)</th>
<th>OP (N=6)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>50.5 (24-78)</td>
<td>47 (27-76)</td>
<td>NS</td>
</tr>
<tr>
<td>EBL (cc)</td>
<td>120 (10-450)</td>
<td>150 (25-280)</td>
<td>NS</td>
</tr>
<tr>
<td>OR time (hrs)</td>
<td>5.1 (3.5-8.4)</td>
<td>4.6 (4.0-4.75)</td>
<td>NS</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>2.75 (2-4)</td>
<td>5.7 (3-9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Pre-op pain</td>
<td>7 of 8 patients</td>
<td>3 of 6 patients</td>
<td></td>
</tr>
<tr>
<td>Post-op pain</td>
<td>1 minor</td>
<td>3 (2 minor/1 severe)</td>
<td></td>
</tr>
<tr>
<td>Duration of F/U (mos)</td>
<td>21 (2-59)</td>
<td>34 (3-97)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusions: LP compares favorably with OP in solitary kidneys, with shorter hospital stay, and similar duration of surgery, intraoperative blood loss, improvements in painful symptoms, and post-operative CrCl.
Routine Transposition of Anterior Crossing Vessels During Laparoscopic Pyeloplasty: Is it Necessary?

Inderbir S. Gill, Monish Aron, Mihir M. Desai, Georges-Pascal Haber, Jose R. Colombo Jr

Purpose: To assess need for routine transposition of an anterior crossing vessel during dismembered laparoscopic pyeloplasty.

Materials and Methods: We reviewed data from 70 patients undergoing laparoscopic pyeloplasty at our institution from March 2000 to December 2004 for ureteropelvic junction obstruction (UPJO). An anterior crossing vessel was identified intraoperatively in 31 patients (44%). The decision to transpose was made by the surgeon’s intraoperative assessment of the obstructive nature of the vessel. Outcomes between the groups undergoing transposition of the vessel (n=8) were retrospectively compared to the group not undergoing transposition (n=23). Success was defined strictly as significant improvement or complete resolution of symptoms and evidence of improved drainage on diuretic renogram or urography imaging.

Results: All 31 patients had resolution of obstruction. There was no statistically significant difference between the two groups with regards to pre-operative and post-operative differential function and t_{1/2} on diuretic renogram. However, there was a significant difference in the laparoscopic approach between the two groups. The majority of patients in whom the vessel was transposed underwent transperitoneal laparoscopic pyeloplasty (87.5% vs. 12.5%). In contrast, the majority of patients in whom the vessel was not transposed underwent retroperitoneoscopic pyeloplasty (73.9% vs. 26.1%). As such, only 1 of 18 (5%) of patients treated retroperitoneally received a transposition compared to 7 of 13 (54%) of patients operated transperitoneally.

Conclusions: Routine transposition of an anterior crossing vessel may be unnecessary. The decision to transpose appears to be governed by the subjective assessment of the surgeon and the choice of laparoscopic approach to facilitate ease of reconstruction.
Section 11

Basic Science
Test, Re-Test Reliability, and Development of an Automated System for Assessment of Bladder Autonomic Sensory Function in a Novel Animal Model

Firouz Daneshgari, Elliott J. Rouse, Yasuhiro Yamada, Guiming Liu, Robert Abouassaly, Fernando Casas

Introduction and Objectives: We have previously reported on development of a device to measure the bladder sensory perception threshold (BST) in rats using the Neurometer®. In this model, the afferent fibers Aβ, Aδ, and C are stimulated using frequencies of 2000 Hz, 250 Hz, and 5 Hz, respectively. In our previous work we have used the animal’s startle movement as indication of response to stimuli. Others and we have also observed that animal vocalization correlates to stimuli intensities. Presently, evaluation of the BST is done manually. The aims of our study were: a) to test the inter and intra-reader reliability of the BST assessment, b) to enhance the user friendliness of the device by developing and integrating an automated audio data collection and analysis system capable of interfacing with the Neurometer®.

Methods: The LabView-based computerized system featured ultrasonic audio data collection and signal analysis for vocalizations up to 60 kHz. Hardware included an ultrasonic microphone and signal conditioning amplifiers. Parameters for each trial such as stimuli amplitude and time evolution were defined using the interface and relayed to the Neurometer®. Real-time audio data captured from the microphone, its spectral decomposition, and the stimuli parameters were displayed graphically and stored for analysis. BST values from 6-8 weeks old female, Sprague-Dawley rats (n=5) were acquired by 2 observers at 2 different times. Electrodes were implanted in the bladder mucosa 7 days prior to measurement. The animals were positioned in an acrylic tube to limit movement. A total of 108 BST measurements were collected. The observer’s results were concealed from each other.

Results: The overall Spearman’s correlation coefficient in the measurement of the BST values by the two observers was $r=0.975$ ($p<0.001$). A paired t-test revealed no statistically significant differences between all the BST values measured by two observers (Aβ-fibers $p=0.975$, Aδ-fibers $p=0.181$, C fibers $p=0.50$).

Conclusion: These results indicate that a) our novel method of testing the bladder sensory function has an acceptable reliability and internal validity; b) the automated system can successfully manipulate the Neurometer®, and capture all test data during the determination of the BST in a fully automated fashion. These steps are prerequisites for our animal model to be available to other laboratories.
Anatomical and Electrophysiological Assessment of the Canine Prostate and Neurovascular Anatomy: Suitability as a Nerve-Sparing Radical Prostatectomy Model

Inderbir S. Gill, E El-Gabry, Troy Gianduzzo, Jose R. Colombo Jr, Georges-Pascal Haber

Introduction: The canine is oft-used as a radical prostatectomy model, however precise anatomical and electrophysiological (EP) details of canine neurovascular bundle (NVB) anatomy are lacking. Herein the anatomical and EP features of the canine prostate, pelvic plexus and NVBs are described to establish its suitability as a radical prostatectomy research model.

Materials and Methods: Each penile corpus was cannulated and the intracavernosal pressures recorded in 12 dogs. Pelvic plexus branches were individually identified and stimulated using a Cavermap® probe, and the peak intracavernosal pressure (ICP) response recorded as a percentage of mean arterial pressure (ICP%MAP). Histological assessment was performed in 6 dogs.

Canine pelvic plexus branches and prostate

Results: The prostate mean weight was 35.3 (range 6-62)g, measuring 30.3 (range 7-45)mm in transverse dimension, 24.7 (range 7-40)mm longitudinally and 25.8 (range 12-40)mm in sagittal dimension. The pelvic plexus (PP) is located 5-10mm lateral to the prostate base. In 1 dog, no discernible plexus was present and a branch from the pelvic nerve joined the hypogastric nerve directly. The PP is supplied by the hypogastric nerve (HN) cranially and the pelvic nerve (PN) laterally. A vesical branch (VB) courses toward the bladder from the PP. Prostato-vesical branches (PVB) course to the prostato-vesical junction. Some of these then run forward along the posterolateral aspect of the prostate as the NVBs. A dominant cavernous nerve (CN) (2-5mm diameter, 3-6 cm length) courses distally from the PP along the lateral aspect of the NVB. Cavermap stimulation of the individual efferent PP branches confirms their erectogenic roles. (median ICP%MAP: HN 33.5%, PN 92%, PVB 95.5%, CN 95%). The HN had a significantly lower ICP rise (P<0.001) indicating its sympathetic supply. Histological analysis demonstrated neural and vascular tissue along the posterolateral aspect of the prostate beneath the lateral prostatic fascia as far laterally as the CN.

Conclusions: The canine neurovascular anatomy closely resembles that of the human and is a suitable model to assess prostatectomy related erectile dysfunction. Particularly the dominant CN may be useful for specific study of cavernous nerve function and nerve grafting techniques.
The Effect of Intravesical Resiniferatoxin, Oxybutynin, and Lidocaine on the Afferent Autonomic Bladder Sensory Threshold in Rat

Firouz Danesghari, Yoshiro Yamada, Guiming Liu, Osamu Ukimura

Introduction and Objective: Clinical efficacy of intravesical administration of Resiniferatoxin (RTX), Oxybutinin and Lidocaine have been reported. However, mechanisms of effects of these pharmacological agents remain unknown. Recently we have developed a novel animal model that allows assessment of bladder sensory function using Neurometer®. The aim of this study was to evaluate effect of intravesical RTX, Oxybutynin, and Lidocaine on the sensory bladder thresholds (BST) in rats.

Methods: A total of 28 female Sprague-Dawley rats were used. We implanted our newly developed device in the bladder. The Neurometer® was used to apply sine-wave electrical stimulation at 250 Hz and 5 Hz (selective for A-delta and C-fibers, respectively) at increasing intensity until a startle response of the animal was observed. The minimum intensity, at which that response was seen, was defined as BST. Three days after implantation, RTX, Oxybutynin, Lidocaine or saline was instilled intravesically. Conscious BST measures were recorded prior to administration and at 1 and 24 hours post-instillation.

Results: Intravesical Oxybutynin and saline did not affect the BST values at either 250 or 5 Hz. A significant increase in BST was observed 24 hours post-instillation of RTX at a stimulus frequency of 5Hz (p=0.028). One hour post-instillation of Lidocaine, a significant increase in BST was observed at frequencies of 250 and 5 Hz (p=0.028, and p=0.028, respectively), however, 24 hours post-instillation BST returned to near baseline values.

Conclusions: We were able to assess fiber-selective responses of bladder afferent pathways by measurement of bladder sensory threshold. Our animal model could be used for assessment of afferent bladder pathways in various pathological conditions, as well as for evaluating the effect of therapeutic agents on afferent bladder sensory function.

continued
<table>
<thead>
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<th>Agent</th>
<th>Frequency (Hz)</th>
<th>Baseline BST</th>
<th>Post-instillation BST</th>
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<tr>
<td></td>
<td></td>
<td>1 hour</td>
<td>24 hours</td>
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<tr>
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<td>24.8±7.5</td>
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<td>Oxybutynin (0.5mg/ml)</td>
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<td>30.0±7.9</td>
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<td></td>
<td></td>
<td>13.2±6.0</td>
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<tr>
<td>Resiniferatoxin (1microM)</td>
<td>250</td>
<td>29.6±5.4</td>
<td>32.1±11.5</td>
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<tr>
<td></td>
<td>5</td>
<td>12.6±4.5</td>
<td>12.5±4.1</td>
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<tr>
<td></td>
<td></td>
<td>18.4±3.2</td>
<td>*</td>
</tr>
<tr>
<td>Lidocaine (4% solution)</td>
<td>250</td>
<td>26.6±8.6</td>
<td>40.5±6.4 *</td>
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<tr>
<td></td>
<td>5</td>
<td>12.5±5.3</td>
<td>22.9±6.8 *</td>
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<tr>
<td></td>
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<td>14.1±5.8</td>
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*, P<0.05, statistically significant difference from baseline values
Over-Expression of Stem Cell Homing Cytokines in Urogenital Organs Following Vaginal Distension

Raymond R. Rackley, Margot S. Damaser, Lynn L. Woo, Adonis Hijaz, Mei Kuang, Marc S. Penn

**Purpose:** Vaginal delivery is a risk factor for stress urinary incontinence (SUI). Rat models of simulated childbirth have demonstrated hypoxia of the urogenital organs as well as the development of SUI following vaginal distension (VD). SDF-1 and MCP-3 have been identified as cytokines which are over-expressed after myocardial ischemia and signal stem cell migration to ischemic sites in a rat cardiac model. Given the focal hypoxia observed with VD, we sought to characterize SDF-1 and MCP-3 expression by pelvic organ tissues after VD.

**Materials and Methods:** 16 female rats were randomized into 4 groups: 2 groups underwent VD with harvest of pelvic tissues either immediately or 24 hrs after VD; a sham group underwent anesthesia only; a control group underwent no intervention. RT-PCR was performed on RNA extracted from the urogenital organs.

**Results:** MCP-3 expression in the urethra was increased 20- and 6-fold immediately and 24hrs after VD, respectively. MCP-3 was 8- and 4-fold increased in the vagina after VD. There was no difference in MCP-3 expression by the rectum or bladder in any group. SDF-1 was significantly under-expressed immediately after VD in all tissues.

**Conclusions:** MCP-3 is significantly over-expressed in rat urethral and vaginal tissues immediately following VD with above-normal but decreasing expression 24hrs later. The association between MCP-3 over-expression and targeted stem cell migration is under investigation. The successful characterization and control of such a repair mechanism in the lower urinary tract would introduce the potential for novel, non-operative treatments and/or preventive measures for SUI.
**Time –Dependent Light Microscopic Changes in Diabetic Rat Bladders**

*Firouz Daneshgari, Courtenay Moore, Guiming Liu, Xiao Huang, Lateef Saffore, Jennifer Brainard*

**Purpose:** To examine the gross and microscopic changes associated with diabetic cystoplasty, 3 to 20 weeks after induction of streptozolocin induced diabetes in a rat.

**Methods:** 3, 6, 9, 12 and 20 weeks after induction of diabetes by intraperitoneal induction of streptozolocin (60 mg/kg) anesthetized cystometrogram using urethane (1.2 mg/kg) was performed on each diabetic animal and on age and sex matched control animals. After cystometry, the bladders of both diabetic and control animals were harvested and weighed. A 10 x 5 strip of the bladder dome was excised, fixed and prepared for light microscopic examination. Light microscopy of each bladder was performed by a pathologist blinded to the condition (diabetic versus control) of the animal. Using standardized methods the changes in gross appearance of the tissue were quantified by the pathologist.

**Results:** Blood glucose levels of diabetic animals were four times that of controls. Diabetic animals weighed significantly less than their age matched controls. Yet, at all points, diabetic animals had a significant increase in bladder weight compared to controls. Therefore, diabetic animals had a greater bladder to body mass index than controls.

On cystometry, diabetic animals had larger bladder capacity, greater bladder compliance, and an increase in resting and post void bladder pressure compared to control animals.

Diabetic animals had a significant decrease in the mean time between bladder contractions.

On a microscopic level, the number of hyaline globules, in the muscularis propria was significantly different between the diabetic and controls as well as diabetic animals. The number of cystoplamic globules increased with the duration of diabetes. Similarly the number of cystoplamic vacuoles in the muscularis propria was increased in diabetes compared to control and with increased duration of diabetes. A significant increase in the edema of the lamina propria was also seen in diabetic bladders compared to control. No difference was found in the number or size of the nerve bundles or blood vessels between the diabetics and the control groups.

**Conclusion:** Diabetic mellitus causes significant gross, microscopic and functional changes in the rat urinary bladder.
Introduction and Objective: Lower urinary tract complications of diabetes mellitus (DM) are among the most prevalent complications causing urinary incontinence and poor bladder emptying. We and others have demonstrated that the temporal course of diabetic bladder dysfunction (DBD) in small animal models of DM include hyperactive bladder during the early stage of DM (<9 weeks) and hypoactive bladder during the late stage of DM (>12 weeks). The early stage changes, including the elevated voiding pressure, are seen similarly with increased diuresis; implicating the bladder’s compensatory response to an increased workload. The aim of this study was to examine the effects of DM on external urethral sphincter (EUS) and its contribution to the temporal course of DBD seen in rats.

Methods: 36 Male SD rats were divided into 3 groups: streptozotocin-induced diabetics, 5% sucrose-induced diuretics, and age, sex-matched controls. Cystometry under urethane anesthesia (CMG) and EUS electromyogram (EMG) were evaluated in all rats after 6- and 20-week of disease induction. After EMG measurement, the mid-urethra were harvested for morphological examination.

Results: CMG measurements showed diabetes and diuresis increase bladder capacity, contraction duration and high-frequency oscillations (HFO). Peak contraction amplitude increased in 6-week but not in 20-week diabetic and diuretic rats. EUS-EMG measurements showed frequency of EUS-EMG bursting discharge during voiding was significantly increased in 6-week but not in 20-week diabetic and diuretic rats. EUS-EMG bursting period increased in diabetic and diuretic rats compare to controls. EUS-EMG silent periods were reduced in 6-week but not in 20-week diabetic and diuretic rats. Morphometric analysis showed moderate atrophy of striated muscle in the EUS after 20-week of DM. Diabetes caused reduction of body weight compared to diuresis and controls, and the bladders of diabetic and diuretic rats weighed more than the controls after 6- or 20-week induction.

Conclusions: This data indicate that the expected urethral relaxation mechanism during reflex bladder voiding in rat is impaired in early stages of DM and diuresis, presenting a detrusor-sphincteric-dyssnergia like phenomena. Anatomical and functional alterations of the EUS may contribute to the DBD manifestation in both early and late stages of DM.
Role of Inducible Nitric Oxide Synthase in Bladder Dysfunction

Firouz Daneshgari, Guiming Liu, Yi-Hao Lin

Introduction and Objective: Pathophysiology of diabetic bladder dysfunction (DBD) includes autonomic neuropathy and detrusor myopathy. Increasingly, an important role for Nitric oxide (NO) in the function and diseases of the lower urinary tract (LUT) affecting the nerves and muscles is identified. The aim of our study was to examine if inability to produce inducible NO synthase (iNOS) would a) alter the function of the bladder; and b) would reverse the effects of diabetes mellitus (DM) on the bladder.

Methods: We employed a mouse strain with the targeted deletion of iNOS gene (iNOS-KO). The bladder function of four groups of male mice was studied: C57BL/6 wild type (WT), iNOS-KO, WT with diabetes (WT-DM), and iNOS-KO with diabetes (iNOS-KO-DM). Diabetes was induced with intraperitoneal injections of streptozotocin (STZ, 100 mg/kg). Animals were maintained without insulin treatment for 8 weeks. 24-hour micturition habits were evaluated using metabolic cages. Two days after suprapubic bladder tube (SPT) implantation, conscious cystometrogram (CMG) was assessed by infusing normal saline into the bladder at 1mL/hour. Data were compared using two sided student t-test with <0.05 as significant.

Results: iNOS-KO, WT-DM, iNOS-KO groups had a higher frequency of micturition than WT group as evidence by 24-hour micturition habits or shorter inter-contraction intervals during CMG (308.72 ± 87.58, 521.08 ± 74.63 sec, respectively). Voided volume was significantly lower in iNOS-KO-DM group than in the WT group (0.084 ± 0.084, 0.185 ± 0.027 ml, respectively). Peak bladder voiding pressure was significantly lower in iNOS-KO-DM group than the WT group (17.26 ± 2.90, 29.76 ± 9.64 cm H2O, respectively), and there was a higher residual volume in WT-DM group compare to other three groups. Blood glucose concentrations and hemoglobin A1c (HbA1C) level were significantly higher in WT-DM and iNOS-KO-DM groups compare to WT and iNOS-KO groups.

Conclusions: Deletion of iNOS gene causes symptoms of overactive bladder, but does not reverse the effects of diabetes on the bladder function in mice. With further characterization of their voiding habits, iNOS-KO mice may be used as model of overactive bladder.
Robotic Nerve-Sparing Radical Prostatectomy using Potassium-Titanyl-Phosphate (KTP) Laser in the Canine Model

Inderbir S. Gill, Jihad H. Kaouk, Cristina Magi-Galluzzi, Troy Gianduzzo, Jose R. Colombo Jr, Georges-Pascal Haber, Kester Nahen, Catherine Mohr, Monish Aron, Jason Hafron, Yi-Chia Lin, Bruno Santos

Introduction and Objectives: Laser energy can potentially provide fine dissection with minimal adjacent tissue injury and good hemostasis. We have previously demonstrated that laparoscopic potassium-titanyl-phosphate (KTP) laser neurovascular bundle (NVB) mobilization minimally affects cavernous nerve function. We therefore examined the feasibility of performing robotic radical prostatectomy solely using laser energy in the canine model.

Methods: KTP laser robotic radical prostatectomy was performed in 10 dogs using the da Vinci S system and a purpose-built prototypic robotic laser delivery device. The Nd:YAG laser was used intermittently for coagulation of larger vessels as required. The procedure was standardised in the first 5 dogs which were sacrificed acutely, while the final 5 dogs were survived 72hrs to assess post-operative hemostasis. The peak intracavernosal pressure (ICP) response to nerve stimulation was recorded as a percentage of mean arterial (ICP%MAP) both before and after prostatectomy in all dogs. Pre and post prostatectomy haemoglobin and hematocrit measurements were taken in the survival animals.

Results: All 20 NVBs were dissected and preserved successfully without the need for any additional hemostatic manoeuvre. No clips, sutures, electrocautery or ultrasonic energy were employed. Pre and post prostatectomy ICP responses (ICP%MAP: pre 99.3%, post 83.7%, p = 0.2) were not significantly different. While haemoglobin (pre 14.3g/dL, post 12.1g/dL, p=0.01) and hematocrit measurements (pre 44.6%, post 37.7%, p=0.006) were reduced, estimated blood loss averaged 59ml including 200ml from a trocar related splenic injury. There was no post-operative haemorrhage. Two dogs had catheter related complications and 1 had an anastomotic leak. There were no complications directly attributable to laser use.

Conclusions: Complete laser robotic radical prostatectomy is feasible in the canine model. It appears to be a promising technique that warrants further assessment in the clinical setting; particularly regarding hemostasis and extent of thermal injury on cavernous nerve function. We have already performed our initial clinical experience in 4 patients with partial use of laser during dissection. No case has yet been completed solely with laser energy; however further assessment is ongoing.
Urinary Incontinence, Bladder Dysfunction, and Pelvic Organ Prolapse in Lysyl Oxidase Like-1 (Loxl1-/-) Mutant Mice: A Complete Animal Model for Female Pelvic Floor Disorders

Firouz Daneshgari, Margot S. Damaser, Una Lee, Guiming Liu, Mei Li, Dan Li Lin, Paul Zaszczurynski, Hui Q. Pan, Tiansen Li

Objectives: Using a Loxl1-/- genetic knockout mouse model, we have previously shown that genetic deficiency of LOXL1, a lysyl oxidase-like enzyme which can polymerize elastin, results in pelvic organ prolapse and increased voiding frequency postpartum. The objective of this study was to determine if Loxl1-/- mutant mice demonstrate either urinary incontinence or decreased urethral resistance.

Methods: Female parous Loxl1-/- mice (n=5), in the stable postpartum period with pelvic organ descent, as well as age-matched female wild type (WT) mice (n=6) underwent conscious cystometry, measurement of residual urine, and leak point pressure (LPP) testing. After completion of testing, bladders were removed and muscle strips were used for contractility studies. Strips were stimulated by varying levels of KCl, electrical fields (EFS), adenosine 5'- triphosphate (ATP), and carbachol (CCh).

Results: There are no significant differences between the weights of the bladder. Loxl1-/- mice void more frequently during cystometry testing than WT mice, consistent with previous work demonstrating increased frequency in these mice. Loxl1-/- mice had a decreased micturition pressure during cystometry than WT mice. Residual urine was not significantly different between WT and Loxl1-/- mice, indicating that the urinary frequency is not a result of outlet obstruction. LPP was not significantly different between WT and Loxl1-/- mice. However, the volume at which LPP was measured was significantly lower in Loxl1-/- mice than WT mice, due to their frequency of voids. In addition, there were no significant difference between the responses of bladder strips from Loxl1-/- mice and WT mice in the responsiveness to various stimulus.

Conclusion: Loxl1-/- mutant mice in the stable phase of prolapse do not have decreased urethral resistance with limited bladder capacity. Confirmation of presence of urinary incontinence in view of previously observed increased frequency of voids in these mutant mice warrants further investigation into the function of lower urinary tract of the animals.
Role of Elastin and Loxl1 in the Function of the Bladder and Urethra in Female Mice

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Introduction and Objective: Loxl1 is an enzyme key for elastic fiber homeostasis. Loxl1 deficient (Loxl1<sup>−/−</sup>) mice have elastic fiber homeostasis defects that result in spontaneous pelvic organ prolapse and altered voiding behavior. Our aim was to examine the bladder and urethral function of nulliparous Loxl1<sup>−/−</sup> mice prior to development of pelvic organ prolapse to evaluate the effect of the Loxl1 deficiency independent of the confounding effects of pregnancy and prolapse.

Methods: We have previously described the creation of Loxl1<sup>−/−</sup> mice. Female nulliparous mice without pelvic organ prolapse and age-matched female C57Bl/6 mice underwent suprapubic tube implantation. Two days later, they underwent conscious cystometry (CMG) and leak point pressure measurement to determine bladder and urethral function. CMG was conducted in modified metabolic cages, the catheter was attached to a pressure transducer and a flow pump (1ml/hr of normal saline), and each void was noted and collected. For LPP testing, mice were anesthetized with urethane, the bladder was filled to half capacity (lower if voiding occurred repeatedly at low volumes), and a Crede maneuver was applied until leakage was noticed. The pressure at leak (P<sub>abd</sub>) was recorded as LPP. LPP was measured 3-5 times in each animal and the mean value was recorded. CMG and LPP data were analyzed with a t-test (p<0.05).

Results: The CMG studies showed that the baseline bladder pressure of the Loxl1<sup>−/−</sup> mice (n=7) was significantly lower (17.1 ± 8.3 cm H<sub>2</sub>O) than that of C57Bl/6 mice (n=13; 31.1 ± 9.8 cm H<sub>2</sub>O; p=0.023). The LPP measurements showed that Loxl1<sup>−/−</sup> mice had significantly higher P<sub>abd</sub> (11.7 ± 6.7 cm H<sub>2</sub>O) than C57Bl/6 mice (4.0 ± 2.9 cm H<sub>2</sub>O; p=0.002). In addition, the fill volume to LPP testing was higher in the Loxl1<sup>−/−</sup> mice (0.52 ± 0.31 ml) compared to the C57Bl/6 mice (0.12 ± 0.10 ml; p<0.001). Bladder capacity during CMG was also higher in the Loxl1<sup>−/−</sup> mice compared to C57Bl/6, but not to a statistically significant degree.

Conclusions: Increased LPP and bladder baseline pressure in nulliparous Loxl1<sup>−/−</sup> mice may suggest an important role for elastic fiber homeostasis and Loxl1 in bladder and urethral function. Abnormal elastogenesis may result in a less resilient urethra and a bladder with lower tone and fewer spontaneous contractions.
Alpha Melanocyte Stimulating Hormone (α-MSH) Protects Against Acute Renal Failure in a Porcine Renal Ischemia Surgical Model

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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.
Laser Nerve-Sparing Laparoscopic Radical Prostatectomy: Effects of Potassium-Titanyl-Phosphate (KTP) Laser on Cavernous Nerve Function in a Survival Canine Model

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**Introduction:** Electrical and ultrasonic energy used in nerve-sparing laparoscopic radical prostatectomy (LRP) can compromise cavernous nerve function. Laser energy may potentially allow fine dissection with good hemostasis and minimal adjacent tissue injury. This study examines the electrophysiological, histological and thermal mapping features of KTP laser dissection on cavernous nerve function in the survival canine model.

**Materials and Methods:** A total of 36 dogs were divided into 3 groups. Laparoscopic unilateral neurovascular bundle (NVB) mobilization was performed using either: (1) KTP laser (n=12), (2) ultrasonic shears (US) (n=12), or (3) clips and cold scissors (C&S) (n=12). The contralateral NVB remained undissected as an internal control. NVB function was assessed acutely in all dogs, and after 1 month survival in 50% of the dogs of each group. Peak intracavernosal pressure (ICP) response to cavernous nerve stimulation was measured as a percentage of mean arterial pressure (ICP%MAP). Strips of peritoneum harvested from 2 dogs were sectioned ex-vivo with the KTP laser and US shears for thermographic mapping.

**Results:** Comparing KTP and C&S groups, the erectile response to nerve stimulation was similar acutely and at 1 month (acute ICP%MAP: KTP 92%, C&S 96% p=0.54; chronic ICP%MAP: KTP 95%, C&S 98% p=0.71). In contrast, US dissection resulted in a significant decrease in the ICP response compared to the KTP and C&S groups (acute ICP%MAP: US 49%, KTP 92%, C&S 96%. US vs KTP p<0.001, US vs C&S p<0.001; chronic ICP%MAP: US 58%, KTP 95%, C&S 98%, US vs. KTP p=0.02, US vs C&S p=0.02). Mean NVB dissection times were similar (KTP 27.5min, US 19.9min, C&S 26.6min, KTP vs US p=0.21, KTP vs C&S p=0.81, US vs C&S p=0.22). Histopathology demonstrated an acute zone of laser-induced necrosis of approximately 500µm with lesser non-necrotic damage noted up to 1-2mm in some areas. Detailed histologic data will be presented. Thermographic assessment demonstrated significantly less collateral thermal spread from the KTP laser compared to US (mean thermal spread >60°C KTP 0.98mm vs. US 6.25mm, p<0.0001).

**Conclusions:** Use of KTP laser for NVB mobilization preserved cavernous nerve function comparable to standard athermal techniques using cold scissors and was superior to ultrasonic shears. KTP laser dissection during LRP appears promising and warrants further evaluation.
Identification of Obese Mice, with or without Diabetes, for Investigation of Bladder Dysfunction and Urinary Incontinence in Obesity Related Research

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Introduction and Objectives: Obesity, with or without associated diabetes mellitus (DM), is one of the contributing risk factors that is correlated with urinary incontinence (UI) and female pelvic floor disorders (FPFD). The pathophysiologic mechanisms of obesity related to UI or FPFD remain unknown. Animal models represent a valuable tool in the hierarchy of research for investigation of mechanisms of diseases. The aim of our study is to identify and evaluate mice models of obesity, with or without associated diabetes, which demonstrate evidence of lower urinary tract dysfunction.

Methods: From the available mice models of the NIH-Animal Models of Diabetic Complications Consortium (www.amdcc.org), we evaluated the lower urinary tract function in several models with obesity, including db/db on the C57Bl/6sj background, ob/ob on the C57Bl/6 background, Low Density Lipoprotein Receptor deficiency (LDLR-/-), LDLR-/- with streptozotocin (STZ)-induced diabetes, and wild type C57Bl/6 female mice (controls). In addition to measurement of the animals’ weight and body mass index (BMI), mice in all groups (n=8) underwent placement of suprapubic tubes two days prior to undergoing conscious cystometry (CMG). After completion of CMG, the animals were euthanized and their bladders were harvested for future in-vitro and molecular studies.

Results: Db/db on the C57Bl/6sj background, ob/ob on the C57Bl/6 background, and LDLR-/- (without STZ-induced DM) mice show two fold increases in their body weights compared to controls (Figure A). Db/db on C57Bl/6sj and ob/ob on C57Bl/6

continued
mice show evidence of hyperglycemia consistent with diabetes (Figure B). All three strains also show evidence of bladder dysfunction as indicated by increased bladder weight (Figure C), frequency of micturition cycles, shortened intercontractile periods, and decreased peak micturition pressure at statistically significant levels compared to control mice (data not shown).

**Conclusions:** Our findings suggest that the db/db mice on the C57Bl/6sj background, ob/ob mice on the C57Bl/6 background, and LDLR/-/- mice without STZ-induced DM represent promising mice models for mechanistic investigation of the effects of obesity, with or without diabetes, on lower urinary tract function.
Introduction and Objective: Petros and Ulmsten describe an “Integral Theory”, where a deficient pubo-urethral ligament (PUL) may be the cause of stress urinary incontinence (SUI) in women. The PUL attachments lie between the ventral surface of the urethra and the pubis, and may contribute to urethral hypermobility and pathophysiology of SUI and mixed urinary incontinence (MUI). We have recently developed a PUL-deficient animal model demonstrating evidence of SUI. Here, we examine the long-term efficacy of this model and examine the effect of PUL deficiency on urethral hypermobility and SUI.

Methods: A total of 16 female age-matched Sprague-Dawley rats (Harlan, Indianapolis, Indiana) were randomly assigned to 1 of 3 groups: PUL-transection (PULT); sham-PULT; and pudendal nerve transection (PNT), in which PNT group would serve as the positive control as long term effects of PNT in causing SUI has been previously demonstrated. PULT was performed through a midline laparotomy incision under direct visualization. Four weeks after surgery and under general anesthesia, the bladder of animals were filled with 50% iodine contrast via a transurethral tube (p50) and 3-D images of the bladder, urethra and pubic bones were obtained in rest and under applied abdominal pressure by GE small animal computed tomography. The distance between the urethro-vesicle junction and dorsal surface of pubic bone were evaluated on the coronal images. Subsequently, the animals underwent placement of a suprapubic tube (SPT). Two days after SPT implantation and under anesthesia, leak point pressures (LPP) were measured using the Crede maneuver according to the previously described methods. LPP was measured 5-6 times by a single investigator and its mean value was documented. Wilcoxon rank sum tests were used to compare the LPP values and urethral hypermobility across and between groups of animals.

Results: Four weeks after PUL transection, LPP was significantly decreased compared to sham (22.3 cm ± 4.63 vs 43 ± 16cm H2O, p<0.001), but not to PNT group (14.5 ± 0.85cm H2O ) indicating the durability of effects of PULT on causing SUI. 3-D images of the urethra and bladder show evidence of hypermobility in PULT animals and not in sham- PULT or PNT.

Conclusion: Injury to the PUL causes long-term functional and anatomical characteristics of an incompetent and hypermobile urethra in female rat. Our newly created animal model of urinary incontinence could be used for investigation of mechanisms and potential therapeutic interventions of SUI.
Role of Pubo-Urethral Ligament Integrity in Leak Point Pressure Alterations in the Rat Model of Stress Urinary Incontinence

Firouz Daneshgari, John C. Kefer

Introduction: Studies of the female urethra by Petros and Ulmsten indicate that a deficient pubo-urethral ligament (PUL) may lead to urethral mobility and stress urinary incontinence (SUI) in women. The PUL attachments lie between the ventral surface of the urethra and the pubis, and Petros and Ulmsten have described the role of the PUL as an “integral theory” into the pathophysiology of SUI. Hypermobility of the PUL has been demonstrated in women with SUI, but the precise functional changes of PUL-deficiency remain unclear. We investigated the role of a deficient PUL in altering leak point pressures (LPP) in a rat model of SUI. Our aim was to create and validate an animal model of PUL deficiency in the female rat through comparison to established animal models of SUI.

Materials and Methods: A total of 22 female age-matched Sprague-Dawley rats (Harlan, Indianapolis, Indiana) were randomly assigned to 1 of 5 groups: PUL-transection or sham-PUL transection with LPP measured at 4 days or 10 days post-op, and pudendal nerve transection (PNT) with LPP measured at 4 days post-op. PUL transection was performed sharply through a midline laparotomy incision under direct visualization. Four or ten days post-procedure the leak point pressure was determined in each anaesthetized animal via a previously implanted suprapubic catheter. Wilcoxon rank sum tests were used to evaluate whether levels of measurements differed across and between groups.

Results: Four days after PUL transection, LPP was significantly decreased compared to sham group (16.3 cm ± 2.74 vs. 36.6 ± 6.39 cm H2O, p<0.00001) and no different from PNT group (14.5 ± 1.06 cm H2O p<0.44). Ten days after PULT, the LPP remained significantly lower that the Sham PULT (17.6 ± 6.36 vs 31.2 ± 5.14 cm H2O, p<0.00001), indicating the durability of effects of PULT on causing SUI.

Conclusion: These results demonstrate that deficiency of the PUL in the female rat causes SUI compared to the established model of PNT. This novel PUL-deficient rat model could be used for investigation of mechanisms and potential therapeutic interventions of SUI. Longer term effects of PULT on LPP requires future investigations.
Stem Cell Homing and Functional Recovery of Stress Incontinence After Vaginal Delivery: A Rat Model for Preventing and Treating Childbirth Injuries

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Background and Objectives: MCP-3 is a stem cell homing factor specifically over-expressed in rat urethral and vaginal tissues immediately after simulated childbirth injury (vaginal distension). Prolonged vaginal distension (VD) in rats has been shown to result in decreased urethral resistance and symptoms of stress urinary incontinence (SUI). We sought to demonstrate targeted stem cell homing to the injured urethral sphincter and determine whether homing resulted in subsequent recovery of continence function.

Methods: 45 female rats were randomized to 4 hours vaginal distension (VD), sham distension (SH), or control. 2 million GFP-labeled mesenchymal stem cells were injected via tail vein in all animals 1 hour after assigned procedure. Urodynamic evaluation of leak point pressure (LPP) was performed on post-procedure day 1, 4, or 10, and urogenital tissues were obtained for immunofluorescence studies.

Results: Qualitative immunofluorescence targeted to the GFP-labeled stem cells demonstrated the presence of stem cells in urethral smooth muscle of rats subjected to VD. The highest concentration of cells was observed in 10 day VD animals followed by 4 day VD animals. No stem cell homing was seen in SH or control animals at any time point, nor were stem cells observed in tissues of the bladder or rectum. LPP of VD rats at day 1 was 30.6(±5) mmH$_2$O compared to 48.3(±20) and 44.2(±10) in control and SH rats respectively. At 4 days, LPP of VD rats was 33.5(±5) mmH$_2$O compared to 42.1(±8) and 48.9(±12) in control and SH rats respectively. At 10 days, LPP of VD rats was 40.4(±6) mmH$_2$O compared to 43.5(±3) and 47.7(±2) in control and SH rats respectively.

Conclusions: Stem cells home to urethral tissues following VD-induced injury, and urethral resistance in animals subjected to VD approaches normal values by day 10. These findings suggest that stem cell therapy may provide a treatment modality for SUI caused by childbirth injury.
Therapeutic Possibilities to Reduce the Risk of Stress Urinary Incontinence in Diabetic Female

Firouz Daneshgari, Courtenay Moore

Introduction and Objectives: Women with diabetes mellitus (DM) are twice as likely as non-diabetic women to develop stress urinary incontinence (SUI), independent of any other risk factors. We have previously shown that vaginal birth trauma caused by vaginal distension (VD) increases the severity and delays the recovery of SUI symptoms in diabetic animals. We have hypothesized that mechanism of incontinence due to vaginal birth trauma is due to neuropathic and ischemic damage to pelvic floor tissues including the accumulation of advanced glycosylation end products (AGEs). Two agents, aminoguanidine and captopril, have been shown to interfere with the formation of AGEs by binding to tissue receptors and promoting breakdown of AGE deposits. Our aim was to examine if exposure to anti-AGE agents will ameliorate or lessen the effects of VD in diabetic animals, thereby reducing the severity of SUI.

Methods: This study was approved by the Institutional Animal Care and Use Committee of the Cleveland Clinic. Virgin female Sprague Dawley rats were divided into five groups: DM +VD, control + VD, DM treated with aminoguanidine +VD, DM treated with captopril + VD, and DM treated with insulin +VD. After 10 weeks of treatment (1 g/L in the drinking water; average intake of AG was about 750 mg/kg-day), animals were anesthetized and suprapubic tubes were placed. Two days after suprapubic tube placement each animal underwent measurement of leak point pressure (LPP), followed by a 2 hour vaginal distension with a 3 cc balloon and post-VD LPP measurement. Ten days after VD, LPPs were evaluated. The LPP values at baseline, pre, post, and 10 days after VD were compared with two sided student t-test with <0.05 as significant.

Results: Ingestion of aminoguanidine or captopril from the onset of DM for 10 weeks has no effect on LPP in the absence of VD, but attenuated the reduction of LPP caused by VD (Figure below). Of the animals which survived to 10 days (35/50) diabetic animal treated with aminoguanidine, or captopril had significantly higher 10 day LPPs than untreated diabetic animals and diabetic animal treated with insulin.

Conclusion: Aminoguanidine and captopril both appear to have protective effects on preservation of continence in diabetic animals after VD, suggesting that the prevention of AGE accumulation decreases the risk of incontinence among diabetic animals.
Effects of Vaginal Distension on Leak-Point Pressure and Urethral Anatomy in Female Mice

**Firouz Daneshgari, Yi-Hao Lin, Guiming Liu**

**Objectives:** To take advantage of future application of transgenic and knock-out technology in research related to animal models of urinary incontinence we aimed to determine the effects of vaginal distension, as a surrogate of child birth injury, with various dilation diameters and pressures on the leak-point pressure (LPP) and urethral anatomy in female C57BL/6 mice.

**Materials and Methods:** Thirty C57BL/6 female mice were distributed into five groups, and four groups underwent vaginal distension using a modified 6 Fr. Foley catheter with different size balloon, i.e. 0.3cc balloon, 0.2cc balloon, 0.1cc balloon, or sham distension for one hour. Two days after vaginal distension, all mice received suprapubic bladder tubing placement. Under urethane anesthesia, the LPP was assessed 4 days after VD according to previously described method of using Crede maneuver, animal in supine position and bladder filled with 50% of its capacity (mean of 0.03 cc). The fifth group of mice was control group and did not undergo vaginal distension, but did have a suprapubic bladder tubing placed and LPP measurement. After measuring LPP, the urethra and vagina were harvested for histologic examination after being stained with haematoxylin/eosin, trichrome, and PGP9.5 antibody against the neurofilaments. The data were analyzed using a one-way ANOVA on ranks, followed by a Bonferroni’s test, with P<0.05 indicating a significant difference.

**Results:** LPP were significantly lower after 0.3cc, 0.2cc, and 0.1cc balloon distension, at 10.29 ± 6.70, 14.65 ± 6.51, 26.59 ± 3.47 cmH$_2$O, than in the control group, at 37.78 ± 5.10 cmH$_2$O (p<0.05 for all three volumes), respectively. There were no significant differences in LPP between the control and sham groups (p=0.386). Histology showed that there is no significant difference in urethral skeletal muscle between five groups, but 0.3cc and 0.2cc balloon of distension resulted in extensive disruption and thinning of vaginal wall, whereas 0.1cc balloon of distension showed less disruption. The immunofluorescence by PGP9.5 antibody in urethra revealed that the densities of neurofilaments were significantly decreased after 0.3cc and 0.2cc balloon distension.

**Conclusions:** These results suggest that vaginal distension as a surrogate of child birth trauma could cause significant reduction of LPP with 0.2 and 0.3 cc volume of 6 French Foley catheters in female C57BL/6 mice. This novel model of SUI in mice could be used for mechanistic studies of stress urinary incontinence (SUI) in female with taking advantage of future use of knock out and transgenic technology.
Section 12

Other
Assessment of Pain in Patients Undergoing Office-Based Urological Procedures as a Function of Staff Surgeon Versus Resident

J. Stephen Jones, Carvell T. Nguyen

Introduction and Objective: Prostate biopsy, cystoscopy, and vasectomy are low-risk urological procedures with minimal morbidity that are routinely performed in the ambulatory setting. We sought to determine from our prospective IRB approved database whether pain experienced by patients undergoing these procedures was affected by whether a staff surgeon or resident was the primary surgeon on the case.

Methods: One staff surgeon residents in their first, second, or fourth year of urological training (n=12) performed procedures entered prospectively in the study. Patients scheduled to undergo office procedures were assigned to either the staff surgeon or a resident as the primary surgeon based primarily on whether the resident was in the clinic at the time. In addition, the surgeon demonstrated the first of any given procedure each month when a new resident rotated on service. Operations performed by residents were done under the direct supervision of the staff surgeon. After completion of prostate biopsy, cystoscopy, or vasectomy, patients were given a visual analogue scale (VAS; 0-100 mm) to assess the pain associated with the procedures. For TRUS-guided prostate biopsy, patients were asked to immediately assess pain after each portion of the procedure, including probe insertion, periprostatis block (PPB), and the biopsy itself.

Results: Mean VAS scores were calculated for all three surgical procedures performed by either the staff surgeon or the resident cohort and are summarized in the table below.

Although mean VAS scores appeared slightly lower for procedures when performed by the staff surgeon, the differences between staff surgeon and residents were neither statistically nor clinically significant. Furthermore, there was no significant difference in mean VAS scores for the various surgical procedures between residents of different training years.

Conclusions: Our data demonstrate that office-based urological procedures can be safely performed by residents under a surgeon's supervision with discomfort comparable to a staff surgeon.
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