Urology & Kidney Disease News

Glickman Urological & Kidney Institute
A Physician Journal of Developments in Urology and Nephrology
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In This Issue:

8 XMRV in Prostate Cancer and Chronic Fatigue Syndrome
10 First Major Outcomes Study in PSA Era Shows Benefits of Screening and Surgery
17 Bladder Neck Preservation During Robotic Prostatectomy
19 Intentional Weight Loss in Chronic Kidney Disease
22 New Membrane for Bioartificial Kidney Shows Improvements Over Polymer Membranes
26 Understanding the Role of Nerve and Muscle Injury in Incontinence
27 A More Accurate Prognostic Tool for Invasive Bladder Cancer
30 The Challenge of Post-Vasectomy Pain
32 Decision Tree Aids in Choosing Testicular Cancer Therapies
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Cleveland Clinic Excels in Latest U.S. News Rankings
Urology ranked No. 2 in the nation; Kidney disorders ranked No. 3

The Cleveland Clinic Glickman Urological & Kidney Institute’s urology program was ranked among the top 2 programs in the United States for the 11th consecutive year by U.S. News & World Report. The institute’s kidney disorders program ranked 3rd in the nation.

The 2010 “America’s Best Hospitals” survey recognized Cleveland Clinic as one of the nation’s best hospitals overall, ranking the hospital as No. 4 in the country. Cleveland Clinic ranked in 14 of the 16 specialties surveyed by the magazine.

Fourteen of its specialties were listed among the top 10 in the United States. For details, visit clevelandclinic.org.

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Chairman’s Report
3 Cleveland Clinic Hosts First Summit on XMRV

News from the Glickman Urological & Kidney Institute
New Chair, Department of Urology

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Prostate Cancer
XMRV in Prostate Cancer and Chronic Fatigue Syndrome
First Major Outcomes Study in PSA Era Shows Benefits of Screening and Surgery
Patient Management Following a Negative Prostate Biopsy
The Importance of Detecting “Negative Biopsy”
Prostate Cancer Screening: Measures of Outcomes and Prognostic Factors for Favorable Outcomes

Illustration of an XMRV virus particle. For more on XMRV and its role in prostate cancer and chronic fatigue syndrome, see page 8.

Urology & Kidney Disease News
Benign Prostatic Disease
Laparoscopic Single-Site Surgery: Retractabale Urinary Repair
Bladder Neck Preservation During Robotic Prostatectomy

Kidney Cancer
Conventional treatments have been the mainstay of therapy. However, new therapies are on the horizon with the potential to improve outcomes.

Chronic Kidney Disease
Intentional Weight Loss in Chronic Kidney Disease
The Patient Experience in a Certified Nurse-Practitioner-Run Chronic Kidney Disease Clinic
Renal Failure
Urinary HO-1/HCa Complex and Hepatic Sulfatase as Early Biomarkers of Diabetic Nephropathy
New Needle for Breast/Bowel Kidney Stones
Improvements Over Polymer Membranes
A New Approach to Antibiotics in the ICU

Female Urology
Improving Efficiency and Quality in Patients Undergoing Vaginal Surgery
Single-Stage Extraperitoneal Radical Cystectomy
New Insights into Obesity, Type 2 Diabetes, Childhood and Incontinence
Urethral Bulking Agents Used in the United States
Comparison of FDA Studies
Understanding the Role of Nerve and Muscle Injury in Incontinence

Bladder Cancer
A More Accurate Prognostic Tool for Invasive Bladder Cancer
Putative Role for Mammalian Target Rapamycin (mTOR) in Urinary Bladder Cancer

Sensory Health
Using the TUNEL Test to Identify Intrahepatic Intestinal Bacterial Overgrowth
The Challenge of Post-Vasectomy Pain

Testis Cancer
Decision Tree Aid in Choosing Testicular Cancer Therapies

Transplantation
Expanding the Donor Pool for Kidney Transplantation
Marked Variation in Kidney Transplant Patients’ Progressions Based on Transplant Center of Choice
Hyperplasia and Chronic Kidney Disease

Author Index

Services for Physicians and Patients
Inside Back Cover

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Author Index

Services for Physicians and Patients
Inside Back Cover
It is my pleasure to present this issue of *Urology & Kidney Disease News* from the Glickman Urological & Kidney Institute. Among the exciting activities of 2009 were the XMRV Summit, the Transplant Summit, and the Single-Port Laparoscopy, NOTES®, and Endoluminal Surgery Summit, all hosted at Cleveland Clinic by the Glickman Urological & Kidney Institute.

In November, about 80 researchers gathered at Cleveland Clinic to share information about the Xenotropic Murine Leukemia-Related Virus (XMRV). This was the first symposium centered on the virus and the data exchanged that day gave us a reference point for how far we’ve come in understanding it, including its association with not only prostate cancer, but with chronic fatigue syndrome as well. (Read more about the XMRV Summit on page 4.)

Earlier in the fall, the two-day Transplant Summit, “Controversial Issues in Organ Transplantation-A Colloquium,” gave representatives from academic, clinical, political, regulatory, industry, patient advocacy, and research communities the opportunity to share information and debate current issues in organ transplantation.

The three-day single-port/NOTES summit, held in May, was a collaboration among several Cleveland Clinic subspecialty areas including urologic, gynecologic, colorectal and bariatric surgery. The summit provided an educational opportunity for physicians and surgeons interested in becoming skilled with the techniques of minimally invasive surgery using natural orifices and single-site incisions.

This past year we also were pleased to establish the Novick Center for Clinical and Translational Research. The center, born of an idea by the late Andrew Novick, MD, facilitates interaction between researchers and clinicians within our institute while seeking to promote clinical and translational research and assure compliance with federal and institutional regulations.

We have been fully operational within the Glickman Tower for a full year now. The tower, which was completed in the fall of 2008, provides close proximity between our nephrologists and urologists, which promotes collaboration and patient-centered care – the tenets of Cleveland Clinic’s institute model of care. We have further deepened our commitment to the institute model of care with the expansion of several interdepartmental programs that bring medical and surgical collaboration together for the advancement of medicine. These programs include kidney/pancreas transplant, stone disease, acute kidney injury, chronic kidney disease, refractory hypertension and the bioartificial kidney.

We are pleased to have added a new leader to the institute – Edmund Sabanegh, MD, was recently named Chairman of Urology. (Read more about Dr. Sabanegh on page 5.) Dr. Sabanegh joins J. Stephen Jones, MD, Chairman of Regional Urology, Martin Schreiber, MD, Chairman of Nephrology & Hypertension, Lawrence Hakim, MD, Chairman of Urology at Cleveland Clinic Florida, and myself in leading the fine staff of our institute into another year of excellence in innovation, outcomes and patient experience.

We hope you find this issue of *Urology & Kidney Disease News* useful. We are pleased to share this compilation of the current activities within our institute with our colleagues and friends across the country.

Sincerely,

Eric Klein, MD
Cleveland Clinic Hosts First Summit on XMRV

In November, a small, select group of virologists, epidemiologists and clinicians converged on two institutes at Cleveland Clinic – the Lerner Research Institute and the Glickman Urological & Kidney Institute. Approximately 80 researchers came together to take measure of what is known about Xenotropic Murine Leukemia-Related Virus (XMRV) and chart a collaborative effort toward greater understanding of the newly found retrovirus. XMRV is only the third retrovirus known to infect humans and one of only a few viruses that have been associated with prostate cancer and, more recently, chronic fatigue syndrome (CFS). The exact role the virus might play in either illness has yet to be defined.

XMRV was discovered in 2006 by Robert Silverman, PhD, and Eric Klein, MD, Cleveland Clinic, in collaboration with colleagues at the University of California, San Francisco. Drs. Silverman and Klein were honored by Cleveland Clinic in February with the F. Mason Sones Innovation Award for the discovery.

“A lot of new XMRV-related research has appeared during the past year, and especially in the last six months. In particular, there were 2 studies, one each from the University of Utah and from Emory University suggesting that as many as a quarter of all prostate cancer patients may be infected with this virus and linking the virus to the aggressiveness of the cancer. Another study, conducted by the Whittemore Peterson Institute in Nevada, the National Cancer Institute, and Cleveland Clinic, found the virus to be present in up to two-thirds of patients with CFS. It was also found in 4 percent of normal, healthy controls,” said Dr. Silverman.

The potential clinical impact of the XMRV and the substantial range of uncertainties surrounding its role in human diseases led to the organization of the conference entitled “Defining the Role of XMRV in Human Cancer,” the world’s first XMRV Summit. “If the early findings presented at this meeting are confirmed, the discovery of XMRV could result in new ways of detecting, treating and preventing both prostate cancer and CFS,” said Dr. Klein.

“The purpose of the meeting was to provide a forum for assessing what we know about the virus, to frame key questions, and to establish relationships that will enhance collaborative research. We were able to convene a high-powered group of scientists, epidemiologists and clinicians to discuss the implications of XMRV for human health,” said Dr. Silverman.

The meeting did not make a big splash in the media because the press and public were excluded in an effort to ensure an open and comprehensive exchange of data and opinion. Much of the data exchanged during the one-day summit was in raw form or being reviewed for publication and, therefore, subject to change and peer-review before being made public.

Dr. Silverman defined progress to date in general terms.

“What we know is that the virus is present in at least some men with prostate cancer. The numbers in the studies vary but it could be as high as 25 percent. Another study found the virus in 67 percent of patients with CFS,” said Dr. Silverman. He noted the additional finding that the virus was present in 4 percent of healthy controls was troubling because it suggests that it could be present in a significant fraction of the general population, perhaps several million Americans, raising concerns for viral transmission via blood donation, a possibility now being investigated by several government agencies. One of the summit’s discussions encompassed an assessment of progress in developing an assay or test for the virus. Such a test would be an essential tool for epidemiologists, one that would also provide insight into the virus’ mode of transmission. Recently published work from Cleveland Clinic suggests that XMRV can be transmitted sexually, similar to other retroviruses.

Some of the researchers attending the meeting are seeking to determine if the virus is susceptible to anti-retroviral therapies. XMRV, like the human immunodeficiency virus (HIV), is a retrovirus and there are a number of agents that show efficacy against HIV. It would be a boon to find a treatment already on the shelf. For instance, research presented at the meeting from the Mayo Clinic, now published, showed that the anti-HIV drug, AZT, blocks XMRV infections.

Interest in XMRV continues to gain momentum. The first paper was published in 2006. One paper was published in 2007, five in 2008 and 10 last year. “The field is moving very fast. What we got at the symposium was a snapshot of our progress in understanding this virus as of November 11, 2009. This is exciting research that has the potential to make a substantial impact on human health,” he said.

Dr. Silverman holds the Mal and Lee Bank Chair in the Department of Cancer Biology at Cleveland Clinic’s Lerner Research Institute. Dr. Klein is Chairman of the Glickman Urological & Kidney Institute, holds the Andrew C. Novick, MD, Distinguished Chair in Urology, and is joint-appointed in the Lerner Research and Taussig Cancer institutes.
As we go forward, our focus will be in two major areas. First, we seek to set the standard for quality patient care. Whether in the operating room, intensive care unit, surgical ward, or after a patient has returned home, we are diligently working to improve all aspects of the patient experience.

Initiatives are under way, led by Howard Goldman, MD, and his team in the Center for Quality Patient Care, to further refine our quality strategy and establish our outcomes as the benchmarks for the field. We have a number of projects under way to maximize patient satisfaction. Currently all sections within our department are working on specific, measurable quality projects — the outcomes of which will be critically analyzed by the entire department. We conduct regular experience rounds in which members of our leadership team visit with our inpatients to assess their needs and opportunities for us to further improve their care.

Recent projects have included care pathways to efficiently manage post-op patients, studies determining appropriate length of perioperative antibiotic use, protocols to decrease radiation use during fluoroureodynamics, and initiatives to improve patient education across all aspects of our healthcare system. A number of these projects have been presented at the American Urological Association meetings or published in peer-reviewed journals.

Secondly, we strive to pioneer surgical innovation, following in the long legacy of Cleveland Clinic for advances in the field of urologic surgery. We continue to work hard to push the envelope with urological innovation, understanding our ultimate goal is to minimize the impact of our interventions on the patient while maximizing outcomes. New advances, led by our minimally invasive surgical team, with robotic laparoendoscopic single-site radical prostatectomy with pelvic lymphadenectomy and robotic assisted single-site partial nephrectomy hold promise to allow comparable or better cancer control with much more rapid recovery. Natural orifice translumenal surgery with transvaginal nephrectomy takes our hopes one step further, as we seek to avoid any external evidence of surgery. New basic science research into the mechanism of ischemia-induced acute kidney injury allows us to test targeted interventions such as alpha melanocyte stimulating hormone analog AP214, which may someday decrease ischemic renal injuries observed with renal transplantation or partial nephrectomy.

It is a privilege to partner with you as we take patient care to the next level and I look forward to talking with you more regarding our vision for the future. Because, at the end of the day, I want this to be the place for my family to get their urological care... and your family too.
New Staff
The Glickman Urological & Kidney Institute welcomes the following new urology staff members:

Paul Nelson, MD, received his medical degree from the University of Kansas Medical School. He underwent postgraduate training at the University of Texas Medical Branch Hospitals in Galveston and completed fellowship training in transplantation surgery at Massachusetts General Hospital in Boston.

Dr. Nelson’s specialty interests include renal transplantation, general and endocrine surgery, crossing the ABO barrier in transplantation, improving access to transplantation for minority groups, innovation and improvement in organ donation, and donor management. Dr. Nelson joins the Glickman Urological & Kidney Institute’s Renal Transplant Program at St. Vincent Indianapolis Hospital in Indiana as Director of Transplant Services.

Georges-Pascal Haber, MD, earned his medical degree from Joseph Fourier University in Grenoble, France, and received postgraduate training at University Hospital of Lille in Lille, France. He recently completed a research fellowship and clinical fellowship in advanced laparoscopic and robotic urology at Cleveland Clinic.

Dr. Haber’s specialty interests include robotic surgery for prostate, kidney and bladder cancer; robotic and laparoscopic surgery for adrenal lesions; image-guided kidney tumor ablation (cryosurgery); and single-port laparoscopic and robotic surgery.

Upcoming Conferences

October 7-9, 2010
The Changing Landscape of Urologic Oncology: Initiating Systemic Therapies, Interventional Skills, and Clinical Trials
Program Chair: Neal D. Shore, MD, FACS, CPI Carolina Urologic Research Center
Program Co-Chair: Jihad H. Kaouk, MD
This course offers live laparoscopic renal ablation surgery, renal ablation hands-on lab experience, clinical trials workshop and more.
Glickman Tower, Cleveland Clinic
Cleveland, Ohio
For details, visit suonet.org.

October 18-20, 2010
Genito-Urinary Symposium (by invitation only)
Course Directors: Eric Klein, MD, and Derek Raghavan, MD
This three-day course will cover major tumor types including bladder, prostate, testis, kidney and pediatric GU cancer, and Tumor Board activities for uncommon cancers.
Glickman Tower, Cleveland Clinic
Cleveland, Ohio

October 22-23, 2010
2nd International Symposium on Robotic Kidney and Adrenal Surgery
Course Director: Jihad Kaouk, MD
Glickman Tower, Cleveland Clinic
Cleveland, Ohio
Get conference updates at ccfcme.org/kidney10.

Please check our websites for more details on these programs as they become available at clevelandclinic.org/glickman

Abstracts/Books
Glickman Urological & Kidney Institute research abstracts from both urology and nephrology are available online. To view them, visit clevelandclinic.org/glickman
Awards and Appointments

Christina Ching, MD, won the Traveling Fellowship Award from the Society for the Study of Male Reproduction.

Edward Diaz, MD, and John Klein, MD, were re-elected to the Society of Endourology in March.

Farzeen Firoozi, MD, won a best video award at the American Urological Association’s annual meeting for the video “Transvaginal Rectopexy.” Dr. Firoozi also won an award for his paper, “Translating Initial Success with Group Shared Appointments to Improve Patient-Perceived Outcomes after Neuromodulation,” at the Society for Urodynamics & Female Urology’s annual winter meeting.

Bradley C. Gill, BSE, and Margot Damaser, PhD, won best poster of the basic science session at the Society for Urodynamics & Female Urology’s annual winter meeting for “Effects Of Obesity And Type 2 Diabetes On Recovery From Pudendal Nerve Injury In Female Zucker Rats.”

Robert Heyka, MD, was elected to the Medical Advisory Board of the Renal Network, Inc. The Renal Network, Inc. is a not-for-profit organization that monitors the quality of dialysis care in Pennsylvania, Delaware, Indiana, Kentucky, Ohio and Illinois.

Michael Ingber, MD, won the Society for Urodynamics & Female Urology Traveling Fellowship Award.

Jihad Kaouk, MD, has been named Vice Chair for Surgical Innovation, Glickman Urological & Kidney Institute.

Courtney Lee, MD, won an award for her paper, “Educating Physicians on the Principles of Neurostimulation,” at the Society for Urodynamics & Female Urology’s annual winter meeting.

Karl Montague, MD, has been named President-Elect of the Society of Urologic Prosthetic Surgeons.

Amit Patel, MD, was awarded a fellowship to attend and participate in a Bladder Cancer Think Tank meeting in Jackson Hole, Wyo., in August 2009.

Mary Katherine Samplaski, MD, won the 2010 Elisabeth Pickett Research Award from the Society of Women in Urology.

Daniel Shoskes, MD, has been named Director of the Novick Center for Clinical & Translational Research, named after the late Andrew Novick, MD, former Chairman of the Glickman Urological & Kidney Institute. The Novick Center was established to expand and accelerate the growth of clinical, basic and translational research. Dr. Shoskes, whose specialty interests include renal transplantation and chronic prostatitis, is also a Professor of Surgery at Cleveland Clinic Lerner College of Medicine.

Matthew Simmons, MD, won two best poster awards related to his work on renal surgery at the European Association of Urology’s meeting. Dr. Simmons’ article on the C-index was featured on the cover of the March issue of the Journal of Urology.

Robert Stein, MD, Co-Director of Robotic Surgery, received a traveling fellowship as an invited faculty member and lecturer at the Society of Brazilian Urology’s biannual meeting in Goiania, Brazil.

Andrew Stephenson, MD, was named Director of the Center for Urologic Oncology, Glickman Urological & Kidney Institute.

Christopher Weight, MD, was awarded the George and Grace Crile Traveling Fellowship Award.

Nancy May, MSN, RN-BC, Nursing Director for the Glickman Urological & Kidney Institute, has received the Excellence in Administrative Ambulatory Nursing Practice Award from the American Academy of Ambulatory Care Nursing. The award recognizes a member’s unique ability to lead others toward the successful completion of their organization or workplace’s mission and goals. Nancy’s team also has been recognized with several Cleveland Clinic awards recently.

Elroy Kursh, MD, received the American Urological Association’s Distinguished Contribution Award at the 2010 annual meeting. Dr. Kursh received the award for “outstanding leadership of the AUA North Central Section, education and career advancement of young urologists, and commitment to the highest quality of patient care,” according to the AUA. The award is presented each year to those who have made outstanding contributions in urology.
XMRV in Prostate Cancer and Chronic Fatigue Syndrome

Eric A. Klein, MD, and Robert H. Silverman, PhD

In 2006 we described the discovery of XMRV, a gammaretrovirus, isolated from the prostate of men with a hereditary predisposition to prostate cancer. Several other groups have now reported confirmatory studies, demonstrating detection of XMRV in independent cohorts of prostate cancer patients, and one study has reported that a significant proportion of patients with chronic fatigue syndrome may also be infected with XMRV.

As in our original study, investigators from Emory University confirmed the presence of XMRV in stromal cells of prostate cancers and an association with the QQ allele of the HPC1/RNASEL gene. The study combined 3 different methods, a serum-based assay for neutralizing antibodies against XMRV, PCR, and FISH. Neutralizing antibodies were detected in the serum of 11 of 40 prostate cancer cases (27.5%), of whom 8 of 20 (40%) were RNASEL QQ. FISH demonstrated the presence of XMRV in a small number of prostatic stromal cells, but not in epithelial cells, as we initially reported. Two studies, however, have now demonstrated that XMRV is present in the epithelial compartment of prostatic cancers.

In the first study, investigators at the University of Washington found that a cell line (22Rv1) derived from a human prostate tumor and grown in nude mice contained at least 10 integrated copies of XMRV. Presence of XMRV in prostate cancer epithelium was also reported in another study from the University of Utah, where using immunohistochemistry 23% of 233 prostate cancers and 4% of 101 benign prostate cases were XMRV positive. Unlike prior studies, there was no correlation between the RNASEL QQ genotype and the presence of XMRV infections. Another study showed a
higher incidence of XMRV infections in Japanese prostate cancer patients (6.3%) than controls (1.7%). The infections were detected in serum by Western blot assays. Not all published studies have confirmed these findings, suggesting differences in technical aspects of virus detection and/or the possibility that XMRV infection is not geographically uniform, a situation that is mirrored for other known infectious causes of cancer.

In animals, other gammaretroviruses are known to cause a wide range of disorders including leukemia, lymphoma, immune deficiency and neurologic diseases, so it is plausible that XMRV, while discovered in the context of prostate cancer, could be related to other diseases. Although its etiology is unknown, it is suspected that chronic fatigue syndrome (CFS), characterized by debilitating fatigue, dysregulation of RNASEL, and chronic immune system activation resembling a viral infection, involves viral infections. These observations led to the study of XMRV in a cohort of patients at the Whittemore Peterson Institute. Study of peripheral white blood cells produced evidence of XMRV infection in 67% of CFS patients and 3.7% of control healthy individuals. The viruses from 3 patients were sequenced and found to be >99% identical to the original XMRV isolated from prostate cancer patients. It was also clear they were the same virus. The presence of XMRV in the blood of the CFS patients was confirmed by four independent methods. One remarkable observation in this study was that plasma from CFS patients, but not from controls, was shown to transmit live XMRV to prostate cancer cells in culture. Subsequent studies from other parts of the world have so far not confirmed these findings in other cohorts of CFS patients.

It is currently not known if XMRV causes prostate cancer, CFS, or other diseases. However, several intriguing observations suggest potential mechanisms for this agent. Several investigators have demonstrated that XMRV grows preferentially in cultured cells derived from the prostate compared to other organs. We have shown that the part of the XMRV genome that regulates its replication is very sensitive to androgens and can be blocked by antiandrogens. In conjunction with our prior observations that XMRV integrates into host DNA near genes that are transcriptionally active, this study suggests that integration of the XMRV LTR in host cells could impart androgen regulation on integrated host genes, conceptually similar to how TMPRSS2-ETS gene fusions impart androgen regulation on otherwise androgen insensitive genes.

Due to the high sequence similarity with endogenous mouse viruses, it seems that XMRV evolved from rodents, though it is not known how or when XMRV first infected humans. While transmission of other retroviruses occurs through transfer of bodily fluids [e.g., HIV and HTLV: semen and blood; MMTV: breast milk], the mode of transmission of XMRV is unknown. Prostatic acid phosphatase, the predominant protein in human semen, forms fibrils that substantially enhance HIV-1 and XMRV infectivity by capturing viral particles and enhance viral attachment and entry through cell surface receptors. Human semen also induces increased infectivity in cell culture, especially at low viral doses. Coupled with our observation that XMRV is detectable in expressed prostatic secretions of 15% of patients with prostate cancer, these observations suggest sexual transmission, although this requires confirmation by seroprevalence and other epidemiologic studies. The presence of XMRV infected blood cells similarly suggests that blood transfusions might transmit infections, and preliminary efforts are under way to determine if the blood supply needs to be screened for XMRV.

Several studies have evaluated available antiviral drugs for their efficacy against XMRV replication in cell culture studies. Those that effectively inhibit XMRV replication include the RT inhibitors, AZT (ZDV), and tenofovir (TDF) and the integrase inhibitors, raltegravir (RAL) and L-000870812. Combination treatments appear to be synergistic and may help slow or eliminate the emergence of drug resistant strains.

For references, please email the editor.
First Major Outcomes Study in PSA Era Shows Benefits of Screening and Surgery

Andrew Stephenson, MD

Only a minority (4%) of men diagnosed with prostate cancer today have a greater than 5% risk of dying of the disease, according to the findings of a large multi-institutional study of prostate cancer specific and all-cause mortality. These encouraging findings have implications for newly diagnosed patients and physicians facing treatment decisions.

The outcomes identified by the study team may result from the efficacy of newer surgical procedures, current PSA screening practices that can detect the slow-growing disease at an earlier stage, or both. The study, which focused on men diagnosed between 1987 and 2004, found that 71% of the cohort diagnosed after 1998 had low-risk malignancies (clinical stage T1c or T2a, PSA <10, and biopsy Gleason grade ≤6).

Researchers at Cleveland Clinic’s Glickman Urological & Kidney Institute and Department of Quantitative Health Sciences, the Sidney Kimmel Center for Prostate and Urologic Cancers and Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, and the University of Michigan Department of Urology analyzed the incidence of prostate cancer specific mortality (PCSM) in a multi-institutional cohort of 12,677 patients treated with radical prostatectomy between 1987 and 2005.

They found that the PCSM in this cohort ranged from 12% in the quartile with the lowest risk of recurrence (as defined by PSA velocity) to 38% in patients in the highest quartile. Using a nomogram that was developed from study data and externally validated, the researchers concluded that only 4% of contemporary patients had a predicted 15-year mortality greater than 5%.

This is the first major study that used death as an endpoint to evaluate the efficacy of surgery in the era of widespread PSA screening. Earlier studies of prostatectomy using death as an outcome were conducted prior to the introduction of PSA screens when a significant percentage of cancers were being detected at later stages of development. After PSA screening became common, the rate at which the slow growing cancer progresses handicapped researchers’ ability to evaluate cause-specific mortality over a 15- to 20-year span.


Points

Primary Gleason Grade

Secondary Gleason Grade

Prostate Specific Antigen

Clinical Stage

Total Points

10-year Prostate Cancer-Specific Mortality

15-year Prostate Cancer-Specific Mortality

Key Point:

The long-term risk of prostate cancer specific mortality among men treated with radical prostatectomy in the PSA era is low. Our multi-institutional study was the first to use death as an endpoint to evaluate the efficacy of surgery in the era of widespread PSA screening. We created a nomogram using current clinical standards of primary and secondary Gleason Grade, PSA and clinical stage to predict both 10- and 15-year outcomes.
B. Calibration of the nomogram.

Dashed line indicates reference line where an ideal nomogram would lie.

Instructions: Locate the patient’s primary Gleason grade on the respective axis. Draw a straight line up to the Points axis to determine how many points toward prostate cancer–specific mortality he receives for his primary Gleason grade. Repeat this process for the other three parameters. Sum the points and locate this number on the Total Points axis. Draw a straight line down to find the patient’s probability of dying as a result of prostate cancer within 10 or 15 years of treatment.

Calibration Plot:

Surgical technique also has substantially evolved since the 1980s as is demonstrated by study data showing that the hazard ratio associated with surgery declined sharply from 1987 until 1998 when it stabilized, though the stage migration from screening and changes in tumor grading practices over this time period also may have contributed to this finding.

Early studies of prostatectomy outcomes used PSA recurrence as a primary endpoint for evaluating outcomes but PSA recurrence is highly variable and poses only a limited threat to longevity in some men with the disease.

This study is unique in that its data are drawn from a large cohort of men diagnosed from the late 1980s forward. The nomogram created from these data was validated to a concordance index of 0.82. The nomogram uses current clinical standards of primary and secondary Gleason Grade, PSA and clinical stage to predict both 10- and 15-year outcomes.

Other studies have attempted to explore the predictive potential of PSA velocity in combination with other clinical factors with mixed results. This study found that PSA velocity did not significantly improve the accuracy of the nomogram. In addition, few patients in the study had a predicted 15-year PCSM greater than 5%. This underscores our ability to identify patients at high risk based on clinical parameters alone. Novel markers specifically associated with aggressive cancers seen in high-risk patients are needed.
The Importance of Defining “Negative Biopsy”

J. Stephen Jones, MD, FACS

Most men who undergo prostate biopsy will not be found to have cancer; and importantly, a significant number of those men may harbor cancer that was simply not identified. This is especially likely when inadequate biopsy strategies are employed, or when entities associated with a likelihood of underlying cancer such as High Grade Prostatic Intraepithelial Neoplasia (HGPIN) or Atypical Small Acinar Proliferation (ASAP) are identified, begging the question of what is meant by the term “negative biopsy.” There is little consensus on management of this heterogeneous and challenging population.

The PCPT risk calculator has shown that there is a substantial risk of positive biopsy following one negative biopsy regardless of PSA dynamics, although we recently published that this risk calculator does not perform well in current clinical practice. Furthermore, it is widely assumed that rising PSA following negative biopsy is more likely to indicate cancer, although this logic is currently under investigation at Cleveland Clinic, and preliminary data suggest it may be flawed.

Stating that a patient has had a “negative biopsy” can imply a widely divergent set of findings. Depending on the number and location of cores obtained, the number of biopsy sessions the patient has undergone, and the presence or absence of HGPIN or ASAP, cancer might be effectively ruled out, or it might actually be highly likely that the patient has prostate cancer that was simply not identified. A single sextant biopsy may miss as many small cancers as it detects, and so clearly does not rule out prostate cancer. Even modern extended biopsies using 8-14 cores will fail to identify cancer in approximately ¼ of men, so having a low threshold to perform at least one repeat biopsy is in order. We have published that even a 20-core, transrectal saturation biopsy, as a singular technique, cannot rule out cancer. But when used as a repeat biopsy strategy, the likelihood that the patient will be found to have prostate cancer in the future is approximately 4%, and this occurred in our series almost exclusively in men with PSA values >10 ng/dl.

The impact of HGPIN on the likelihood of undiagnosed prostate cancer is controversial. However, we have found cancer rates by year 1, 3 and 5 are 9%, 30% and 49%, respectively, for patients with PIN, and 5%, 17% and 30%, respectively, for patients without PIN – all statistically significant demonstrations of the significant impact of HGPIN on the development of prostate cancer.

Even more suggestive of undiagnosed prostate cancer is ASAP. Repeat biopsy is highly recommended with this finding because even with saturation biopsy, ASAP is related to a 40-50% chance of undiagnosed cancer. Therefore, we conclude that ASAP can be interpreted as a message from the pathologist that it is believed the patient has cancer, but there is insufficient evidence on the slides to prove so. In that case, a repeat biopsy should be performed to provide more tissue, especially from the suspicious area. Alternatively, a pathological second opinion may clarify the diagnosis if subspecialty pathology has not been involved in the initial reading.

Thus, simply stating a patient has had a “negative biopsy” is meaningless. Describing the number of cores obtained, number of sessions, and presence or absence of HGPIN or ASAP is mandatory in order to consider the likelihood that the patient has unrecognized prostate cancer. Patients with a single “truly negative” (i.e., no HGPIN and no ASAP) biopsy usually merit one repeat biopsy if PSA remains high, subject to interpretation in the PSA range of 2.5-4.0.

MRI- and template-guided biopsy have been proposed but not validated in this setting, although elegant work by Villers, Karakiewicz, Vigneron and others is highly encouraging. Medical manipulation using antibiotics or 5-ari medications has been met with limited acceptance in this setting. So far we have been disappointed in the utility of this approach, but must await maturing data to determine its ultimate role.

The Key Questions: What is a “negative prostate biopsy,” and what are indications for repeat biopsy?

The first step in managing a patient after negative biopsy is to determine whether the biopsy was truly negative (i.e., no HGPIN or ASAP), and if it was performed adequately using at least 12 cores distributed to include the lateral, apical and anterior areas known to be “safe harbors” for unrecognized prostate cancers. The threshold to repeat biopsy should be low, and we still prefer to use a 20-core transrectal saturation biopsy in the office setting under periprostatic block, especially if the patient has undergone more than one prior biopsy but clinical suspicion persists for any reason. Medical management with antibiotics should be limited to the setting of infection, but 5-ari medications may improve cancer detection, suggesting malignancy if failing to reach 40-50% decrease in PSA, or if the PSA rises substantially during their administration.
Prostate Cryoablation: Measures of Outcomes and Prognostic Factors for Favorable Results

David A. Levy, MD, and J. Stephen Jones, MD

In November 2008, a panel of experts from the American Urological Association published the Best Practice Statement on Cryosurgery in the Journal of Urology. While this was a thorough review of the published literature, technological advancements, procedure-related morbidity and patient selection criteria, no statement could be made regarding measures of treatment outcomes due to a lack of available data. To this end we embarked on a series of studies to identify evidence-based measures of such outcomes in both the primary and salvage cryoablation populations.

Our initial study involved a review of biochemical outcomes of 2,427 patients from the Cryo On-Line Data (COLD) Registry. This study delineated the prognostic value of an initial post cryoablation PSA < 0.6 ng/ml for long-term (5-year) biochemical progression-free survival (bPFS) employing the Phoenix definition. For 2,072 individuals with an initial post cryoablation PSA < 0.6 ng/ml, the 60-month bPFS was: Low risk: 86%, intermediate risk: 67%, and high risk: 51%. If the initial PSA was > 0.6 ng/ml, the 24-month biochemical progression rate was at least 29.5%. The conclusion from this study was that initial post cryoablation PSA is prognostic for bPFS.

In a parallel study from the COLD Registry on 455 salvage cryoablation patients treated in the absence of hormonal influence, we found similar prognostic value for an initial post cryoablation PSA < 0.6 ng/ml, which was associated with a 67% 36-month biochemical progression-free survival rate. This study also revealed that an initial post cryoablation PSA > 0.6 ng/ml, the 24-month biochemical progression rate was at least 29.5%. The conclusion from this study was that initial post cryoablation PSA is prognostic for bPFS.

Based on the outcomes of these two studies, we sought to identify prognostic factors for achievement of favorable (< 0.6 ng/ml) post cryoablation PSA. An institutional study of 122 primary cryoablation patients treated at Cleveland Clinic identified such factors. On univariate analysis, the number of cores positive (p = 0.031) and maximum percent core positive (p = 0.024) were prognostic of PSA outcome. On multivariate analysis, number of cores positive (p = 0.010), maximum percent core positive (p = 0.034) and ratio of number of positive cores to prostate gland volume (cc’s) (p = 0.023) were prognostic for favorable PSA outcomes. The conclusion was that relative disease burden as defined by the number of and percent core positive, and the ratio of number of cores positive to prostate gland volume (cc’s) are highly prognostic for favorable initial post cryoablation PSA.

A follow-up prognostic salvage cryoablation study was conducted and revealed similar prognostic findings. Specifically, in an analysis of 58 consecutive Cleveland Clinic salvage cryoablation patients, 31% of whom had unfavorable initial post cryoablation PSA (> 0.6 ng/ml), disease burden as reflected by the number of positive biopsy cores (p = 0.012), ratio of positive cores to prostate volume (cm3) (p = 0.004), and marginally the percent of cores positive divided by total number of cores biopsied (p = 0.060) were prognostic for favorable PSA outcomes. A higher ratio of number of cores positive to prostate volume (3rd quartile) had a lower (35%) chance of a favorable PSA than a lower ratio (1st quartile) (OR = 0.35, 95% CI: 0.14 - 0.84, p = 0.019).

These studies represent confirmation of an evidence-based identification of a specific measure of treatment outcome, PSA < 0.6 ng/ml, which correlates with favorable long-term biochemical progression-free survival. Based on these findings, we will continue our efforts at developing a definition of treatment success for the cryoablation patient.

For references, please email the editor.
Post Brachytherapy Urinary Retention: The Best Approach?

James C. Ulchaker, MD, FACS

One of the most challenging patient scenarios to treat involves men who have undergone definitive therapy for prostate cancer, especially external beam radiation therapy, brachytherapy or cryotherapy, and subsequently develop urinary retention. Initially these men are treated with intermittent catheterization or indwelling Foley catheterization. All men find these options unpleasant and most who experience prolonged retention desire a long-term surgical remedy.

Numerous therapeutic surgical interventions have been utilized with varied success.

Transurethral resection of the prostate in both a monopolar and bipolar fashion has been used with some success. However, the risk of incontinence is significantly greater than when performed for non-radiated patients.

Other options have included the Greenlight Laser 532 nanometer (nm), but irritative post-procedural symptoms remain an issue, as does fiber tip damage secondary to the reflection of light off the brachytherapy seed. More recently, the 980 nm laser has been evaluated. This treatment option’s limitations also include fiber tip damage from the reflected light, but also significant prostatic tissue slough. This is thought to occur secondary to an increased penetration of the laser energy into the previously radiated prostatic tissue. If the patient is unable to successfully pass this sloughed tissue, it can collect in the prostatic fossa, and may once again cause recurrent urinary retention.

A new option, known as the plasma vaporization button electrode, is currently in its early stages of evaluation for this challenging patient population at Cleveland Clinic. This technology has the benefit of a shallow penetration of energy depth into the prostatic tissue, which may lead to a decrease in the amount of tissue slough and a subsequent decline in recurrent urinary retention. Whether improvements in urinary incontinence rates will be seen has yet to be determined. Thus, the optimal form of treatment for these challenging patients continues to be a work in progress. We remain optimistic that this optimal form of therapy will be defined in the near future.

Laparoscopic Procedures Help Patients with Uncommon Adrenal Diseases

S.C. Jeff Chueh, MD, PhD

Dr. Chueh directs the Cleveland Clinic laparoscopic urology program at Charleston Area Medical Center in Charleston, W.Va.

Rare adrenal pathologies such as bilateral adrenal hyperplasia caused by Cushing’s disease refractory to pituitary surgery or radiation, occult ectopic ACTH-secreting Cushing’s syndrome, and idiopathic bilateral adrenal macronodular hyperplasia necessitate bilateral total adrenalectomies; whereas bilateral functioning adrenal adenomas require bilateral partial adrenalectomy for better preservation of the residual adrenal function.

We employed laparoscopic simultaneous bilateral adrenal surgery (LSBAS) to treat the above-mentioned diseases in 12 patients. These patients underwent LSBAS over a 10-year period, with bilateral total adrenalectomies (TA) used in 4 with Cushing’s disease refractory to pituitary surgery and/or radiation, in one with occult ectopic ACTH Cushing’s syndrome (Figure 1), and in one with bilateral adrenal macronodular hyperplasia (Figure 2). Six patients (5 with primary aldosteronism and one with Cushing’s syndrome) had bilateral functioning tumors (Figure 3) and had bilateral partial adrenalectomies (PA). Some surgery was facilitated with a special device with alternating inflation cuffs behind the patient’s back to alleviate the need for changing the patient’s position during the operation. All 12 operations were completed with no complication, conversion, re-operation or death. The mean operative duration was 323 (range: 180–560) minutes, and the mean estimated blood loss was 79 (range: 20–200) mL. Patients who had a PA had significantly longer surgery
than those treated with TA, with a mean (standard deviation) operative time of 390 (36) vs. 255 (27) minutes.

Large complex or potentially malignant adrenal cysts are uncommon. Eight patients with potentially malignant or complex cysts were treated by laparoscopic adrenalectomy in the past 10 years by the author. The operative techniques strictly abided by the principles of surgical oncology. In short, the entire adrenal gland, including the cyst, was excised en bloc via a lateral transperitoneal laparoscopic approach and moved into a LapSac® bag. After the exterior abdominal surface was well protected, the opening of the LapSac was pulled out of the periumbilical wound and the cyst wall was opened to siphon all the fluid content with a sucker tip dipped into the cyst cavity. Then the remaining cyst components and the adrenal gland were removed with the bag from the periumbilical wound. All of the laparoscopic operations were successful without any intraoperative or postoperative morbidities, open conversion, or mortality. Mean operative time was 135 minutes with minimal blood loss. Histopathologic examinations revealed five hemorrhagic adrenal pseudo cysts, two adrenal endothelial cysts, and an adrenal cystic pheochromocytoma. There was involvement of peria drenal adipose tissues by the chromium-staining tumor cells in the case of cystic pheochromocytoma, and malignancy could not be excluded from the pathological criteria. At a mean follow-up of 40 months, all patients were asymptomatic and had no radiographic evidence of disease recurrence or dissemination.

For references, please email the editor.

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Laparoendoscopic Single Site Surgery: Retrocaval Ureter Repair

Robert J. Stein, MD, Riccardo Autorino, MD, Rakesh Khanna, MD, Michael White, MD, Bo Yang, MD, Sylvain Forest, MD, Fatih Altunrende, MD, Georges-Pascal Haber, MD, and Jihad H. Kaouk, MD

Laparoendoscopic single site surgery (LESS) performed through a small umbilical incision allows major urological operations to be performed with a nearly scar-free result. To date, our experience with these techniques numbers more than 160 procedures, which includes more than 30 robotic procedures. In terms of reconstructive procedures, a wide spectrum of cases including pyeloplasty, ureteroneocystostomy, and ileal interposition have been performed using both standard and robotic techniques.

Recently, a 25-year-old woman presented with chronic intermittent right flank pain. Preoperative imaging with proximal hydroureteronephrosis suggested retrocaval ureter. A right-sided retrograde pyelogram confirmed the diagnosis and a double-J ureteral stent was placed (Figure 1). After creating a small intraumbilical incision, a single-port device was positioned and the ureter was dissected proximal and distal to the inferior vena cava crossing (Figure 2).

At this point the ureter was transected posterior to the inferior vena cava and the distal segment was transposed laterally to a normal anatomic position. With the assistance of a separate 2-mm grasper, a uretero-ureterostomy was performed. The patient was discharged 2 days postoperatively after her transumbilical drain was removed (Figure 3).

Four weeks postoperatively the ureteral stent was removed, and 4 weeks thereafter a radionuclide scan demonstrated a post-diuretic $T_{1/2}$ of 1 minute. At a postoperative interval of 8 months the patient reports symptom resolution.

Since 2007, urologists have increasingly used LESS techniques. The evident advantage of the surgery is the aesthetic benefit, especially valued by younger patients, as in this case. Theoretical benefits include decreased postoperative pain, earlier convalescence, and less scarring with fewer incisions. With preliminary retrospective comparisons thus far there have been mixed results regarding any perioperative and recovery benefits. With greater experience and more robust comparative analyses, the true advantages of the LESS technique will become clearer. Robotics may make these procedures more practical for many surgeons.

Key Point:

We recently performed a laparoendoscopic single site surgery (LESS) for retrocaval ureter repair. Our experience includes more than 160 LESS procedures, 30 of which were robotic procedures. LESS has aesthetic benefits, but there have been mixed results regarding any perioperative and recovery benefits. With greater experience and more robust comparative analyses, the true advantages of the LESS technique will become clearer. Robotics may make these procedures more practical for many surgeons.
Bladder Neck Preservation During Robotic Prostatectomy

Anthony Avallone, MD

Bladder neck transection is one of the more challenging steps during robotic prostatectomy. Although there are many advantages of using robotic technology, an inherent disadvantage is the lack of tactile feedback. This makes the bladder neck dissection especially challenging during robotic prostatectomy as few visual clues exist to help determine the exact junction of the bladder neck and prostatic base. Furthermore, there is a wide variation in the anatomy of this area. Although most patients demonstrate a consistent anterior apron of bladder neck tissue, beneath this layer there can be varying amounts of prostatic base protruding into the bladder lumen. Combined with the lack of tactile sensation, the very efficient monopolar cutting current of the hot shears used for the dissection can make it easy to inadvertently enter prostatic base tissue and compromise margins. For this reason, many surgeons have utilized wide resection of the bladder neck, which often requires extensive reconstruction.

We have found, however, that by using preoperative cystoscopy to establish a roadmap that defines the anatomical relationships of the prostatic base, bladder neck, and trigonal structures, preservation of the bladder neck can be safely accomplished. This has proven to be applicable even for large prostates (>80 gms) and those with large intravesical lobes.

To evaluate the role of cystoscopy in bladder neck preservation, we performed preoperative cystoscopy in 74 consecutive patients before robotic prostatectomy. During dissection of bladder neck tissue from the prostatic base, the relative movement of each structure, combined with information of median lobe enlargement obtained by cystoscopy, was used to overcome the lack of tactile sensation inherent in robotic surgery. Preoperative clinical stage was evaluable in 60 patients, including T1c in 47 and T2a/b in 13. Mean PSA was 6.0 ng/dl. Preoperative Gleason score was 61% Gleason 6, 30% Gleason 7, and 9% percent Gleason 8. The postoperative prostatic volume was 53.51 gms (35-130 gms.) Fourteen (24%) had prostate volumes of equal to or greater than 80 gms (80-130 gms.)

Key Point:
We have found that combining preoperative cystoscopy with intraoperative bladder neck preservation allows bladder neck negative margin status during robotic prostatectomy. Identifying the intraurethral anatomy and median lobe status followed by establishing a plane of dissection utilizing the movement of the bladder neck relative to the prostatic base overcomes the loss of tactile sensation in robotic surgery.

Using the robotic grasper to manipulate the anterior bladder neck tissue in a gentle cephalad-caudad fashion helps identify the correct plane of dissection and facilitates bladder neck preservation.

The positive margin rate for the posterior apex, posterior base, and lateral base was 8%, 3%, and 3%. No patient had a positive bladder neck margin.

We have found that combining preoperative cystoscopy with intraoperative bladder neck preservation allows bladder neck negative margin status during robotic prostatectomy. Identifying the intraurethral anatomy and median lobe status, followed by establishing a plane of dissection utilizing the movement of the bladder neck relative to the prostatic base overcomes the loss of tactile sensation in robotic surgery.
Nephroureterectomy Significantly Impacts Eligibility for Adjuvant Chemotherapy

Andrew Stephenson, MD

Neoadjuvant cisplatin-based combination chemotherapy may confer benefits on patients who present upper tract urothelial carcinoma (UTUC), but only a minority, fewer than 25%, can be considered eligible for the treatment. It is important to identify these patients prior to invasive procedures because the decline in kidney function that commonly follows nephroureterectomy prohibits adjuvant chemotherapy.

Upper tract urothelial carcinoma is uncommon. Cases of invasive UTUC account for about 5% of urinary tract cancers, most of which appear in the bladder. The disease is often confirmed only during nephroureterectomy, and the standard treatment is surgical excision or distal ureterectomy in those select patients with distal tumors.

Outcomes for patients with extensive disease following surgery are poor with estimates of cancer-free survival ranging from 60% to 80% at five years. These results may be attributed to, but not limited to, delays in diagnosis and treatment, more aggressive tumor biology, and inferior treatment strategies.

The relative rarity of invasive UTUC has hindered the development of multimodal therapies. The therapies applied today are often derived from experience with invasive bladder cancer.

Bladder cancer patients at risk of recurrence typically undergo radical cystectomy and perioperative cisplatin-based combination chemotherapy administered in a neoadjuvant or adjuvant setting. Neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin confer an approximate 7% improvement in overall survival compared to cystectomy or primary radiotherapy alone.

However, this regimen can have profound deleterious effects on patients with chronic kidney disease and on that substantial portion of patients who will experience a significant decline in kidney function following nephroureterectomy. One recent study found that while 26% of kidney cancer patients evidenced chronic kidney disease preoperatively, 65% presented with the disease following radical nephrectomy.

Our team sought to identify those patients whose renal function before and following nephroureterectomy would make them potential candidates for neoadjuvant cisplatin-based combination chemotherapy (CBCC). This would also allow determination of that portion of patients who were likely to be excluded from adjuvant therapy following surgery. Patients with UTUC are typically older than the renal cell carcinoma population. The median age of the cohort we studied was 72. They also have a higher prevalence of comorbid conditions that may compromise renal function.

Key Point:

In our retrospective analysis of 470 patients with known or suspected urothelial carcinoma of the renal pelvis and/or ureter, slightly more than half had chronic kidney disease when diagnosed. The proportion increased to 78 percent following nephroureterectomy. The impact that nephroureterectomy has on kidney function indicates that if patients are to derive benefits from cisplatin-based combination chemotherapy, it should be administered preoperatively.

We looked at 470 patients (mean age 72) with known or suspected urothelial carcinoma of the renal pelvis and/or ureter. Sufficient data were available in 336 cases for analysis of renal function and outcomes. Preoperative and postoperative creatinine levels were obtained from their records and the estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease study equation. Chronic kidney disease was defined as eGFR <60 mL/minute/1.73m2, according to National Kidney Foundation guidelines.

The criteria indicated that chronic kidney disease was present in slightly more than half (52%) of patients when they were diagnosed with UTUC. This proportion increased to 78% following nephroureterectomy. Using a minimum eGFR of 60ml/min/1.73m2 to determine eligibility for CBCC, we found that 61% of nephroureterectomy patients (and 49% of high-risk patients) were rendered ineligible for CBCC by the procedure. The impact that nephroureterectomy has on kidney function indicates that if patients are to derive benefits from CBCC, it should be administered preoperatively.

The impact that radical nephrectomy has on the development of kidney disease emphasizes the need for nephron-sparing approaches to small renal masses. The American Urological Association recently updated its guidelines to recommend nephron-sparing approaches when feasible. Given the incidence of kidney disease in patients with UTUC and the risks of nephrectomy-induced kidney disease, it seems appropriate at this time to re-evaluate the role of nephroureterectomy in all patients with UTUC. For instance, uroscopic laser ablation may be a reasonable alternative for patients with small, low-grade lesions that pose a low risk of progression.
Intentional Weight Loss in Chronic Kidney Disease

Sankar Navaneethan, MD

Currently, more than 25 million Americans suffer from chronic kidney disease (CKD) and it is estimated that in 2015 there will be more than 700,000 prevalent cases of end stage renal disease (ESRD) in the United States. Nearly two-thirds of U.S. adults are overweight (body mass index >25) and of these, one-half are obese (body mass index >30). Obesity is an independent predictor of cardiovascular disease, mortality, and development of CKD and ESRD in the general population. Obesity also contributes to the progression of kidney disease in patients with pre-existing kidney disease.

In a retrospective study, we noted a potential improvement in renal function with bariatric surgery in patients with pre-existing kidney disease. Our recent systematic review of the current available evidence on this topic showed that in CKD patients, weight loss attained through non-surgical interventions was not associated with a change in glomerular filtration rate (GFR), but statistically significant improvement in proteinuria was observed over a short period of follow-up. On the other hand, weight loss attained through bariatric surgery was associated with a normalization of glomerular hyperfiltration (i.e., decrement in GFR to normal range). After weight reduction achieved through either intervention, systolic blood pressure and total cholesterol levels were reduced. There is a lack of long-term studies that analyzed the impact of these different weight loss interventions on patient-centered data such as development of ESRD. Furthermore, most studies used creatinine-based equations rather than iothalamate studies (gold standard for assessing GFR). Creatinine-based GFR is unreliable in obese CKD patients.

We also aimed to assess the mechanistic effects of weight loss with bariatric surgery in reducing urinary albumin excretion in severely obese patients with diabetes. We noted decrease in urinary albumin excretion with Roux-en-Y Gastric Bypass (RYGB) surgery. The decrease in albuminuria correlated with the improvement in insulin sensitivity and HMW adiponectin in the RYGB group, but not with BMI and other adipokines. The reduction in albumin excretion was higher in patients with pre-existing microalbuminuria.

Key Point:

Preliminary data show possible benefit from weight loss in kidney disease but these benefits have not been studied using optimal methodology. We are initiating a prospective cohort study on the impact of weight loss attained with bariatric surgery or lifestyle modifications.

Even though preliminary data from our group and others show possible benefit from weight loss in kidney disease, these benefits have not been studied using optimal methodology. This is important given the ‘obesity paradox’ reported in dialysis patients with obese patients living longer than patients who are non-obese. Whether such associations exist in non-dialysis-dependent CKD is unknown. We are initiating a prospective cohort study in which data will be collected pre- and post-intervention to study the impact of weight loss attained with bariatric surgery or lifestyle modifications on adipokines, such as total and HMW plasma adiponectin levels, markers of inflammation, insulin resistance, urinary protein excretion and renal function (using iothalamate studies) in obese CKD patients who are not on dialysis.

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The Patient Experience in a Certified-Nurse-Practitioner-Run Chronic Kidney Disease Clinic

**Key Point:**
Better blood pressure control and satisfactory cholesterol control in our patients are some of the favorable outcomes we have begun to see in our CNP-run CKD Clinic.

*Jennifer Lyons RN, MSN, CNP*

Our CKD Clinic opened in May 2006 and currently more than 400 patients receive care there. The majority of the patients’ office visits are with a Certified Nurse Practitioner (CNP) and at least once a year they are seen by their referring nephrologist.

Most patients have a 45-minute office visit with the CNP, in comparison to the 20-minute visit with their physician. The purposes of the office visit are to address blood pressure (BP) control, glucose control (in diabetics), anemia management, mineral and bone disorders and lipid management. Many patients come to the office visit with primary care complaints, which are handled as well.

The goals of the CKD Clinic are to educate the patient about his or her medical condition, eGFR and possible progression of kidney disease. It is important that these patients are educated on medications and what needs to be done to halt the progression of CKD, such as BP and glucose control. Patients also need to be educated on what to expect if things do progress.

We currently offer patients a dedicated visit to provide education on treatment options for end stage renal disease, including hemodialysis, peritoneal dialysis and renal transplant. Detail is given on AV fistula placement and avoidance of a dialysis catheter. These patients are also offered a visit with a renal nutritionist to help them adhere to a renal diet.

CKD is considered a very strong risk factor for coronary events and an MI equivalent. Care for the CKD patient is directed toward decreasing risk factors such as hypertension, hyperlipidemia and uncontrolled diabetes.

We have begun to see favorable outcomes from our CNP-run CKD Clinic. BP control in our patients has been better than noted in patients previously treated solely by a physician. A random sample of 100 patients revealed BP control ≤ 130/80 mmHg in 70% of the patients. This is outstanding data and is achieved rather easily. A big part of this equation is empowering the patient through education. CKD patients are taught to know their medications and why they take them, and have a written schedule for taking them. They are given a home blood pressure digital monitor with an appropriately sized cuff. This monitor is either purchased by the patient or bought with money that is received in donation. Patients are taught how to use the monitor in the office and have frequent follow-up by phone and in the office.

Another favorable outcome is satisfactory cholesterol control by way of LDL cholesterol < 100 mg/dl. Of the random sample noted above, 76% of the patients had an LDL < 100 mg/dl, and 46% had an LDL < 80 mg/dl.

As the CKD Clinic continues to grow, there will be ample opportunity to track various outcomes and report positive data that can be associated with having a CNP-run CKD Clinic.

For references, please email the editor.

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Urinary HC-HA Complex and Heparan Sulfate as Early Biomarkers of Diabetic Nephropathy

*Aimin Wang, PhD*

Diabetic nephropathy (DN) is the single most important cause of renal failure in adults in the Western world and is responsible for 25% of all new cases of uremia. Albuminuria is the first clinical marker in diabetic patients who are developing DN, but there is no biomarker for the changes in the early stage of DN. Since the early 1980s, numerous studies have been undertaken to define the contents of urinary glycosaminoglycans (GAGs), including hyaluronan (HA), chondroitin sulfates (CSs), dermatan sulfates (DSs), and heparan sulfates (HSs), as markers of the early stages of DN and of the disease progression using ~400 diabetic patients at various stages of DN. However, the methods used in these early studies only report the changes in total amounts of GAGs and do not yield definitive data reflecting their metabolic states. The data are discrepant and sometimes even contradictory. Nevertheless, they all come to the same conclusion that urinary GAGs, particularly HSs, are early biomarkers of this disease.

**Key Point:**
We plan to adopt a ‘Metabolomic’ approach to define urinary GAGs as early biomarkers of diabetic nephropathy (DN) in both human diabetic patients and animals at levels of: 1) total amount of each subclass; 2) disaccharide composition and the domain structures; and 3) size and protein-GAG complexes. This study will reveal significant new insight regarding key structural profiles of urinary GAGs that are the early biomarkers of clinical diagnostics and treatment of DN and provide a non-invasive method to detect and monitor the development and progression of DN at early stages.
We have developed rapid, versatile, user-friendly, and highly sensitive methods to determine both the concentrations and fine structures of GAGs using specific enzyme digestion of CSs, HA and HSs and analysis by fluorophore-assisted carbohydrate electrophoresis (FACE) and have established the correlation between structural changes of GBM HS and progression of DN in the STZ-diabetic rat model. We plan to adopt a ‘Metabolomic’ approach to define urinary GAGs as early biomarkers of DN in both human diabetic patients and animals at levels of: 1) total amount of each subclass; 2) disaccharide composition and the domain structures; and 3) size and protein-GAG complexes.

The maintenance of the defined fine structure and/or negative charge density of the renal GAGs, particularly glomerular HSPGs and HS oligosaccharides, is essential for normal kidney physiology. Structural fingerprints of the GAGs are tightly controlled by multiple pathways regulated by enzymes in both intra- and extracellular compartments. Thus the urinary metabolites of GAGs will reflect the renal cellular and tissue responses and metabolic activities to hyperglycemic stress that are associated with development and progression of DN.

A chronic local inflammation caused by infiltrated monocytes/macrophages in both glomerular and interstitial regions is the early event in DN. Glomerular mesangial cells and renal interstitial epithelial cells under hyperglycemia synthesize and deposit a HA matrix that is specifically recognized by inflammatory cells that are recruited into the tissue within a week after diabetic onset. This pro-inflammatory HA is modified by a unique reaction that transfers heavy chain (HC) proteins from an unusual serum macromolecule, inter-alpha-trypsin inhibitor (IαI) (Figure). The HC transfer is catalyzed by the TNF-α-induced protein 6 (TSG-6), a protein that is often up-regulated in inflammations. HCs are the only known proteins that are covalently bound to hyaluronan.

Previous studies have also shown increases of hyaluronan in both serum and urine of diabetic patients as well as a higher frequency of urinary trypsin inhibitor (UTI), the urinary version of serum IαI. Thus, the HC-HA complex is likely to be a robust marker of diabetic renal inflammation.

This study will reveal significant new insight regarding key structural profiles of urinary GAGs that are the early biomarkers of clinical diagnostics and treatment of DN and provide a non-invasive method to detect and monitor the development and progression of DN at early stages. Furthermore, chronic inflammation and podocyte damage are two common factors in other kidney diseases, and thus this study could have a broad application in clinic diagnostics and treatments of the kidney diseases of interest to the field.
New Membrane for Bioartificial Kidney Shows Improvements Over Polymer Membranes

William Fissell, MD

Working with engineers at the University of California, San Francisco and Pennsylvania State University, we have developed the first entirely new membrane for renal replacement since the high-flux polysulfone dialyser. The membrane is made from a silicon chip, just like a microprocessor, and has pores that are shaped like slots, rather than round holes, mirroring the elongated slot-shaped pores that have evolved in many animals. We tested the novel membranes and predicted the membrane’s benefit would be in permeability — letting salt and water through, but retaining proteins — and the predictions were correct. In a recent paper, Andrew Zydne, Chair of Chemical Engineering at Pennsylvania State University and a close collaborator on the bioartificial kidney project, demonstrated that the novel membranes also were able to discriminate between smaller molecules and larger molecules more effectively than membranes with round pores. This finding was borne out by experiments showing that the new membranes could retain albumin and other large proteins while passing 2-microglobulin, a molecule that accumulates in renal failure.

For references, please email the editor.

A New Approach to Antibiotics in the ICU

William Fissell, MD

Acute renal failure is a common complication of severe illness and affects patients with medical and surgical diseases. Many patients with acute renal failure die of infection, and almost all are treated with antibiotics at some point during their illness. Selecting a drug dose to prescribe for a patient in the ICU is challenging, as almost all of the physiology that controls drug elimination is abnormal in critically ill patients with renal failure. Plasma protein binding, blood flow to the liver and other vital organs and kidney function are altered. At the American Society of Nephrology’s Renal Week 2009, we showed that present antibiotic dosing schemes may not always be adequate for patients on continuous dialysis. In an exciting innovation, we were able to use a spent dialysate — a waste product — to measure the patient’s blood antibiotic levels. This is an inexpensive way to bypass complicated and expensive sample preparation for HPLC and avoids drawing even more of the patient’s blood — always an issue in the ICU.

For references, please email the editor.
Improving Efficiency and Quality in Patients Undergoing Vaginal Sling Surgery

Sandip Vasavada, MD, and Howard B. Goldman, MD

Although vaginal sling surgery is one of the more commonly performed operations in the United States, very little has been done to standardize the perioperative practice as it relates to antibiotic use or postoperative catheterization protocols. We have conducted several studies currently in press that attempt to streamline practice in vaginal sling surgery and assure that both AUA Best Practice standards are adhered to and patients are discharged safely with the least morbidity possible.

We initially sought to identify practice patterns among U.S. urologists who perform vaginal sling surgery. We were interested in the current state of management of these patients with respect to antibiotic usage, methods to determine adequate voiding for discharge and postoperative catheterization management. What was noted is overall poor adherence to AUA Best Practice Standards with more than 50% of surgeons using more than 5 days of postoperative antibiotics in patients undergoing synthetic mid urethral slings. Furthermore, the main reason cited for this was to prevent sling erosions. A retrospective comparative trial was performed at Cleveland Clinic to evaluate single dose antibiotic prophylaxis before mid urethral sling surgery compared with 3 days of postoperative antibiotics (all performed before 2007). We noticed overall outcomes were no different in subgroups with regard to postoperative infections, yet complications from antibiotic use were higher in the prolonged antibiotic patient population.

Over the last several months, our Center for Female Pelvic Medicine and Reconstructive Surgery has performed a prospective trial on more than 100 patients undergoing mid urethral synthetic slings to evaluate the optimal method for postoperative catheter management. We have developed the FAST protocol (Force of Stream after Sling Therapy). Patients undergoing standard outpatient mid urethral synthetic slings have their bladders filled within one hour after surgery with 300 cc of sterile fluid. Patients are then asked to rate their stream postoperatively on a visual analog scale, such that if they rate their stream at more than 50% of preoperative status, they may be discharged regardless of the post-void bladder scan residual. The study is complete and appears to show that post-void bladder scans add little value in patients in this setting provided they are voiding with streams self-rated at more than 50%. A multitude of additional outcomes are being evaluated in this now complete prospective analysis. Thus, we hope to show that we can continue to efficiently optimize patient outcomes without adding morbidity.

For references, please email the editor.

Single-stage InterStim Implant Decreases Possibility of Device Infection

Gamal M. Ghoniem, MD, FACS

Sacral neuromodulation is performed either as a single-stage full implant after successful percutaneous nerve evaluation (PNE) or as a two-stage procedure. Infection is a serious complication that may lead to device explantation. Contemporary series report a rate of 3-5% device explantation due to infection.

We conducted a retrospective IRB-approved single-surgeon case series study for patients who underwent InterStim® implant. Total number of patients was 126 with mean age of 64.1; 93 were females and 33 were males. The primary aim of this study is to identify the general rate of infection in our institution. The secondary aims: A. to compare the rate of infection of full implant procedure with that of staged procedure; B. to identify the risk factors for infection; and C. to review the effectiveness of our infection control protocol.

The procedure was classified into either full implant or two stages with/without PNE. In patients with staged procedure, the time between the two stages was set to 10-14 days. Our antibiotic protocol included preoperative 2nd generation cephalosporin, GU antibiotic solution irrigation, and postoperative oral fluoroquinolones. All patients with signs of infection were evaluated and, if diagnosed with wound infection, were admitted, a swab culture of discharge was taken, and they received IV vancomycin.

Sixty-one had full implant after successful PNE, and 61 had staged procedure with no prior or equivocal result of PNE. Of the 61 patients who underwent staged procedure, 44 patients (72%) proceeded to second stage. Five cases of infection were diagnosed (3.96%). All cases occurred after staged procedure. Four out of the 5 cases occurred after first stage and one after second stage. Two cases experienced explantation of the device (1.6%). Both patients had MRSA wound infection. In other cases of infection, patients presented with wound pain, redness, no fever, and cultures were negative. They improved with IV vancomycin and gentamicin.

We concluded all infections occurred with staged procedure. It seemed that a short duration between first and second stage in addition to good preparation of the patient for surgery contributed to our low rate of infection. Early recognition and proper management of infection led to better salvage of the device, and lower explantation rate. This study calls for improvement and modification of PNE technique to lessen the number of patients requiring two-stage implant.

This article is written for educational purposes only and as a convenience. Cleveland Clinic has no financial interest in nor is it endorsing any product or device described in this article.
Vaginal delivery is a risk factor for stress urinary incontinence (SUI), as are both type 2 diabetes and obesity. Considering the current obesity epidemic and the increasing incidence of type 2 diabetes, understanding how these conditions influence the development of SUI is of increasing clinical value.

We studied obese and non-obese rodents that had either normal or elevated blood glucose levels to identify the different effects of obesity and type 2 diabetes. Once rodents developed obesity and type 2 diabetes some received simulated childbirth injuries consisting of a bilateral pudendal nerve crush, a well-studied model of childbirth injury involving the neuromuscular continence mechanism comprised of the nerve itself and the external urethral sphincter, which it innervates.

Following nerve injury and a 4-week recovery period, the lower urinary tract underwent functional testing. Function was assessed with electrophysiological recordings of the external urethral sphincter and pudendal nerve, as well as leak point pressure.

Uninjured animals with obesity and without diabetes had significantly reduced urethral sphincter activity. Additionally, nerve-injured obese and non-diabetic rodents showed a significantly less recovery of pudendal nerve activity following injury. Therefore, it appeared that obesity reduced urethral sphincter activity without injury and impaired pudendal nerve recovery following nerve injury.

Uninjured animals with obesity and diabetes had significantly reduced pudendal nerve activity. Similar to the obese and non-diabetic group, urethral sphincter activity was also significantly lowered without injury. Following nerve injury, obese and diabetic rodents had significantly reduced recovery of urethral sphincter activity. Thus, obesity and type 2 diabetes reduced pudendal nerve and urethral sphincter function without injury and impaired urethral sphincter recovery following nerve injury.

Overall, obesity appeared to negatively affect sphincter function and impair recovery in these animal models. We hypothesize that adipokines, or cytokines produced by adipose cells, such as leptin may be involved in the changes observed. Because the rodents in this study were leptin-resistant due to genetic knockout, leptin levels were greatly elevated. As a result, we intend to investigate the effects of obesity on lower urinary tract function using a non-leptin-resistant model of obesity in which levels of the adipokine more closely follow human physiology.

Pudendal nerve dysfunction occurred with type 2 diabetes but not with obesity. We hypothesize that diabetic peripheral neuropathy is likely causative of the observed reduction in nerve function. As our study continues, we intend to explore this theory further by studying the pudendal nerve for evidence of diabetic neuropathy such as advanced glycosylation end products, oxidative damage, and other markers of glucose-induced cellular damage.

Overall, we have gained insight into the effects of obesity and type 2 diabetes on lower urinary tract function. Further work is necessary to identify the mechanisms through which these changes occur. Our data support clinical recommendations for women to maintain healthy weights and blood glucose during pregnancy.

Weights and blood glucose levels of groups in the study. Black squares indicate normal weight (solid line) and normal blood glucose (dashed line). Dark gray circles indicate obesity (solid line) and normal blood glucose (dashed line). Light gray triangles indicate obesity (solid line) and diabetes (dashed line). These groups enabled research of the effects of both diabetes and obesity on incontinence.
Female Urology

Gamal Ghoniem MD, FACS

There are currently 4 urethral bulking agents (UBAs) in the United States approved for the treatment of adult female stress urinary incontinence. Contigen® was the first FDA approved UBA to which Coaptite®, Macroplastique® and Durasphere® have been compared. All 3 studies used different methods of analysis, making it difficult to compare treatment outcomes. Intent-to-treat using last observation carried forward (ITT LOCF) was used for Coaptite, ITT for Macroplastique and as-followed for Durasphere. The objective of this review and methods analysis is to compare published FDA data by using the same intent-to-treat and as-followed analyses.

UBAs’ study inclusion criteria were homogenous including adult women with major complaint of stress urinary incontinence secondary to ISD. Techniques for injection were similar and used either the periurethral or transurethral technique. The primary endpoint for all studies was improvement of ≥1 Stamey grade from baseline to 12 months. Using the same ITT and as-followed methodology, a reanalysis of Stamey improvement was conducted in the 3 studies.

Mean total volumes injected per patient were: 4.0, 6.8 and 7.6 cc for Coaptite, Macroplastique and Durasphere, respectively. Contigen volumes (controls) were 6.8, 7.2 and 9.6 cc, respectively. Mean number of treatments per patients were 1.9, 1.5, 1.7 for Coaptite, Macroplastique and Durasphere, compared to 2.0, 1.6 and 1.6 for Contigen.

Only Macroplastique had significant treatment outcomes compared to Contigen using ITT analysis. None of the UBAs were inferior to Contigen. See table.

These results emphasize the importance of analytic method when critically comparing treatment outcomes. This study is limited by not being a head-to-head clinical study. However, similarities of design allows for a reasonable comparison of the efficacy of UBAs.

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<th>12-Month FDA IDE Study</th>
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<td>Macroplastique Contigen</td>
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<td>60/125 (48.0%)</td>
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Understanding the Role of Nerve and Muscle Injury in Incontinence

Bradley C. Gill, Hai-Hong Jiang, MD, PhD, Charuspong Dissaranan, MD, Brian M. Balog, Margot S. Damaser, PhD

Stress urinary incontinence (SUI) is 240% more likely to occur in women who delivered vaginally than women who did not. Vaginal delivery has been associated with damage to the urethral sphincter and pudendal nerve, which innervates and controls the urethral sphincter. Together, the nerve and muscle comprise the neuromuscular continence mechanism, which is responsible for preventing SUI by closing the urethra during periods of increased bladder pressure. When this mechanism is damaged, either from injury to the pudendal nerve, urethral sphincter, or both, SUI results if recovery is inadequate.

Peripheral nerve injury results in an overexpression of neurotrophins in the tissues and organs innervated by the damaged nerve. Neurotrophins act in a retrograde fashion, signaling receptors on the damaged nerve that stimulate neuroregeneration. Following pudendal nerve injury, brain-derived neurotrophic factor (BDNF) was overexpressed in the urethral sphincter. However, after sphincter injury, overexpression did not occur. Furthermore, when nerve and sphincter injury were combined, the sphincter injury was predominant, preventing nerve injury from causing BDNF overexpression, resulting in slowed neuroregeneration and recovery.

The BDNF responses in sphincter and nerve injury, which can be combined to simulate damage to the continence mechanism during childbirth, are the motivation behind current research on regenerative therapies for SUI. We are studying the treatment of pudendal nerve with BDNF following injury, and we are investigating electrical stimulation and its BDNF response.

Because sphincter damage prevents the overexpression of BDNF needed to stimulate neuroregeneration of the pudendal nerve, treating the nerve directly with BDNF may help restore the neuroregenerative response. Initial results appear to support this. In rodents treated with BDNF, compared to placebo, continence was improved 2 weeks following simulated childbirth injury. Additionally, electrophysiological recordings of urethral sphincter activity also showed improvement with BDNF compared to placebo. Therefore, at this time it appears BDNF improves continence and urethral sphincter function following childbirth injury. The next phase of this project will investigate the neuroregenerative response to gain insight into the molecular mechanisms of this effect. It appears that electrical stimulation can improve neuroregeneration following childbirth injury. The next phase of this project will involve studying the functional effects of stimulation on continence and electrophysiological activity of the neuromuscular continence mechanism.

These results are exciting in that they may be the first steps toward developing a preventative treatment given after delivery that can reduce the incidence of SUI. Additionally, such treatments also may hold value as an adjunct to surgical therapies, such as minimally invasive slings, where structural repair cannot adequately restore continence due to a dysfunctional neuromuscular mechanism.

Key Point:

We are studying the treatment of the pudendal nerve with brain-derived neurotrophic factor (BDNF) following injury and investigating electrical stimulation and its BDNF response. At this time it appears BDNF improves continence and urethral sphincter function following childbirth injury. The next phase of this project will investigate the neuroregenerative response to gain insight into the molecular mechanisms of this effect. It appears that electrical stimulation can improve neuroregeneration following childbirth injury. The next phase of this project will involve studying the functional effects of stimulation on continence and electrophysiological activity of the neuromuscular continence mechanism.

Immunofluorescent image of the pudendal nerve innervating the external urethral sphincter from a healthy, uninjured specimen. Striated muscle cells of the urethral sphincter are blue. Neurofilaments within the pudendal nerve are green. Neuromuscular junctions, where the pudendal nerve innervates the muscle cells, are red.
A More Accurate Prognostic Tool for Invasive Bladder Cancer

Andrew J. Stephenson, MD, Michael C. Gong, MD, PhD, Steven C. Campbell, MD, PhD, Amr F. Fergany, MD, and Donna E. Hansel, MD, PhD

We have developed a method that appears to predict recurrence-free survival and overall survival in post-cystectomy bladder cancer patients with greater accuracy than the current TNM (tumor-node-metastases) system.

Aggregate lymph node metastasis diameter (ALNMD) is an analytic approach that derives its potential to be a more reliable predictor of survival from the acquisition of a more clearly defined estimate of the extent of lymph node involvement. The improved prognostic accuracy provided by ALNMD permits a more rational application of adjuvant therapy, a more sound design for clinical trials, and enhances patient counseling.

The TNM system is now used to stratify patients with respect to survival, but several studies indicate its utility is limited when predicting treatment outcomes for lymph node (LN) positive patients. The system recommends that the size of involved lymph nodes be incorporated into staging criteria rather than the size of the metastatic deposit. Our study of 134 patients with LN-positive urothelial cancer of the bladder found that in a third of the patients, the largest lymph node was twice the size of the largest metastatic deposit. In these patients, the largest lymph node would not be an accurate assessment of the extent of metastatic disease.

We hypothesized that the largest LN metastatic deposit and/or the ALNMD would be a better predictor of overall survival (OS) than the TNM system as it is currently utilized. To test this hypothesis we looked at 134 LN-positive patients who had undergone open cystectomy (124) or laparoscopic cystectomy (10) for urothelial carcinoma of the bladder between 1999 and 2007. All patients had the standard pelvic lymph node dissection and additional dissection as warranted. Those LN-positive patients with good performance status and adequate renal function were recommended to receive adjuvant chemotherapy.

In addition to undergoing a range of analyses, individual lymph nodes were measured along the greatest dimension to the nearest millimeter. This measure was then correlated with the gross measurement. Each metastatic deposit was measured to the nearest millimeter and correlated to the gross measurement in matted LN and grossly identifiable metastases.

The median follow-up among survivors was 23 months. At this writing, 71 patients have died of progressive bladder cancer, 5 of other causes and 13 of unknown causes. The median recurrence free survival (RFS) was 14 months and the 4-year RFS was 23%. The median OS was 17 months and the 4-year OS was 25%.

Univariate analysis found that ALNMD was associated with OS (hazard ratio [HR] 1.1, P = 0.021) and RFS (HR 1.1, P = 0.017). Multivariate analysis of pathologic T stage, lymphovascular invasion LN density, surgical margins, extranodal extension, and Charlson score, found that when ALNMD was added to these parameters, it was significantly associated to OS (HR 1.1, P = 0.035). The multivariate analysis also found that ALNMD to be significantly associated with RFS (HR 1.1, P = 0.04) Importantly, these analyses showed that ALNMD predicted OS more accurately than the TNM staging system. The study now needs validation.

Even at this stage of development, our study and other studies of the strengths and weaknesses of the TNM system indicate that it might now be appropriate and beneficial to revise that system to incorporate ALNMD, LN density, extranodal extension, and the total number of positive and negative LN.

**Key Point:**

ALNMD derives its potential to be a more reliable predictor of survival in post-cystectomy bladder cancer patients from the acquisition of a more clearly defined estimate of the extent of lymph node involvement. Its improved prognostic accuracy permits a more rational application of adjuvant therapy, a more sound design for clinical trials, and enhances patient counseling. Our analyses showed that ALNMD predicted overall survival more accurately than the TNM staging system.
Putative Role for Mammalian Target of Rapamycin (mTOR) in Urothelial Carcinoma

Christina B. Ching, MD, and Donna E. Hansel, MD, PhD

A significant proportion of bladder cancer patients advance to muscle-invasive disease and 30-50% of these patients, ultimately develop and succumb to metastatic disease. For patients with advanced bladder cancer, radical cystectomy with or without chemotherapy remains the standard of treatment, although the benefits of such therapy are often limited. New treatment options are a necessity given the likelihood of poor outcomes for many patients.

Activation of the mammalian target of rapamycin (mTOR) signaling pathway has been implicated in various cancers, with recent attention focused on urothelial carcinoma (UCC). As a downstream effector of PI3-kinase/AKT signaling, mTOR mediates key cellular functions, including cell proliferation and protein translation. We have investigated the role of mTOR signaling and inhibition in UCC using both in vitro and in vivo models and have identified effects on clinical outcomes, cellular proliferation and tumor growth. Furthermore, the effects of mTOR on the latter two processes can be abolished by inhibition of mTOR by rapamycin, a well-characterized mTOR inhibitor.

In the first part of our study, we evaluated 121 radical cystectomy specimens from patients with muscle-invasive UCC (≥pT2) for mTOR activity via phosphorylated-mTOR (p-mTOR) and phosphorylated S6 (P-S6), a downstream target of mTOR activation. mTOR pathway activation occurred in the majority of patients examined and appeared to predict depth of invasion and ultimately patient survival. Analysis of mTOR effects in immortalized UCC cell lines indicated a prominent role for mTOR in mediating cell proliferation in all lines tested, with a dose-dependent inhibition demonstrated by rapamycin. We confirmed these effects were specific for the mTOR pathway by using an mTOR siRNA to demonstrate that, once treated with mTOR siRNA, rapamycin was unable to exert any effect on cell growth. In an associated T24-xenograft mouse model, rapamycin also reduced proliferation rates and reduced tumor size to 45% of control.

Key Point:

We found that a large proportion of patients with urothelial carcinoma have increased activity of the mTOR signaling cascade and that activation of the mTOR pathway affects cell proliferation and patient survival. These results may indicate a new potential target in the treatment of this disease.

Overall, we found that a large proportion of patients with UCC have increased activity of the mTOR signaling cascade and that activation of the mTOR pathway affects cell proliferation and patient survival. Our results are supported by recent findings that mTOR activation appears upregulated in invasive bladder cancer relative to normal urothelium and that loss of upstream PTEN and p53 appear to contribute to mTOR pathway activation in mouse models. Increased mTOR pathway activation also appears to play a significant role in development of upper tract UCC arising in a background of PTEN loss. These results support the putative role for the mTOR pathway in the pathogenesis and progression of UCC and may indicate a new potential target in the treatment of this disease.

For references, please email the editor.
Using the TUNEL Test to Identify Infertile Men with Sperm DNA Damage

Ashok Agarwal, PhD, Rakesh K. Sharma, PhD, Sajal Gupta, MD, and Edmund Sabanegh Jr., MD

A number of studies have shown that DNA strand breaks are higher in infertile men than fertile men. Evaluation of sperm DNA damage can help better predict the outcome of spontaneous pregnancy and assisted reproductive techniques (ART) than traditional sperm parameters. Therefore, assessment of sperm DNA damage is critical to allow stratification for various medical and surgical treatments as well as ART.

The two most commonly used assays to measure DNA damage are the terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay and the sperm chromatin structure assay (SCSA). While SCSA has been extensively standardized, TUNEL has not, which has limited its clinical use in the past. The TUNEL assay measures a definitive end point (presence of free 3' hydroxyl groups), can measure both single and double strand DNA fragmentation, and can provide more meaningful information on the implantation potential of an embryo. It is technically less challenging and does not require a dedicated flow cytometer, unlike the SCSA assay. The routine use of the TUNEL assay in andrology laboratories has been limited due to lack of statistically validated threshold values (cutoff values and sensitivity/specificity) for measuring sperm DNA damage in infertile men.

Continued on next page
Our andrology laboratory has established the normal range for sperm DNA damage to differentiate infertile men from fertile men using the TUNEL test. We screened 194 infertile patients who were seeking medical advice for male factor infertility (idiopathic infertility, varicoceles, infection and other known etiologies) as well as 25 normal men of proven and unproven fertility (donors) selected on the basis of normal semen analysis. We measured the inter- and intraobserver variability, inter- and intra-assay variability, and established the cutoff value, sensitivity and specificity of sperm DNA fragmentation levels in healthy men and in patients with male factor infertility.

Our results show that at a cutoff value of 19.3% the sensitivity was 64.9% and observed specificity of 100% (Figure 1). We also examined the distribution of DNA damage in control and infertile men and categorized this as: 0-10%, 10-20%, 20-30%, 30-40% and >40%. All controls and 64.9% of patients had DNA damage below the cutoff value of 19.3 (Figure 2). The results of our study demonstrate that the TUNEL test is an excellent predictor of infertility and should be added to the armamentarium of tests utilized in a fertility evaluation. We are currently examining the association of DNA damage with pregnancy outcome in ART setting.

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**The Challenge of Post-Vasectomy Pain**

*John B. Klein, MD, and Edmund Sabanegh Jr., MD*

As many as 1% of patients will incur significant morbidity after vasectomy, despite its long-term effectiveness and safety profile. One of the most concerning long-term complications is testicular pain, or post-vasectomy pain syndrome (PVPS), which is defined as pain lasting at least 6 months post procedure.

Early pain after vasectomy occurs in 30% of men; however long-term pain requiring intervention is present in 1 in 1,000 men. Newer studies suggest that PVPS is more common, identified in 33% of patients and prompting 5% to seek medical attention. No pre- or postoperative factors have been identified that portend the development of PVPS.

Pathophysiology of PVPS remains controversial. Some authors attribute PVPS to high-pressure obstruction/dilation of the epididymis, causing fibrosis. Others suggest extravasation of sperm around the area of vasal transaction and “blown out” portions of the epididymis cause peri-neural fibrosis, neural tissue distortion and inflammation. However it is unclear why some patients develop persistent PVPS, and others only self-limited postoperative symptoms. Previously, infection was thought a possible cause, but culture results from epididymectomy series and clinical review do not support this theory.

Clinical presentation of PVPS is variable, with orchalgia in 90%, at a median onset of 2 years post-vasectomy. Other common symptoms are pain with intercourse or ejaculation and tenderness in the epididymis or prior vasectomy site. PVPS is a diagnosis of exclusion, and all other possibilities must be investigated. The differential diagnosis of orchalgia post-vasectomy includes testis tumor, nerve injury, varicocele, hydrocele, infection, intermittent torsion, hernia, referred pain, and psychogenic causes. These causes can be excluded with a history and physical, urinalysis and flow Doppler ultrasound to exclude tumor and evaluate the scrotal contents.

At Cleveland Clinic, we have worked to develop a new treatment algorithm to address this troubling problem. Treatment progresses in a stepwise fashion, with non-surgical management attempted first. The first tier involves a spectrum of conservative treatment including scrotal support, thermal therapy, physical and sexual activity limitations when pain occurs, and medications such as NSAIDs or narcotics. A psychiatric evaluation is indicated in cases where depression, psychosexual issues, or chemical dependency is suspected. Antibiotic therapy does not appear to be effective in most patients, and is not supported by data. Conser-
Testicular or epididymal pain for ≥ 3 months post vasectomy

Conservative therapy should be considered for at least 3 months prior to considering interventional therapies. The second tier of therapy involves a variety of pain management strategies including spermatic cord blocks, injections of local anesthesia and steroid into the pelvic plexus, acupuncture, and epidural blocks administered by pain management specialists.

Those patients who fail conservative and local therapy are candidates for surgical intervention. The pain must be localized and found to be consistent in location on serial physical exams prior to considering surgery. Many options are available in carefully selected patients, though a thorough discussion of complications and success rates is necessary to set realistic patient expectations. Surgical options performed at Cleveland Clinic include excision of sperm granuloma, epididymectomy, spermatic cord denervation, and vasectomy reversal in highly resistant cases.

Excision of sperm granuloma is performed when pain is localized to this site and a granuloma is present. Excision of the granuloma and occlusion of the vas with intraluminal cautery durably relieves the pain. Patients must be carefully selected for this procedure.

Patients with focal epididymal dilatation and tenderness may benefit from epididymectomy. Up to half of patients with PVPS can be cured by epididymectomy. Epididymectomy technique includes resecting all proximal vas and previous vasectomy site, and all scar tissue. The presence of chronic inflammatory changes of the epididymis, testicular or groin pain, concurrent ED, and normal epididymis on ultrasound portend worse outcomes.

Spermatic cord denervation is another possible treatment option, which may be particularly effective in patients who have previously had transient relief after cord block. Via an inguinal approach, the ilioinguinal nerve and vas deferens are divided. Only the gonadal and testicular arteries, with corresponding lymphatics, are left intact. Potentially 76% of men can be rendered pain free via this approach, although there exists potential for gonadal ischemia after this procedure.

In appropriately selected patients, microsurgical vasovasostomy can produce resolution of pain, with series from our institution and others reporting complete resolution of pain in 60-84%.

Inguinal orchiectomy can be performed to relieve intractable testicular pain, with 73% of patients achieving pain relief. This is a last resort, with obvious potential endocrinologic concerns, especially if symptoms are bilateral or metachronous contralateral PVPS develops.

For references, please email the editor.
Patients with clinical stage 1 nonseminomatous germ cell testicular cancer (CS1 NSGCT) and their doctors must weigh three primary options (surgery, chemotherapy and surveillance) and the potential consequences of those options when making therapeutic decisions. The complexity of this challenge is amplified by the absence of level 1 evidence that would identify an option with maximum survival benefits and minimal side effects.

For instance, patients unfamiliar with the rigors and consequences of chemotherapy can find it difficult to properly imagine and balance the potential of extended life against the possibility of late toxicity, secondary malignant neoplasms and cardiovascular disease that may not appear for decades.

Investigators at Cleveland Clinic’s Glickman Urological & Kidney Institute, Department of Quantitative Health Sciences and Taussig Cancer Institute have created and evaluated a decision model for CS1 NSGCT that for the first time offers reasonable estimates of quality adjusted survival (QAS) for each of the disease’s three initial therapies — retroperitoneal lymph node dissection (RPLND), primary chemotherapy and surveillance.

The model is believed to be the first that weighs both quantity and quality of life. It is designed to offer physicians a means of formulating a course of therapy for individual patients and offer patients a mechanism that allows them to evaluate therapies in terms of survival and side effects. Although the patient, with the help of the physician, must still choose a therapeutic option, the model puts that decision on a much sounder clinical foundation.

Each of the three initial therapies — surveillance, RPLND and chemotherapy — is associated with excellent long-term survival probabilities and acceptable short- and long-term adverse effects. Because the outcomes are similar, treatment recommendations and subsequent patient decisions have historically been based on physician bias. The decision tree created by our team offers patients a grasp of the
probabilities of specific clinical events, the opportunity to see both the decisions they may have to consider in the future and the long-term potential outcomes associated with each of the three initial therapies.

To create the decision tree, we developed a model that incorporates literature-derived estimates of survival, treatment-related morbidity, and patient utilities for each of the health states that might be a consequence of each of the three initial treatments. Patient utilities (a measure of an individual’s preference for a state of health under conditions of uncertainty) were derived from 24 healthy volunteers with no history of cancer. The utilities incorporated in the model included living with untreated cancer, small bowel obstruction, infertility, cardiovascular disease, second malignant neoplasm, peripheral neuropathy and ototoxicity. The volunteers were asked two questions to ascertain their attitudes toward the conditions in regard to death and their acceptance of the risk of death versus definitive treatment.

Noting that the risk of relapse in NSGCT can be predicted with reasonable confidence using the histology of the primary tumor and computed tomography staging, the rating scale analysis showed that all patients except those at high risk of relapse preferred surveillance as the primary treatment. Active treatment with RPLND or chemotherapy became the clearly preferred treatment when the risk of relapse exceeded 46% to 54%. These findings are consistent with treatment guidelines that recommend surveillance for those patients at low risk for relapse. The QAS differences among the three treatment options are small, and the physician and patient, when evaluating the merits of a therapy, should base decisions on QAS conditions that are clinically relevant to the individual patient.

Quality-adjusted life expectancy associated with retroperitoneal lymph node dissection (RPLND), primary chemotherapy, and surveillance by the risk of relapse on surveillance based on utility assessment by a (A) rating scale and (B) standard gamble.
Expanding the Donor Pool for Kidney Transplantation

Paul W. Nelson, MD, FACS

Dr. Nelson recently joined the staff of the Glickman Urological & Kidney Institute and serves as Director of Transplant Services at St. Vincent Indianapolis Hospital. (For a more detailed biography, see page 6.) Dr. Nelson joins Alvin Wee, MD, at the institute’s expanded kidney transplant program there.

Bashir Sankari, MD, has returned to the institute’s expanded kidney transplant program at the Charleston Area Medical Center in Charleston, W.Va. There, he practices with S.C. Jeff Chueh, MD, PhD.

Most patients needing kidney transplantation wait 3 or more years due to the scarcity of suitable donor organs. Some patients with blood group B or O have a willing healthy living kidney donor who is blood group A2 or A2B. About 15% of people with type A and AB blood are the A2 or A2B subtype. We have shown that in many blood group B or O recipients (those with low anti-A IgG titers) transplantation of an A2 kidney results in equivalent graft survival to traditional ABO compatible (B to B, O to O) transplants. Reaction between A2 cells and anti-A isoagglutinin is much weaker than that with A1 cells.

This is true for both living donor and deceased donor patients. Prospective living donors who are blood group A or AB should be sub typed to determine if they are A2 or A2B. There is no desensitization or special immunosuppression required and no increased incidence of rejection. This methodology, originally developed by our team at the Midwest Transplant Network, has now been successfully used in several areas of the United States with equivalent results. Recipients of A2 kidneys have shorter waiting times than do those as a whole receiving a B or O kidney. The incidence of blood group B is about 3 times higher in African-American or Asian recipients than in Whites, and the incidence of chronic kidney disease leading to a need for transplant is much higher in African-Americans than in Whites. It appears that African-American patients with blood group B will be particularly advantaged by the option of receiving an A2 kidney. This technique is only successful (at least without immunologic desensitization) in patients with low anti-A IgG titers. Patients with blood group B are much more likely than those with O to have these low, advantageous titers.

For references, please email the editor.
Marked Variation in Kidney Transplant Patients’ Prognosis Based on Transplant Center of Choice

Jesse D. Schold, PhD

There are currently more than 80,000 patients waiting for a kidney transplant in the United States. This number has grown steadily over the past decade while transplant rates have remained relatively stagnant. The consequences of these trends are longer waiting times for patients and increased mortality for end-stage renal disease (ESRD) patients who are otherwise viable for a transplant. There are numerous factors that affect ESRD patient progression on the waiting list and mortality risk including various demographic characteristics and presence of co-morbidities. However, another important consideration for potential transplant candidates is the center at which patients list for the procedure.

While many patients may list at a center relatively passively, based on physician referral or geographic proximity, the potential to discern which center to select for care may be underappreciated. There is accumulating evidence that facility-level factors in fact have a prominent role in transplant patients’ long-term prognoses. Facility-level factors that have previously been demonstrated to improve transplant candidates’ survival include higher transplant volume, shorter waiting times, past performance level (based on risk-adjusted outcomes) and limited use of high-risk donor organs. In fact, the combination of these factors portend a 50% difference in expected survival rates for candidates from the time of listing (Figure 1).

Unfortunately, much of this information may not be disseminated to patients, or may only be appreciated by those that are proactive to research these factors or those that have the logistical capability to use the information (i.e., travel to different centers). For the sake of equity in the transplant population, significantly more work needs to be done to effectively inform patients about the impact of the decision in which to select a provider of care.

The patient groups that are perhaps most affected by the heterogeneity in facility-level outcomes are the elderly. This is primarily because one of the primary risks for elderly transplant candidates is dying prior to reaching the time in which a deceased donor transplant would become available. In fact, based on projections of growing waiting times, nearly half of elderly patients now listed for kidney transplantation in the United States will not survive their expected interval on the waiting list. While transplantation still nearly doubles life expectancy for these patients, for those listed at centers with extended waiting times, receiving a transplant is not likely in many cases. Waiting times significantly vary by center as well as region of the country. In fact, the probability of dying prior to transplantation among the elderly now listed varies between 6 and 81% by the 11 United Network for Organ Sharing transplant regions (Figure 2).

Cumulatively, more work needs to be done in this field to improve shared decision-making between physicians and patients, determine the most effective modes of dissemination of information to patients, and re-examine policies that drive some of the regional variations. Through ongoing research, our team of investigators at Cleveland Clinic continues to work to understand and develop the most effective and efficient models of healthcare delivery that can improve outcomes for the rapidly growing ESRD population. Current projects include examining the role of new regulatory oversight on quality of care, understanding the impact of polices on ethnic minorities and developing prediction tools that may provide information to patients and caregivers in a transparent fashion. Our broad goals are not only to provide effective care at our institution, but to assist in developing policies and best care practices throughout the nation.

![Figure 1. Life Expectancy Following Listing for Transplantation by Center Characteristics](image1.png)

![Figure 2. Projected Probability of Death Prior to Deceased Donor Transplantation for Candidates Aged 60+](image2.png)
Hyperlipidemia and Chronic Kidney Disease

Brian Stephany, MD

Convincing epidemiologic evidence points to at least an association, and potentially a causal effect, between hyperlipidemia and chronic kidney disease (CKD). The mechanism(s) by which hyperlipidemia may induce renal damage remain speculative and largely based on animal studies. Early work demonstrated that lipogenic diets induce accelerated glomerulosclerosis as well as glomerular macrophage infiltration and foam cell formation. Resident renal cells, including mesangial and podocytes in various animal models, bind non-oxidized and oxidized lipoproteins, which can be directly cytotoxic and/or induce cytokine and growth factor production (e.g., platelet-derived growth factor, monocyte chemoattractant protein-1, interleukin 6, and nuclear factor) and which ultimately lead to mesangial cell proliferation, extracellular matrix expansion, and glomerular injury. Additionally, hyperlipidemia may be a marker of and potentially potentiate endothelial dysfunction, thereby aggravating intrarenal hemodynamics that ultimately impair glomerular filtration rate.

The wealth of clinical trials investigating the treatment of hyperlipidemia in non-transplant patients with or without demonstrable CKD point to a beneficial effect on renal function in patients treated with lipid lowering therapy. Interestingly, whereas studies using fibrates or cholestyramine demonstrate muted (or absent) beneficial renal effects, the renoprotection afforded by statins is more striking, implying these agents may act beyond their ability to lower lipids per se, but may be mainly due to their pleiotropic anti-inflammatory, anti-apoptotic, anti-fibrotic, and anti-albuminuric effects. The data in transplant patients specifically is less robust. A randomized trial of fluvastatin in 2,102 kidney transplant recipients failed to show a beneficial effect on allograft function or loss, though it should be pointed out that this was a secondary outcome in a trial designed and powered to detect differences in cardiac endpoints. A large multicenter randomized trial (i.e., SHARP – Study of Heart and Renal Protection) investigating pre-specified cardiovascular and renal end points in chronic kidney disease patients, including a large proportion of kidney transplant patients, randomized to statin therapy or placebo has finished enrollment with preliminary results anticipated later in 2010. Hopefully this study will provide definitive answers on the matter.

Key Point:

We collected data on 230 lung recipients transplanted between January 1997 and December 2003 and stratified them based on elevated lipid levels early post-transplant. A faster decline in glomerular filtration rate was seen in those with hyperlipidemia early post-transplant, a difference that persisted over extended follow up at five years. Further investigation is ongoing. Our goal is to determine if faster loss of renal function and a greater degree of endothelial dysfunction track with hyperlipidemia and whether initiation of statin therapy ameliorates these adverse findings.
Implicit in studying renal function in kidney transplant recipients both immunologic (i.e., acute or subclinical rejection) and non-immunologic factors can affect glomerular filtration rate adversely and lead to progressive CKD. As such, interpreting the effect on renal function of a single intervention such as treatment of hyperlipidemia with statin therapy can be difficult. In non-renal solid organ transplantation, especially lung transplant recipients, where immunologic injury to the allograft does not directly affect glomerular filtration rate, there is an opportunity to more cleanly investigate the effect of hyperlipidemia and its treatment on renal function.

Cleveland Clinic has the world’s busiest lung transplant program, averaging one transplant every three days. As such, we have ample number of patients to investigate. To this end, we collected data on 230 lung recipients transplanted between January 1997 and December 2003 and stratified them based on elevated lipid levels early post-transplant. A faster decline in glomerular filtration rate was seen in those with hyperlipidemia early post-transplant, a difference that persisted over extended follow up at five years (Figure 1). Additionally, on univariate and multivariate analysis, those with the highest lipid levels early post-transplant were most likely to develop stage 4 CKD or worse (i.e., a glomerular filtration rate of < 30 ml/min/1.73m²) (Figure 2). Finally, those patients in our cohort prescribed statins post-transplant experienced a lower risk of developing CKD (HR 0.77, p=0.03), supporting the findings of trials in non-transplant patients that indeed statins are renoprotective. Further investigation is ongoing to tease out exactly the mechanism(s) of renoprotection afforded by the use of these agents. Specifically, we are initiating measurements of endothelial function and glomerular filtration rate in prospective transplant recipients before and after transplant in those with and without hyperlipidemia. Our goal is to determine if faster loss of renal function and a greater degree of endothelial dysfunction track with hyperlipidemia and whether initiation of statin therapy ameliorates these adverse findings.

Figure 2. Kaplan Meier Curve of survival free of chronic kidney disease post-lung transplant stratified by six month LDL quartiles. (- - - 4th quartile; ---- 2nd and 3rd quartiles; — 1st quartile. 1st vs. 2nd and 3rd, P = 0.02; 2nd and 3rd vs. 4th, P = 0.02; 1st vs. 4th, P < 0.001)
Author Index

Agarwal, Ashok ......................................................... 29
Avalone, Anthony .................................................... 17
Campbell, Steven C. .................................................. 27
Chueh, S.C. Jeff ......................................................... 14
Damaser, Margot S. ................................................. 24, 26
Fengany, Amr F. ...................................................... 27
Fissell, William ....................................................... 22
Ghoniem, Gamal M. ............................................... 23, 25
Goldman, Howard B. .............................................. 23
Gong, Michael C. .................................................... 27
Gupta, Sajal .............................................................. 29
Haber, Georges-Pascal ........................................... 16
Hansel, Donna E. .................................................... 27, 28
Jones, J. Stephen ..................................................... 12, 13
Kaouk, Jihad H. ....................................................... 16
Klein, Eric A. .......................................................... 8
Levy, David A. ........................................................ 13
Lyons, Jennifer ....................................................... 20
Navaneethan, Sankar ............................................... 19
Nelson, Paul W. ...................................................... 34
Sabanegh, Edmund ............................................... 29, 30
Schold, Jesse .......................................................... 35
Sharma, Rakesh K. ................................................... 29
Silverman, Robert H. .............................................. 8
Stein, Robert J. ........................................................ 16
Stephany, Brian ....................................................... 36
Stephenson, Andrew .............................................. 10, 18, 27, 32
Ulchaker, James C. .................................................. 14
Vasavada, Sandip .................................................... 23
Wang, Aimin .......................................................... 20