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Chairman’s Report

Eric A. Klein, MD
Chairman, Cleveland Clinic Glickman Urological & Kidney Institute

The last 12 months have been eventful ones for The Glickman Urological & Kidney Institute. On September 12, 2008, we dedicated the new, high-tech, state-of-the-art Glickman Tower, a 12-story facility on the main Cleveland Clinic campus. The institute occupies the top four floors of the tower, comprising more than 200,000 square feet of space for clinical and academic activities. The Glickman Tower has been carefully designed to provide patients with care for all urological and kidney diseases, to optimize every aspect of the patient experience, and to create an environment in which physicians and scientists from different disciplines can work together synergistically in patient care, education and research.

Highlights of the new Glickman Tower include space for physician academic offices and staff support, work space for residents and fellows, an integrated patient care and clinical research area for the Center for Kidney/Pancreas Transplantation, a new 21-bay outpatient dialysis unit, and dedicated space for the support staff of the Center for Quality Patient Care, Center for Outcomes Research, and the newly named Novick Center for Clinical and Translational Research. The 7th and 8th floors comprise 80 patient exam rooms, including seven dedicated for pediatric urology. Patient, nursing and physician movements are monitored by a built-in Versus Information System, an RFID-based real-time locating system that displays patient wait times and location on easily accessible screens to optimize flow through the outpatient clinic. The 9th floor includes a new urodynamics lab, 12 procedure rooms, and four operating rooms equipped for general anesthesia. A state-of-the-art 88-seat amphitheater resides on the first floor, equipped with Internet access, video links to the operating theatre, and satellite-link capabilities for world-wide real-time transmission of lectures and surgery. (See the photos of the Glickman Tower, page 10-13.)

Sadly, just a few weeks after dedicating the Glickman Tower, Andrew C. Novick, MD, the inaugural chair of the Glickman Urological & Kidney Institute, died suddenly and unexpectedly of complications related to lymphoma. Andy was a true surgical pioneer in the areas of renal transplantation, surgical revascularization of diseased kidneys, bench surgery and the surgical management of kidney cancer. Under his tutelage, the Department of Urology went from six to 61 faculty between 1985 and 2008, and he laid the foundation for the integration of urology and nephrology to become the multidisciplinary institute, integrating patient care, resident and fellow education, and basic and clinical research. John Barry, MD, summed up Andy’s career best, writing on learning of Andy’s death, “Well done, Andy, well done.” (See more in the tribute to Dr. Novick, included with this mailing.)

In April 2009, Inderbir Gill, MD, a pioneer in laparoscopic urologic procedures, departed Cleveland to assume the Chair of the Institute of Urology at the University of Southern California. D. Karl Montague, MD, currently serves as Interim Chair of the Department of Urology, and a new permanent chair of the department is expected to be named by year’s end. J. Stephen Jones, MD, remains as Chair of the Department of Regional Urology; Martin Schreiber, MD, chairs the Department of Nephrology, and Lawrence Hakim, MD, is the Chair of the Department of Urology, Cleveland Clinic Florida. New Center Directors in the last year include Howard Goldman, MD, Director of the Center for Quality Patient Care; Jihad Kaouk, MD, Director of the Center for Laparoscopic and Robotic Surgery; Jeffrey Palmer, MD, Director of the Center for Pediatric and Adolescent Urology; Daniel Shoskes, MD, Director of the Novick Center for Clinical and Translational Research; and Andrew Stephenson, MD, Acting Director of the Center for Urologic Oncology.

Several individuals and programs were awarded important recognition in the last year. William Fissell, MD, of the Department of Nephrology, received a Career Development Award from the American Society of Nephrology to foster his work on development of a bioartificial kidney, which could someday allow for continuous outpatient dialysis using a device the size of a 12-ounce aluminum can. Karl Montague, MD, received the ACGME’s Courage to Teach Award in recognition of his dedication during a long career as an educator and residency director; Andrew Stephenson, MD, received a grant from the Robert Wood Johnson Foundation to study decision analysis techniques for helping patients decide on the best treatment for their prostate cancer; and we were named a Center of Excellence for Prostate Cancer by Medical Economics. At the annual meeting of the American Urological Association held in Chicago in April 2009, our residents, fellows, and faculty were awarded 5 “Best Paper” honors and the “Best Video” award. Both the Department of Nephrology and the collective departments of Urology ranked highly (5th and 2nd, respectively) in U.S. News & World Report rankings.
Our educational programs remain a significant focus. In the milieu of the largest post-graduate medical education program in the world at Cleveland Clinic, at any given time we have six nephrology fellows, 24 urology residents and 20 urology fellows (distributed among eight individual fellowship programs). Many of these individuals go on to become academic leaders in their fields. Based on an application approved by the Residency Review Committee last year, in July 2009 the urology residency was able to expand to five per year (see story, page 74). This expansion will help to cover continued growth in clinical and research activities, and will enable the development of a community-based in- and outpatient rotation for upper level residents. In the six-year residency, we continue to offer a dedicated year of protected time devoted to basic, translational or outcomes-related investigation, one of the few remaining programs in the country to do so.

The demand for clinical services offered by our urology and nephrology programs remains robust, reflecting the strong regional and national reputation of our physician staff. During 2008, we performed 20,975 urological operations.

Our departments of urology collectively recorded a total of 91,582 outpatient visits, while our Department of Nephrology recorded 26,424 outpatient visits and 12,188 dialysis treatments.

Despite the changes we have experienced in the last year, we remain excited by the opportunity for the institute to continue a legacy of significant innovation and contributions to our core mission of patient care, education and research. We are pleased to share current activities with our colleagues and friends in this second annual issue of *Urology & Kidney Disease News*.

Eric A. Klein, MD

A four-story grand hall in the new Glickman Tower features artwork, a café and an educational health resource center for patients. For more photos, see the Glickman Tower photo essay, page 10.
New Staff The Glickman Urological & Kidney Institute welcomes the following new staff members:

Urology

Anthony N. Avallone, MD, FACS, received his medical degree and underwent postgraduate training at the University of California, San Francisco. He completed fellowship training at the University of Texas M.D. Anderson Cancer Center and received additional training at L’Institut Mutualiste Montsouris in Paris.

Dr. Avallone’s specialty interests include urologic oncology, general urology, laparoscopic and robotic surgery. Prior to joining Cleveland Clinic, Dr. Avallone was Director of Urologic Oncology at the Center for Cancer Care within the Goshen Health System in Goshen, Ind.

Ryan K. Berglund, MD, received his medical degree from the Columbia University College of Physicians and Surgeons in New York. He underwent postgraduate training at Cleveland Clinic and Memorial Sloan-Kettering Cancer Center in New York.

Dr. Berglund’s specialty interests include adrenal cancer, bladder cancer, kidney cancer, elevated PSA, general urology, kidney cancer, penile cancer, prostate cancer, prostate/BPH, prostatitis, testis cancer, and ureteropelvic junction obstruction.

Shih-Chieh Jeff Chueh, MD, PhD, earned his medical degree at the Taipei Medical University in Taiwan. He received his doctorate degree from the Postgraduate Institute of Clinical Medicine, College of Medicine, National Taiwan University in Taipei.

Prior to joining Cleveland Clinic, Dr. Chueh practiced at National Taiwan University Hospital and was a professor in the Department of Urology at the National Taiwan University College of Medicine. Dr. Chueh’s specialty interests include laparoscopic surgery and renal transplantation. He is helping to lead the Glickman Urological & Kidney Institute’s renal transplant program at the Charleston Area Medical Center in West Virginia.

David Levy, MD, received his medical degree from Chicago Medical School and underwent postgraduate training at the University of Texas M.D. Anderson Cancer Center and University Hospitals of Cleveland.

Dr. Levy’s specialty interests include adrenal cancer, bladder cancer, kidney cancer, elevated PSA, general urology, kidney stone disease, prostate cancer, penile cancer, priapism/hydrocele, prostate/BPH, prostate cancer, testis cancer, ureteropelvic junction obstruction, and vasectomy.

Hadley Wood, MD, received her medical degree from Johns Hopkins University School of Medicine and went through postgraduate training at Cleveland Clinic.

Dr. Wood’s specialties include genitourinary prosthetics, impotence (surgical only), male urinary incontinence, prostate /BPH, Peyronies, priapism/hydrocele, lower urinary tract reconstructive surgery, penile cancer, and urethral stricture.

Nephrology

Jesse Schold, PhD, earned his doctorate in Health Services Research, Management and Policy from the College of Public Health and Health Professions at the University of Florida in Gainesville. He received a master’s degree in statistics and mathematics education from North Carolina State University. He has a bachelor’s degree in psychology from Emory University in Atlanta.

Prior to joining Cleveland Clinic, Dr. Schold was an assistant professor at the University of Florida. His specialty interests are outcomes research and medical informatics. Dr. Schold will be Director of Outcomes Research and Medical Informatics for Kidney/Kidney Pancreas Transplantation. He will have joint appointments in the Department of Quantitative Health Sciences in the Lerner Research Institute, Division of Research, the Department of Nephrology and Hypertension, and the Transplant Center.
Upcoming Conferences

October 29-30, 2009

1st International Symposium on Robotic Kidney and Adrenal Surgery
Course Director: Jihad Kaouk, MD

A comprehensive 2-day course, live-cases and hands-on lab for practicing and academic urologists seeking to acquire or enhance their abilities to perform robotic renal and adrenal surgery.

Space is limited to the first 80 registrations.

November 11, 2009

Defining the Role of XMRV in Human Cancer
Directors: Robert A. Silverman, PhD, and Eric A. Klein, MD

This symposium will bring together the world's leading researchers to share the latest discoveries on XMRV, a novel virus discovered in men genetically predisposed to prostate cancer.

November 12-15, 2009

World Congress on Hypospadias and Disorders of Sex Development
Co-Chairs: Jeffrey S. Palmer, MD, FACS, FAAP, and Joao Luiz Pippi Salle, MD

This multi-professional conference (urology, gynecology, endocrinology, social work, medical genetics, genetic counseling, psychology and psychiatry) will have a portion of time dedicated to each specialty and a plenary session for all specialists.

Sponsored by Cleveland Clinic, this congress will take place both at the The Hospital for Sick Children (SickKids) and at the Marriott Hotel Toronto Eaton Centre.

April 23-24, 2010

5th Annual Ambulatory Urology Symposium
Directors: J. Stephen Jones, MD, FACS, and Edmund Sabanegh, MD

This course is intended to update urologists on ambulatory urology from both a practice and medical standpoint.

Cleveland Clinic Excels in Latest U.S. News Rankings

Urology ranked No. 2 in the nation; Kidney disorders ranked No. 5

The Cleveland Clinic Glickman Urological & Kidney Institute’s urology program was ranked among the top 2 programs in the United States for the 10th consecutive year by U.S. News & World Report. The institute’s kidney disorders program ranked 5th in the nation.

The 2009 “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 15 of the 16 specialties surveyed by the magazine.

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

Please check our websites for more details on these programs as they become available. clevelandclinic.org/urology, or clevelandclinic.org/nephrology
Staff Awards and Appointments


Kenneth W. Angermeier, MD, was named president of the Society of Genitourinary Reconstructive Surgeons. He will hold the post through May 2010.

William Fissell, MD, received the Carl W. Gottschalk Research Scholar Grant from the American Society of Nephrology. The grant provides $100,000 per year for two years.

J. Stephen Jones, MD, FACS, received the 2009-2010 Silver Platter Award for Contribution to Excellence in the Field of Cryosurgery from the International Society of Cryosurgery in St. Petersburg, Russia.

Eric Klein, MD, Chairman of the Glickman Urological & Kidney Institute, was named president of the Society of Urologic Oncology. Dr. Klein will hold a two-year term.

Drogo K. Montague, MD, Director of the Center for Genitourinary Reconstruction, and Interim Chairman of Urology, received the Parker J. Palmer Courage to Teach award in March. Dr. Montague was one of only 11 residency program directors in the nation to receive the award, which is granted annually by the Accreditation Council for Graduate Medical Education. The award honors outstanding teachers and leaders in graduate medical education. Dr. Montague was program director for the urology residency program from 1985 until 2006. He is currently associate program director.

Joseph Nally, MD, was named the National Kidney Foundation’s new Vice Chair for Public Policy for the Kidney Disease Outcomes Quality Initiative.

Andrew Stephenson, MD, was one of 20 physicians selected for the Physician Faculty Scholars Program Class of 2012 by The Robert Wood Johnson Foundation. Dr. Stephenson will develop and test a Markov-based decision analysis model for patients with localized prostate cancer.

Institute Leadership News

Eric Klein, MD, Chairman of the Glickman Urological & Kidney Institute, now holds the Andrew C. Novick, MD, Distinguished Chair in Urology. The chair, established in 2005 by Cleveland Clinic benefactors Babs and Carl Glickman, Gloria and Irving Fine, Eugenia and Dr. William Kiser, and Ronald Weinberg, was rededicated to Dr. Klein in June.

J. Stephen Jones, MD, FACS, Drogo K. Montague, MD, and Martin S. Schreiber, Jr., MD, have been named Vice Chairmen of the Glickman Urological & Kidney Institute. They will maintain their Departmental Chair positions as well.

Christopher Ching, MD, received the Most Bizarre and Interesting Case award at the North Central Section of the AUA meeting, September 2008.

Hai-Hong Jiang, MD, PhD, was named an AUA Foundation Research Scholar for 2009 for his research: Electrostimulation After Delivery Injury to Treat Urinary Incontinence.

John Kefer, MD, received an Outstanding Paper award from the Engineering & Urology Society annual meeting in April.

John Kefer, MD, received an Outstanding Paper award at the annual meeting of the AUA, 2009.

Wesley Kong, MD, received a Best Poster Award at the annual meeting of the AUA, 2009.

Brian Lane, MD, received a Best Poster Award at the annual meeting of the AUA, 2009.

Una Lee, MD, was awarded the Bruce Hubbard Stewart Memorial Award, 2009.

Pravin Rao, MD, received a Best Poster Award at the annual meeting of the AUA, 2009.

Matthew Simmons, MD, was awarded the George and Grace Crile Traveling Fellowship award, 2009.

Vairavan Subramanian, MD, won the Resident Bowl Competition of the North Central Section of the AUA meeting in September 2008.

Vairavan Subramanian, MD, received a Best Poster Award at the annual meeting of the AUA, 2009.

Anil Thomas, MD, won best podium for the adrenal/kidney/ureter benign and malignant podium session at the North Central Section of the AUA meeting in September 2008.

Christopher Weight, MD, won 2nd prize at the annual meeting of the Ohio Urology Society, 2009.

Christopher Weight, MD, won best poster from the Kidney/Ureter Malignant poster session at the North Central Section of the AUA meeting, September 2008.

Christopher Weight, MD, received the 2009 SLS Outstanding Laparoendoscopic Resident Surgeon award.
Care in the 21st Century: 
One Size Does Not—and Should Not—Fit All

Urology & Kidney Disease News has arisen from its predecessors, Nephrology News and Urology News, as a tangible example of the specialties’ integration into Glickman Urological and Kidney Institute. The role of medical editor has become even more exciting by the breadth of these two specialties at Cleveland Clinic, and I am thrilled to share the second integrated edition with you.

The work depicted in this issue demonstrates several clear trends within the institute. Innovation to improve patient care has only grown during these economically challenging times, especially notable in the areas of robotic and laparoscopic surgery, bioartificial kidney, and female urology. Patient care initiatives continue to receive ever sharper focus on aligning the power of technology with the brainpower of collaborative care. Examples in this issue involve prediction modeling, outcomes research, neoadjuvant therapy initiatives, clinical guidelines development, and lifestyle modification programs. This alignment becomes particularly evident when considering the innovative models of care for patients with benign renal conditions and hypertension. Meanwhile, traditional major surgical care remains at the center of everyday life in urology at Cleveland Clinic, as shown by reports on reconstructive urology and sexual health.

This brings us to the most significant trend found across most of these pages, but most evident in the prostate cancer section—the inexorable migration away from universal application of major intervention, and toward individualized intervention. The goal is to balance disease-specific risk with the ability to manage cancer with the least cost, effort, time and justifiable morbidity possible. As a result, patients in our practice currently are offered a spectrum of treatments from open radical prostatectomy to minimally invasive options ranging from robotic assisted radical prostatectomy to focal cryotherapy. As it becomes ever more evident that most patients with prostate cancer will not die as a result of their disease, potentially regardless of treatment approach, we continue to enthusiastically pursue these options that minimize morbidity.

It would be impossible to count the number of raised eyebrows when we began performing focal cryotherapy in 2005 on a highly selective basis for patients whose repeat, or “staging,” saturation biopsy confirmed the presence of small, unilateral, low-grade tumors that appeared to pose low risk of disease progression. Nevertheless, four years later we routinely host surgeons from a number of the nation’s premier institutions to observe the program, which ultimately has led several to model their own focal therapy initiatives based on its success.

Regardless of how minimally invasive focal therapy is, it remains invasive. Thus, the fastest growing program at Cleveland Clinic is now active surveillance with selective deferred intervention. We have almost 400 patients who would traditionally be treated with radical therapy but instead are under active surveillance—intermittent PSA, biopsy and MRI—for up to six years. To date, not a single patient has developed incurable disease, and far fewer than half of the men who started on the program have gone on to active treatment. This experience is markedly different from reports that suggest that even if supported by the urologist, few men will be willing to simply observe their prostate cancer. Quite contrary, we believe that the single most important factor in whether men remain on surveillance is how accurately the information is conveyed to them, and we have not found this to be difficult to achieve at all.

Nevertheless, we find that many physicians believe that active surveillance presents unacceptable medicolegal risk. I had an epiphany on this when challenged by a large group of highly qualified urologists at a recent meeting. I asked whether anyone had ever heard of a urologist being sued for active surveillance. All quiet. I then asked if any of them had been sued—or knew someone who had—for treating a patient with prostate cancer. Everyone in the room immediately recognized the reality—there is a clear medicolegal risk with treatment; by contrast, properly selected men who undergo surveillance for prostate cancer are at low risk of untoward effects, and I am not aware of a single patient who has sued the urologist for offering him all reasonable management options and helping him understand which ones will best meet his individual goals.

I hope you enjoy this publication, which highlights all the work from our institute, and I encourage you to contact us with your thoughts and suggestions.
Last fall, the Glickman Urological & Kidney Institute moved into the newly built Glickman Tower on Cleveland Clinic’s main campus. The building provides a tangible environment for the hospital’s innovative, recently established model of care that brings together clinical areas organized by organ and disease systems. One of the many institutes formed under this new model of care, the Glickman Urological & Kidney Institute unites our nephrologists and urologists. Together, under the roof of the new tower, these specialists deliver top-quality, innovative patient care, while collaborating on education and research.
Natural light filters into one of several bright, airy waiting rooms, providing patients with comfortable surroundings while waiting for appointments.

Four rooms are specifically equipped with urodynamic chairs that provide leading-edge diagnostic capabilities for adults and children with bladder disorders.

A patient service representative holds out a Versus Technology, Inc., real-time location information system tag. The technology is being used to track patients within Glickman Tower, thus improving their experience by facilitating smoother transitions between appointments, tests and procedures.

A scan produced by the TargetScan Touch™ prostate biopsy and treatment guidance system. Cleveland Clinic urologists are investigating the new technology (see article, page 15), housed in a state-of-the-art dedicated room.
At 12 stories, the Glickman Tower is the tallest building on Cleveland Clinic’s main campus. Its 200,000 square feet contain 77 physician offices, 16 technologically sophisticated procedure rooms, 12 outpatient procedure rooms and 74 exam rooms, all organized in clusters to protect patient privacy. An auditorium is fully equipped with technology for telemedicine and video conferencing. The tower features a chapel and meditation room where patients and families can relax and spend quiet time.
The 21-bed dialysis unit is designed with floor-to-ceiling windows offering scenic views of the outdoors.

Above: A technologically advanced dialysis unit in the new building includes a water treatment system that uses heat to purify the water used in the dialysate made on the premises.
Viruses are etiologic agents of various human cancers, including cervical carcinoma (HPV), Kaposi sarcoma (HHV-8), hepatocellular carcinoma (HBV and HCV) and adult T-cell leukemia (HTLV-1). Genetic and epidemiologic evidence suggest that prostate cancer may also have an infectious etiology, although a causative agent has not been identified. Several years ago we described the discovery of a novel gammaretrovirus, XMRV, which has become a candidate human tumor virus based on its association in human prostate tumors with a reduced activity variant of the antiviral gene, RNASEL (also known as hereditary prostate cancer 1 or HPC1) and because it is a member of a viral family known to cause leukemias and lymphomas in certain mammals.

Little is known about how XMRV establishes infections in the prostate. In this study we obtained expressed prostatic secretions (EPS) by manually milking prostates after radical prostatectomy of prostate cancer patients. XMRV Env RNA was detected in EPS by qRT-PCR and verified by nested RT-PCR in EPS from 4 of 32 (12.5%) unselected prostate cancer cases (Figure 1). Additional experiments showed that 1) a fragment of prostatic acid phosphatase, the predominant protein in human semen, promotes the infectivity of XMRV in both prostatic stromal and epithelial cells by 44 – 90 fold (Figure 2); 2) intact human semen has a similar effect; and 3) XMRV infects both HeLa cells (derived from cervical carcinoma) and human foreskin fibroblasts. Together the results suggest that XMRV is sexually transmitted, and that intrinsic properties of the prostatic milieu promote efficient infection of the prostate. Efforts are ongoing to determine XMRV is carried in the lower genital tract of women and if it is oncogenic in the prostate.

This study was published online in the Journal of Virology, April 29, 2009.

For references, please email the editor.
A Novel Stereotactic Prostate Biopsy and Treatment Guidance System

Georges-Pascal Haber, MD, and Jihad Kaouk, MD

In an effort to decrease false-negative rates of transrectal ultrasound (TRUS) guided prostate biopsy, the Glickman Urological & Kidney Institute is investigating the use of a novel stereotactic prostate biopsy and treatment guidance system.

TargetScan Touch™ system (Envisioneering Medical Technologies, St. Louis, Mo.) uses a stationary 3-D TRUS probe with an attached biopsy needle holder and guide.

First, a 3-D map of the prostate is created; then a computer algorithm calculates an optimum biopsy scheme using the measured dimensions of the prostate. The system then uses a fixed template that allows the physician to biopsy the prostate at specific locations.

The instrument can be used for 12-core template biopsy and saturation biopsy if indicated. TargetScan Touch™ system is designed to facilitate precise targeting, mapping and sampling of multiple biopsy sites, and to store mapped images for accurate repeat biopsies, which could be used to target the same region of the prostate in the future if needed. This would be particularly useful in patients with suspicious histology, such as atypia, on initial biopsy. The 3-D model created may be used for future focal therapy, such as cryotherapy and photodynamic therapy.

Our primary objective in investigating TargetScan Touch™ will be to compare rates of detection of prostate cancer by handheld TRUS-guided vs. TargetScan Touch™-guided prostate biopsy, in terms of: a) total 12 core detection rate and b) rate of detection of cancer in suspicious lesions. Our secondary objectives will include measuring: a) the rates of detection of hypo- and hyperechoic lesions by handheld vs. TargetScan TRUS), b) among patients who undergo prostatectomy, the rates of pathologically significant vs. insignificant prostate cancer detected by handheld vs. TargetScan TRUS biopsies, and c) patients’ perceptions of pain during the two techniques and overall satisfaction of the procedures, by means of responses to numerical pain and satisfaction scales.

There is an urgent need for better performance of prostate biopsies on several levels. First, even the latest handheld TRUS-guided biopsy protocols miss a significant number of potentially aggressive tumors, compelling a second biopsy in the face of a high PSA level or other risk factors, or even delaying diagnosis until the cancer is at an advanced, less curable, stage. A better targeted initial biopsy may reduce the false-negative rate and lessen the need for a repeat biopsy.

Second, when an atypical histological phenotype, such as high-grade PIN, is found in a given biopsy core, knowledge of the precise location of that core should allow better targeted re-biopsy to determine whether a coexistent cancer is in that region.

Third, emerging data suggest that systematic prostate biopsies enable better predictions of tumor grade and volume than random biopsies; increasing the precision of systematic biopsies will likely improve predictions more and may lead to better treatment decisions by physicians.

Finally, more precise localization of prostate tumors may be necessary for the development of targeted focal therapy for men with low risk, unifocal prostate cancer lesions, many of whom may be currently overtreated. Following focal ablation of a prostate tumor, the necessary post-operative biopsy to assess treatment efficacy would be facilitated by knowledge of the precise coordinates of the pre-operative biopsy core that located the tumor. The TargetScan Touch™ platform has the potential to improve prostate biopsies toward all of those ends.
Prostate magnetic resonance (MR) provides high-resolution images of the prostate, seminal vesicles and nearby pelvic structures and organs including the bladder and rectum. High-resolution T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), MR spectroscopy (MRS), and dynamic contrast-enhanced (DCE) T1-weighted imaging all have been shown to have success in detecting prostate cancer. A combination of all four of these techniques is used to maximize the sensitivity and specificity of the examination.

We perform the examination utilizing only the highest field strength magnets available in routine clinical use (3-Tesla), and images are acquired both prior to and after IV gadolinium contrast. We use an endorectal coil whenever possible to improve the image quality.

Prostate MR may be indicated for evaluation of patients with biopsy-proven or suspected prostate cancer; primary uses and contraindications for prostate MR are described below.

**Prostate MR is suitable for**

- identifying areas suspicious for carcinoma to direct transrectal ultrasound (TRUS) guided biopsy in patients with concerning rises in PSA but without documented prostate cancer
- patients with biopsy-proven prostate cancer to detect the possibility of multifocal disease or disease spread before considering focal therapy
- patients with biopsy-proven prostate cancer to identify extension outside the prostatic capsule and involvement of either the seminal vesicles or neurovascular bundle
- patients with suspected or biopsy-proven prostate cancer for lymphadenopathy, rectal or bladder invasion
- patients to assess for the possibility of recurrence after prostate cancer therapy (cryotherapy or prostatectomy)

**Contraindications to Prostate MR**

- Recent biopsy of the prostate (within eight weeks) can mask prostate cancer on MR. If possible, patients should not undergo prostate MR after a recent biopsy.
- In general, MR exams are contraindicated in almost all patients with pacemakers, defibrillators and implanted ferromagnetic metallic foreign bodies. The presence of other implanted medical devices is evaluated on a case-by-case basis. Most modern urological prostheses create no concern for MRI.
- Patients with moderate to severe chronic kidney disease (GFR less than 30 ml/min/1.73m2) are not recommended to have contrast-enhanced MRI exams. However, tailored non-contrast enhanced studies can be performed on these patients.

Figure 1

T2-weighted MR image (Figure 1) through the mid prostate shows low signal intensity mass in the left medial peripheral zone (arrow). This lesion also shows restricted diffusion (bright signal, arrow) on the inverted Apparent Diffusion Coefficient (ADC) map (Figure 2) that is created from diffusion weighted images. Both of these findings are seen with prostate cancer.
Analysis of T1c Prostate Cancers Treated at Very Low Prostate-Specific Antigen Levels

Andrew J. Stephenson, MD, J. Stephen Jones, MD, FACS, Adrian V. Hernandez, MD, PhD, Jay P. Ciezki, MD, Michael C. Gong, MD, and Eric A. Klein, MD

Historically, patients with a normal digital rectal examination (DRE) and a serum prostate-specific antigen (PSA) level >4.0 ng/ml were recommended to undergo prostate biopsy given the 20–30% risk of prostate cancer (pCA). Compared to cancers detected at PSA >4.0, cancers detected in the 2.6–4.0 PSA range are more likely to be organ-confined without a substantial difference in the rate of indolent cancer. As such, a lowering of the PSA threshold for biopsy to 2.5 has been advocated to increase the detection of clinically significant cancers at a more curable stage, and this had been adopted in the guidelines of some professional societies. The Prostate Cancer Prevention Trial (PCPT) has challenged the validity of any PSA threshold for biopsy, since no value had sufficient sensitivity and specificity for the detection of pCA, and a continuum of risk at all PSA values was observed among patients who were biopsied without accepted indications.

We analyzed the outcome of patients with T1c pCA treated at very low PSA levels (<2.5) and compared them to patients with PSA 2.6–4.0 to determine whether any therapeutic advantage exists to justify lowering accepted PSA thresholds for biopsy. Since 1998, 351 patients with clinical stage T1c and PSA <4.0 have been treated at our institution; 84 (24%) of those patients had PSA <2.5. Clinical information was obtained from a prospective database. Treatment was radical prostatectomy (RP), brachytherapy, and external-beam radiotherapy (EBRT) in 261 (74%), 67 (19%), and 23 (7%) patients, respectively.

The outcome of patients with PSA levels <2.5 and 2.6–4.0 was compared in terms of biopsy (18% vs. 22%) or specimen Gleason score 7–8 (44% vs. 56%), non–organ-confined cancer (defined as extraprostatic extension, seminal vesicle invasion, or lymph node invasion), indolent cancer, biologically unimportant cancer, positive surgical margins, bilateral cavernous nerve preservation, and progression-free probability.

No significant differences between the groups were observed in terms of biopsy (18% vs. 22%) or specimen Gleason score 7–8 (44% vs. 56%), non–organ-confined cancer (11% vs. 13%), indolent cancer (34% vs. 24%), or 5-year progression-free probability (89% vs. 93%; p > 0.1 for all). More biologically unimportant cancers (defined as pathologically organ-confined and Gleason <6) were identified among patients with PSA <2.5 (55% vs. 41%, p = 0.050), and indolent cancers were three times more frequent than non–organ-confined cancers among these patients (p = 0.003).

Key Point:
The outcome of patients with PSA levels <2.5 and 2.6–4.0 were found to be favorable and similar when compared after treatment with radical prostatectomy, brachytherapy or external-beam radiotherapy. Based on this we did not identify therapeutic benefit to the diagnosis of cancers below accepted PSA thresholds for biopsy.

The pathologic features and outcome of patients treated at low PSA levels are favorable and similar for patients with PSA <2.5 versus 2.6–4.0. There appears to be a very limited therapeutic benefit to the diagnosis of cancers below accepted PSA thresholds for biopsy.

Adapted from an article published in European Urology March 2009 (Vol. 55, Issue 3, Pages 610-616).
A Nomogram for Predicting Upgrading in Patients with Low and Intermediate Grade Prostate Cancer in the Era of Extending Prostate Sampling

Ayman S. Moussa, MD, Michael W. Kattan, PhD, Changhong Yu, and J. Stephen Jones, MD, FACS

The Gleason score (GS) is considered the most important factor in characterizing the biological potential of a prostate cancer and plays a major role in treatment decision making. However, the GS assigned at biopsy exhibits a limited correlation with the GS assigned following radical prostatectomy (RP). In previous studies, we found that 50% of patients with GS 6 and 26.2% of patients with GS > 7 experienced postoperative upgrading.

For men with biopsy GS 6 and/or 7 (3+4), it is important not to underestimate the disease risk and to assess the accuracy of biopsy GS in predicting the actual pathological GS. Otherwise, patients with unrecognized high-grade cancer may choose less aggressive treatment options and be at increased risk of adverse oncologic outcomes.

To address this issue, we examined the rate of Gleason score upgrading between biopsy and final pathology in a large cohort of patients and constructed a nomogram to predict the probability of biopsy Gleason sum upgrading. Our objective was to provide clinicians with a tool that could estimate the probability of a more aggressive prostate cancer variant, which could suggest a change in the selected treatment.

**Key Points:**

A study of 1,017 prostate cancer patients with theoretically low risk Gleason score 6 and 7 (3+4) at diagnostic biopsy found that nearly one-third will be upgraded to a more aggressive grade at final pathology.

Our nomogram for predicting the probability of Gleason sum upgrading based on multiple variables had a predictive accuracy of 68%. It can provide important additional information to aid the urologist and patient in treatment decision making, especially for patients considering non-surgical options.

GS upgrade nomogram based on 1,017 patients seen at our institution. Each scale position has corresponding prognostic points (top axis). Point values for all predictor variables are determined consecutively and summed to arrive at total point value. This value is plotted on total point axis and directly below it is prediction for upgrading Gleason score. For age, use age at time of current biopsy. For DRE use current DRE result, that is negative (No), suspicious (Yes). For history of HGPIN, ASAP, inflammation and perineural invasion use (Yes) when found. For PSA use current serum PSA. For race, use (A) for African-American, (C) for Caucasian and (O) for others. For T, volume, use total volume at time of current biopsy. For clinical stage, use (T1c), (T2) or (T3). Number of previous biopsies, (0) for initial biopsy, (1) for repeated once and etc. for number of cores, number of positive cores, and maximum percent cancer in any core: use the current numbers from the pathology report of the biopsy session. Secondary Gleason grade: the highest secondary grade present in the biopsy report.
The study included 1,017 patients who underwent transrectal ultrasound biopsy and radical prostatectomy from 2000-2007. Their prostate biopsies showed GS 6 and GS 7 (3+4). The majority of patients received extended biopsies of 10 or more cores.

The final pathological GS was upgraded in 336 patients (33%), downgraded in 58 (5.7%), and unchanged in 623 (61.3%). Notably 51.1% of GS 6 patients were upgraded to GS 7 or higher and 26.1% of GS 7 (3+4) patients were upgraded to GS 7 (4+3) or higher, both potentially placing the patient in a higher risk category.

In constructing our nomogram, we incorporated multiple predictor variables that were selected based on an intensive medical literature review. The variables evaluated included age, race, preoperative prostatic specific antigen (PSA), abnormal digital rectal examination (DRE), number of cores taken, number of positive cores, maximum percent cancer in any core, number of previous biopsies, prostate cancer volume, clinical stage, atypical small acinar proliferation (ASAP), inflammation, high-grade prostatic intraepithelial neoplasia (HGPIN), and perineural invasion.

PSA, increasing age, presence of perineural invasion, absence of inflammation, clinical stage and total prostate volume were found to be significant predictors of GS upgrading. The amount of cancer at biopsy did not predict for tumor upgrading when the extent of biopsy was considered, which is consistent with previous studies. Pathological upgrading was associated with adverse pathological features, including extra capsular extension, seminal vesicle invasion and lymph node metastasis.

The predictive accuracy for all variables was 67.8% under the ROC curve after correcting for optimism with bootstrapping. It exceeded the predictive accuracy of the individual risk factors in our data set which ranged from 50.5% to 60.8%.

To our knowledge, this nomogram is the first in the literature to specifically address the risk of undergrading in a large series of patients with biopsy showing low risk GS 6 and 7 (3+4) cancer. Considering that nearly one-third of these patients will be upgraded to a more aggressive Gleason grade, our nomogram for predicting upgrading can provide important additional information to guide the urologist and patient with low and intermediate grade prostate cancer in treatment decision making. It may prove useful when the possibility of a more aggressive Gleason score may change the treatment options.

Continued on next page
Prostate Cancer

Obesity should be considered as a factor associated with reduced PSA when determining whether to carry out a prostate biopsy as part of early prostate cancer detection. Accordingly, a new PSA screening cutoff value according to BMI may be justified.

Factors affecting the levels of prostate-specific antigen (PSA) within screening programs for prostate cancer have been the focus of current research. Recently, there has been growing evidence of an inverse relationship between PSA levels and body mass indices (BMIs).

To investigate this possible correlation, we reviewed the records of 45,548 American men (average age 62.9) receiving a routine health screening including a serum PSA level and BMI from July 2001 to May 2008. These men were divided into 5 groups according to PSA ranges: group 1 (< 2.5), group 2 (2.51 - 4), group 3 (4.01 - 10), group 4 (10.01 - 20) and group 5 (>20) ng/ml, and the average and median BMIs for each group were calculated (Table). The five groups were plotted against their BMI values (Figure). Group 1 (PSA <2.5 ng/ml) demonstrated the highest values for BMI (average 28.95) while the lowest BMI values (average 26.57) were evident in group 5 (PSA >20 ng/ml).

Overall, the levels of PSA were found to decrease as the BMI values increased and vice versa.

To our knowledge, this is the largest study done until now. Our results confirm an inversely proportional relationship between BMI and PSA levels and highlight the importance of regarding BMI when screening for prostate cancer as it may breach the accuracy of PSA testing.

### Table 2: Summary comparison of biopsy and pathological GS

<table>
<thead>
<tr>
<th>Gleason score at biopsy (Biopsy GS)</th>
<th>Downgraded at RP specimen (Pathological GS)</th>
<th>Same GS at RP specimen (Pathological GS)</th>
<th>Upgraded at RP specimen (Pathological GS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G6 (3+3) N=282 (27.7)</td>
<td>4 (0.4)</td>
<td>134 (13.2)</td>
<td>144 (14.1)</td>
</tr>
<tr>
<td>G7 (3+4) N=735 (72.3)</td>
<td>54 (5.3)</td>
<td>489 (48.1)</td>
<td>192 (18.9)</td>
</tr>
<tr>
<td><strong>Total N=1017</strong></td>
<td><strong>58 (5.7)</strong></td>
<td><strong>623 (61.3)</strong></td>
<td><strong>336 (33)</strong></td>
</tr>
</tbody>
</table>

*Data in parentheses are percentage

### Table 3: Final pathological assessment and the comparison of biopsy and pathological GS

<table>
<thead>
<tr>
<th>BIOPSY GS</th>
<th>G 5*</th>
<th>G 6</th>
<th>G 7</th>
<th>G 8</th>
<th>G 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3,2)</td>
<td>(3,3)</td>
<td>(3,4)</td>
<td>(4,3)</td>
<td>(3,5)</td>
<td>(4,4)</td>
</tr>
<tr>
<td>G 6 (3,3) N=282</td>
<td>D 4 (1.4)</td>
<td>S 134 (47.5)</td>
<td>U 128 (45.4)</td>
<td>U 11 (3.9)</td>
<td>U 3 (1.1)</td>
</tr>
<tr>
<td>G 7 (3,4) N=735</td>
<td>D 2 (0.3)</td>
<td>D 52 (71)</td>
<td>S 489 (66.5)</td>
<td>U 152 (20.6)</td>
<td>U 8 (1.1)</td>
</tr>
</tbody>
</table>

D: downgrade, S: same, U: upgrade; Data in parentheses are percentage

* GS 5 is no longer a viable GS with the modern approach, but these were early in the series when our pathologists still interpreted some patients as having 5 sum.

### The Influence of Body Mass Index on Prostate Cancer Screening in a Large Cohort

J. Stephen Jones, MD, FACS, Ayman S. Moussa, MD, Ahmed M. Ragheb, MD, and Wei Liao

Factors affecting the levels of prostate-specific antigen (PSA) within screening programs for prostate cancer have been the focus of current research. Recently, there has been growing evidence of an inverse relationship between PSA levels and body mass indices (BMIs).

To investigate this possible correlation, we reviewed the records of 45,548 American men (average age 62.9) receiving a routine health screening including a serum PSA level and BMI from July 2001 to May 2008. These men were divided into 5 groups according to PSA ranges: group 1 (< 2.5), group 2 (2.51 - 4), group 3 (4.01 - 10), group 4 (10.01 - 20) and group 5 (>20) ng/ml, and the average and median BMIs for each group were calculated (Table). The five groups were plotted against their BMI values (Figure). Group 1 (PSA <2.5 ng/ml) demonstrated the highest values for BMI (average 28.95) while the lowest BMI values (average 26.57) were evident in group 5 (PSA >20 ng/ml).

Overall, the levels of PSA were found to decrease as the BMI values increased and vice versa.

To our knowledge, this is the largest study done until now. Our results confirm an inversely proportional relationship between BMI and PSA levels and highlight the importance of regarding BMI when screening for prostate cancer as it may breach the accuracy of PSA testing.

### Table

<table>
<thead>
<tr>
<th>PSA levels and BMI values among the study population groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA ng/ml</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>0-2.5</td>
</tr>
<tr>
<td>2.51-4</td>
</tr>
<tr>
<td>4.01-10</td>
</tr>
<tr>
<td>10.01-20</td>
</tr>
<tr>
<td>&gt;20</td>
</tr>
</tbody>
</table>

Obesity should be considered as a factor associated with reduced PSA when determining whether to carry out a prostate biopsy as part of early prostate cancer detection. Accordingly, a new PSA screening cutoff value according to BMI may be justified.
Despite a stage migration effect (largely due to PSA screening) and a decreasing mortality rate, prostate cancer is still the second leading cause of cancer death in American men behind lung cancer. As such, selection of proper treatment for the individual patient is critical to enhancing the chances of cure and survival. Historically, definitive management of men diagnosed with clinically localized prostate cancer was represented by open radical prostatectomy or external beam radiation. In the last two decades, the armamentarium of prostate cancer therapy has greatly expanded to include minimally invasive approaches to surgery (e.g., standard and robotic-assisted laparoscopy), interstitial brachytherapy, energy ablative modalities (e.g., cryoablation and ultrasonic energy), as well as active surveillance with deferred intervention (upon evidence of disease progression).

The patient seeking treatment for his prostate cancer is therefore faced with a myriad of therapeutic options and the dilemma of deciding which alternative is best for him. There are no published prospective randomized trials that directly compare outcome and complications for the standard therapies for localized prostate cancer. The prevailing data from retrospective observational studies comparing surgery and radiation have tended to be conflicting but do suggest equivalent survival outcomes following either modality. Due to the lack of conclusive data, there is currently no consensus on what constitutes optimal management of men with clinically localized disease. As such, the decision between the various treatment options has largely been a matter of patient as well as physician preference.

Effective patient counseling allowing informed decision-making would seem to be best achieved with a formalized system that offers accurate predictions of outcomes for all available treatment approaches. Our goal is to organize the currently available prostate cancer prediction tools toward the formation of a metagram that can be used to tailor management to the individual patient. A metagram is a collection of nomograms or other prediction equations.

A comprehensive review of the literature was performed to identify published prediction tools intended for use in prostate cancer. Tools were categorized by a combination of treatment modality and the outcome being predicted and incorporated into a metagram constructed of 16 treatment options and 10 outcomes related to cancer control, survival and morbidity. The attraction of the metagram is that all relevant prediction tools are organized under a single interface. This allows the physician to enter a patient’s characteristics once and subsequently obtain the 16 x 10 predictions that should form the basis for evidence-based decision making.

A search of the literature revealed 44 prostate cancer prediction tools that assessed at least one of the 160 treatment/outcome combinations that make up the metagram. Only 31 cells of the metagram were populated with currently available tools.

**Key Point:**

We have incorporated the most relevant prediction tools currently available into a prostate cancer metagram, which may offer evidence-based and individualized predictions for multiple endpoints following all available treatment options in clinically localized prostate cancer. The metagram also reveals areas of deficiency in the current catalog of prediction tools. Many more prediction tools are needed.

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**A metagram for determining treatment for clinically localized prostate cancer.**

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>BCR</th>
<th>Metastasis</th>
<th>Survival</th>
<th>Life expectancy</th>
<th>PCSM</th>
<th>Impotence</th>
<th>Incontinence</th>
<th>Bowel dysfunction</th>
<th>Length of stay</th>
<th>Return to work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Surveillance</td>
<td>ORP</td>
<td>ORP + LND</td>
<td>ORP + LND + Neoadjuvant HT</td>
<td>ORP + Adjuvant HT</td>
<td>ORP + LND + Adjuvant HT</td>
<td>LRP</td>
<td>LRP + Neoadjuvant HT</td>
<td>EBRT</td>
<td>EBRT + LNRT</td>
<td>EBRT + Neoadjuvant HT</td>
</tr>
</tbody>
</table>

AS: active surveillance; ORP: open radical prostatectomy; LND: pelvic lymph node dissection; HT: hormonal therapy; LRP: laparoscopic radical prostatectomy; EBRT: external beam radiation therapy; LNRT: lymph node radiation therapy; TPPB: transperineal pros
Active Surveillance with Selective Delayed Intervention for Prostate Cancer

Ryan K. Berglund, MD

Recently, attention has been drawn to the potential overuse of PSA screening to guide men with low-risk prostate cancer features to receive treatment for indolent prostate cancers. The concern is that many men must be treated (48 in the recent ERSPC study) to avoid even one cancer death, and that all available treatments have side effects. One approach to this problem of overtreatment is deferred treatment of patients with low-risk features to active surveillance with selective delayed intervention. This is a program of close follow-up with repeat digital rectal examination, serum PSA value and ultrasound-guided prostate biopsy. The mainstay of active surveillance is the repeat ultrasound-guided biopsy, and aggressive features on repeat biopsy are associated with aggressive features at the time of surgery (see Table). At the time of development of a high-risk feature, definitive therapy of any kind can be initiated.

In a recently published multi-institutional study of active surveillance, which included Cleveland Clinic, 262 patients with low-risk features (PSA < 10 ng/ml, clinical stage T1 T2a, Gleason score < 6, < 3 cores positive at diagnostic biopsy) were followed for a median of 29 months. The inclusion criteria limited the estimated 5-year risk of biochemical recurrence following radical surgery to < 5%. In all, only 43 patients (16%) went on to undergo definitive treatment, and only one patient (0.4%) developed skeletal metastases.

The overwhelming majority of patients (84%) needed no further intervention at last follow-up. The two and five-year probabilities of remaining on active surveillance were 91% and 75% respectively, thus sparing the majority of patients the side effects of treatment during that interval.

Prostate cancer remains a large source of morbidity and mortality in the United States but low-risk disease is over treated. Definitive treatments such as surgery, radiation, cryotherapy, and combined androgen deprivation have improved relative survival rates in prostate cancer patients over the last three decades, but those treatments have side effects. Active surveillance with selective delayed intervention allows for patients with low-risk features to defer or avoid treatment and initiate definitive therapy only at the development of higher risk disease.

For references, please email the editor.

Table. Pathologic results at surgery

<table>
<thead>
<tr>
<th>Pathologic Stage*</th>
<th>No upstaging/upgrading (38)</th>
<th>Upstaged/Upgraded (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2a</td>
<td>15/38 (39%)</td>
<td>0/21 (0%)</td>
</tr>
<tr>
<td>pT2b</td>
<td>17/38 (45%)</td>
<td>9/21 (43%)</td>
</tr>
<tr>
<td>pT2c</td>
<td>2/38 (5%)</td>
<td>2/21 (10%)</td>
</tr>
<tr>
<td>pT3a</td>
<td>4/38 (11%)</td>
<td>9/21 (43%)</td>
</tr>
<tr>
<td>pT4</td>
<td>0/38 (0%)</td>
<td>1/21 (5%)</td>
</tr>
<tr>
<td>pN0</td>
<td>38/38 (100%)</td>
<td>21/21 (100%)</td>
</tr>
<tr>
<td>pN1</td>
<td>0/38 (0%)</td>
<td>0/21 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathologic Grade**</th>
<th>No upstaging/upgrading (38)</th>
<th>Upstaged/Upgraded (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score ≤ 6</td>
<td>22/38 (58%)</td>
<td>2/21 (10%)</td>
</tr>
<tr>
<td>Gleason score 7 (3+4)</td>
<td>14/38 (37%)</td>
<td>17/21 (81%)</td>
</tr>
<tr>
<td>Gleason score 7 (4+3)</td>
<td>2/38 (5%)</td>
<td>1/21 (5%)</td>
</tr>
<tr>
<td>Gleason score 8</td>
<td>0/38 (0%)</td>
<td>1/21 (5%)</td>
</tr>
</tbody>
</table>

* = presence of ≥ p T3a in non-upstaged/upgraded vs. those upstaged/upgraded (11% vs. 48%, p=0.003)

** = presence of Gleason score ≥ 7 in non-upstaged/upgraded vs. those upstaged/upgraded (42% vs. 91%, p=0.001)
Active Surveillance: Are the Epstein Criteria Suitable for Defining Biologically Insignificant Prostate Cancer?

Michael Lee, MD, Andrew Stephenson, MD, J. Stephen Jones, MD, FACS, Cristina Magi-Galluzzi, MD, PhD, and Eric A. Klein, MD

Active surveillance is gaining popularity as a management strategy for low-grade prostate cancer. The use of surveillance is predicated on the belief that tumors of low biological potential that do not require immediate intervention can be identified at the time of diagnosis based on serum PSA level, clinical stage, tumor grade and volume, and that those that exhibit biological progression while under surveillance can still be cured by delayed intervention. Biopsy criteria proposed by Epstein are widely used for identifying potentially biologically insignificant tumors that might be safely managed by initial surveillance. The criteria include PSA density <0.15ng/mL, biopsy Gleason score ≤6, the presence of tumor in < 2 cores, and no more than 50% involvement by tumor in any single core. We examined the ability of these criteria to predict 3 pathological and 1 clinical endpoint: 1) insignificant disease defined as organ-confined, Gleason score < 6, and tumor volume <0.5cm3 (classical definition); 2) insignificant disease defined as organ-confined Gleason < 6 tumor of any volume (liberal definition); 3) the presence of organ-confined tumor of any grade or volume; and 4) biochemical relapse-free survival (bRFS), defined as a post-surgical PSA of 0.4 and rising.

Of 268 consecutive men undergoing prostate biopsy and prostatectomy, 51% met the Epstein biopsy criteria. Cases meeting these criteria were more likely to have insignificant disease by either definition (p < .001) and organ-confined tumors (p < .001) than those not meeting the criteria (Figure 1). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) varied among the endpoints, with sensitivity (74%) and NPV (86%) best for the classical definition of insignificant disease and specificity (74%) and PPV (92%) best for organ-confined disease. No patient who met the Epstein criteria on biopsy suffered a biochemical failure, while 17% of those who did not had a detectable PSA 5 years after surgery (Figure 2). These results demonstrate that men meeting the Epstein biopsy criteria are highly likely to have organ-confined disease and a high likelihood of long-term cure, but that the Epstein criteria were not sufficiently robust to be used clinically for predicting biologically insignificant disease. The observation that men meeting these criteria are usually cured by immediate radical prostatectomy (RP) does not imply that all such men have biologically insignificant cancers; an alternative interpretation is that RP is very effective therapy for biologically significant cancers that are caught and treated early. At present we cannot distinguish between these possibilities.

Key Point:

Biopsy criteria proposed by Epstein are widely used for identifying potentially biologically insignificant tumors that might be safely managed by initial surveillance. We examined the ability of these criteria to predict 3 pathological and 1 clinical endpoint. The results demonstrate that men meeting the Epstein biopsy criteria are highly likely to have organ-confined disease and a high likelihood of long-term cure, but that the Epstein criteria were not sufficiently robust to be used clinically for predicting biologically insignificant disease.

Use of these criteria does not fully exclude the possibility of adverse pathological features present at the time of diagnosis, nor does it exclude the potential for biological progression using a strategy of active surveillance and delayed intervention. There is a real need for the development of biological markers that can predict the potential for tumor progression.
Cleveland Clinic investigators have been instrumental in exploring differences among radiotherapeutic options for prostate cancer. The differences may best be understood by knowing the extent to which radiation is scattered to the tissue around the prostate (Figure 1). Because of the higher energy of the radiation in external beam radiation, there is high energy scatter that radiates a greater amount of the rectum than brachytherapy, which makes use of low-energy radiation that cannot scatter as far. This geometric difference explains the results of the comparison between brachytherapy and external beam radiotherapy.

The first level of comparison is side effects. Cleveland Clinic investigators participated in the largest and most comprehensive assessment of side effects ever performed: the PROST-QA multi-center trial, contributing 42% of all the brachytherapy patients in that trial. At the two-year time point, the increased rectal toxicity of external beam radiation is already apparent. The external beam patients had a 3% incidence of rectal urgency at baseline, and a 16% rate of rectal urgency at 2 years compared to the brachytherapy patients, who had a 4% rate at baseline and a 9% rate at 2 years. The interesting point about this parameter is that, within the first 2 years, the rate is increasing for external beam patients and decreasing for brachytherapy patients (Figure 2).

The second point of comparison is biochemical relapse-free survival (bRFS). While it is a contentious end point, it is often cited because it is a good indicator for the initiation of salvage therapy for many patients. Figure 2 depicts the bRFS comparison between the brachytherapy and external beam patients within risk groups. There is no measurable difference between the modalities within any risk group.

Finally, the outcome of therapy may be compared with disease-specific mortality as an end point. This is seldom done, yet it is the most unambiguous measure of treatment success. Because prostate cancer treatment is associated with such good outcomes, one expects very few deaths in patients.
properly treated patients. Surprisingly, when the low- and intermediate-risk groups are compared, the brachytherapy patients fare as well as those treated with radical prostatectomy, while external beam patients have a much higher prostate cancer-specific mortality (Figure 3). A summary of the three areas of comparison shows how dependent they are on the basic isodose profiles in Figure 1. Because of the scatter radiation of the external beam, one cannot increase the dose to the prostate without also increasing the dose to the rectum. This yields more rectal side effects and very likely a less ablative dose of radiation, resulting in a higher prostate cancer-specific mortality in the external beam patients as compared to the brachytherapy patients. When applying this to treatment decision making, it would appear that brachytherapy is the logical radiotherapeutic choice for low- and intermediate-risk patients. The exception might be those patients incapable of tolerating the anesthesia required for brachytherapy. For high-risk patients, the role of external beam is potentially greater. Despite the inability to escalate dose with external beam, the more extensive scatter may be beneficial in high-risk patients because of the high likelihood of extra-prostatic cancer in this risk group. Whether the greater scatter from external beam is more beneficial than the higher dose with brachytherapy is hypothetical currently.

For references, please email the editor.

Figure 3. Cumulative incidence of prostate cancer-specific mortality in low- and intermediate-risk patients.

EBRT = external beam radiotherapy; PI = brachytherapy; RP = radical prostatectomy.
Cryosurgical ablation of prostate cancer is being utilized more frequently across the country as a minimally invasive approach to the disease. While biochemical standards of prostate cancer treatment success have been established for patients undergoing radiation therapy and surgical extirpation, no such criteria exist for the cryosurgical population. In the 2008 publication of “Best Practice Statement on Cryosurgery for the Treatment of Localized Prostate Cancer” by the American Urological Association, there were no data by which the panel could make a statement about end points by which cryosurgical treatment success could be measured, demonstrating an urgent need for our recent investigations.

We embarked upon establishing such criteria from an evidence-based approach. The Cryo On-Line Data (COLD) Registry provides the potential for comprehensive data analysis of cryosurgical outcomes. We queried the database in an effort to correlate nadir PSA levels with biochemical disease-free survival based upon “Phoenix” (nadir + 2) criteria in a risk-stratified population of primary cryoablation patients.

We stratified 2,427 primary whole-gland cryoablation patients into low-, intermediate- and high-risk based upon the 2003 D’Amico criteria. The cohort was then sub-stratified into post-treatment PSA reference ranges, < 0.1 ng/ml, 0.1-0.5 ng/ml, 0.6-1.0 ng/ml and 1.1-2.5 ng/ml. Kaplan Meier plots were constructed and populated with available PSA data out to 60 months post cryoablation.

Data analysis revealed no significant differences in age, PSA at diagnosis or Gleason score between the specific PSA reference range groups. Results for patients with initial PSA of < 0.1 ng/ml and 0.1-0.5 ng/ml are detailed in the Kaplan Meier plots and accompanying tables.

A total of 191 patients had an initial post cryoablation PSA of 0.6 – 1.0 ng/ml. Within this subgroup the 6-, 12-, and 24-month biochemical disease-free survival was low-risk: 100%, 83% and 70.5%, respectively; intermediate-risk: 95%, 81% and 56%, respectively; and high-risk: 92%, 74% and 46%, respectively. PSA levels of 1.1 – 2.5 ng/ml were associated with 12-month failure rates in low-, intermediate- and high-risk groups of 29.6%, 38% and 74.8%, respectively.
In a parallel study of salvage cryoablation population, 471 patients were identified and studied based on specific PSA ranges. The results of that data analysis is detailed below in the Kaplan Meier graphs and accompanying tables.

The reported data indicate that regardless of risk stratification, in the primary cryoablation population if the initial post cryoablation PSA was 0.6 ng/ml or higher, the 24-month biochemical failure rate was 29.5%. Similarly, in the salvage cryoablation population, a nadir PSA > 0.6 ng/ml was associated with 45% 12-month biochemical failure. It follows that an initial post-cryoablation PSA < 0.5 ng/ml portends a favorable prognosis by PSA criteria for both populations, although at varying time intervals of follow-up. While the implications of these studies are similar for the primary and salvage cryoablation populations regarding nadir PSA levels, the differences between these groups of patients is substantial and one must be conscious of the expected differences.

Our studies indicate that nadir PSA is prognostic for biochemical freedom from disease following cryoablation of the prostate based upon the arbitrary nadir + 2 criteria for failure, which is notably not designed as a definition for cryotherapy outcomes. However, PSA alone cannot be used as a definition of treatment success until correlated with disease-specific survival and metastasis-free survival.

While we believe nadir + 2 criteria are applicable to assess biochemical disease-free survival in the cryoablation population, establishment of standards by which treatment success can be measured following prostate cryoablation remain lacking, and establishment of such standards is a major objective at this time.

We are currently involved with the next phase of defining these standards by looking at prognostic factors of PSA outcomes as well as biopsy status of those individuals with elevated post-treatment PSA levels and patterns of disease progression/failure following prostate cryoablation. We anticipate creation of a validated definition of biochemical disease-free survival in the near future through collaborative work arising from continued study of the COLD Registry database.

For references, please email the editor.
Over the last couple of years, we have evaluated the 980 nanometer (nm) wavelength laser vaporization system in a multitude of ways. We feel that this wavelength of energy has numerous potential advantages when compared to other wavelengths. Herein, we present our current recommendations regarding this technology.

The laser emits a wavelength of 980 nm, which is effectively absorbed by both water and hemoglobin. This is significantly different from the 532 nm wavelength device, which is absorbed extremely well by hemoglobin, but poorly absorbed by water. It also differs from the 2100 nm laser in which the energy is highly absorbed by water, but insignificantly absorbed by hemoglobin. Thus, at 980 nm, prostatic tissue, which is either virgin tissue or has been previously treated with other minimally invasive modalities or TURP, can be effectively vaporized. Also, scar tissue and previously radiated prostate tissue, both of which contain significantly less amounts of hemoglobin, may be effectively and safely vaporized.

The laser energy at 980 nm produces a slightly greater penetration of energy into the prostate gland, producing outstanding hemostasis. To date, no patient has required reoperation for bleeding; catheter times have been 24 hours or less, and delayed hematuria, which can be an issue with other wavelengths, has not occurred.

Lastly, irritative symptoms, which commonly occur post prostatic laser vaporization, have been very manageable. One of the concerns has been that if the energy is driven deeper into the prostatic tissue the result will be an increase in both the severity and duration of irritative symptoms. To date, this has not been observed. However, one complication of delayed prostatic chip formation and slough has been noted, but with a change in operative technique it appears to have lessened in frequency.

This technology also has progressed in the last two years in both its power capabilities and fiber tip design. The early laser boxes were only able to generate significantly less power, and it was not until the 120-watt device was produced that prostatic vaporization became efficient. Currently, we are evaluating the 180-watt device which, in a limited number of cases, appears to be significantly more efficient at vaporization, thus resulting in a shortening of operative times. The fiber tip designs are also under continued assessment and evaluation, and different tip designs may be more or less efficient and desired depending on certain prostatic characteristics. Presently, several fiber tips are available and are under evaluation. Different fibers with different characteristics may have physical advantages in a variety of prostatic conditions, such as extensive middle lobe intravesical extension, or bilobar hypertrophy with “kissing” lobes. This aspect of the technology remains under intensive investigation.

We continue to look at a variety of technologies for post brachytherapy and post cryotherapy urinary retention, in which no good therapeutic option currently exists. The 980 nm wavelength is currently under evaluation.

980: The New Hot Number in BPH Therapy

James C. Ulchaker, MD, FACS, and Khaled Fareed, MD

Key Point:
The 980 nm wavelength has shown consistent promising qualities as a desirable wavelength for prostate vaporization, and will continue to be evaluated and investigated here.
Clinical Phenotyping of Patients With Chronic Prostatitis/Chronic Pelvic Pain Syndrome and Correlation With Symptom Severity

Daniel A. Shoskes, MD, J. Curtis Nickel, Robert Dolinga and Donna Protz

Chronic pelvic pain syndrome (CPPS) is a common condition that significantly affects quality of life. CPPS has a multifactorial etiology and seems to respond best to multimodal therapy. However, there are currently no validated biomarkers for classifying patients in a way that could guide therapy. In large multicenter clinical trials, promising treatments have often shown little or no benefit compared with placebos. The heterogeneous nature of the trial participants might have prevented a positive result for patients with the appropriate mechanism or symptom etiology.

To address this situation, we developed a clinical phenotyping system to classify patients with chronic pelvic pain (CPPS and interstitial cystitis) and direct appropriate therapy. The system, known as UPOINT, includes six clinical domains: urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurologic/systemic and tenderness of muscles.

Each domain has been defined by clinical parameters and is associated with evidence-based treatments. The phenotype is qualitative, with each domain scored as yes or no and symptom severity measured using a validated instrument. UPOINT is designed to be flexible so that new data such as biomarkers and treatments can be added as they are validated. In order to be useful and relevant, this classification should identify a diversity of phenotypes that show some correlation with symptom severity.

In a recent study, we used the UPOINT system to determine the phenotype of a cohort of 90 men with a diagnosis of CPPS seen at Cleveland Clinic. The group included a mix of patients with early-onset and long-term treatment-recalcitrant disease; the mean patient age was 44.3 years (range 21-71), with a median duration of symptoms 30 months (range 3-444).

The symptom severity of each patient had been measured using the National Institutes of Health Chronic Prostatitis Symptom Index (CPSI), with subscores recorded for pain, urinary symptoms, and quality of life, as well as the total score. The patient data used for classification included history, physical examination findings, and urine and expressed prostatic secretions or post-massage urine culture results. Patients were not always questioned about depression and catastrophizing which could mean that the positive results for the psychosocial dysfunction domain were underestimated. Nonetheless, many patients openly expressed feelings of helplessness and hopelessness and more than a third were represented in this domain.

The first key finding was that patients did show a diversity of phenotype patterns for both individual domains and the number of positive domains. The percentage of patients positive for each domain was 52% (urinary), 34% (psychosocial), 61% (organ-specific), 16% (infection), 37% (neurologic/systemic), and 53% (tenderness).

A second key finding was that symptom severity, as measured by CPSI, directly correlated with the number of positive domains. Symptom duration longer than two years was also associated with an increase in positive domains.

A comparison of the total CPSI score with each domain showed significantly increased symptoms in patients positive for the urinary, psychosocial, organ specific, neurologic/systemic and tenderness domains. This analysis was repeated for the pain subscore which was highest for the psychosocial, neurologic/systemic and tenderness domains. Only the psychosocial and neurologic domains influenced quality of life.

Since each domain is associated with specific targeted therapies, patient classification has important implications for treatment. For example, a patient positive only for the urinary and infection domains might benefit most from an antibiotic and α-blocker.

In a prospective study, we hope to perform multivariate analyses on a larger group of patients to explore more fully the interactions among the domains, symptoms and outcome. We hypothesize that multimodal therapy guided by the UPOINT phenotype would have the greatest chance for success.

Key Points:

To better understand the etiology of chronic pelvic pain syndrome (CPPS) and guide multimodal treatment, we proposed a clinical phenotyping system, UPOINT. A cohort of 90 men with CPPS were retrospectively classified in each UPOINT domain (urinary, psychosocial, organ-specific, infection, neurologic/systemic, and tenderness).

The findings showed a diversity of patient phenotype patterns and a direct correlation between the number of positive domains and symptom severity.

Because each domain is associated with specific effective therapies, multimodal therapy may best be guided by the UPOINT phenotype.
Natural orifice transluminal endoscopic surgery (NOTES) represents a fundamental change in the intellectual and physical approach to the surgical management of urologic disease. The concept of employing a natural orifice such as the mouth or vagina or rectum to gain access deep in the patient abdomen to perform surgery is gaining momentum with significant laboratory work already reported. However, such novel surgery is associated with considerable technical complexity. The collective experience with natural orifice surgery in animal experiments, coupled with successful NOTES diagnostic procedures in humans, has helped to assuage many of these concerns and has generated considerable enthusiasm. Herein, we present the first human experience with natural orifice surgery in which we did the surgery through the vaginal wall into the patient abdomen to remove a diseased kidney. The surgery was completely scarless.

Following Institutional Review Board approval, a 57-year-old female patient presented with non-functioning right kidney causing flank pain. The patient had previously undergone an abdominal hysterectomy.

An incision was made in the vagina and the patient belly was distended with carbon dioxide gas. Then a standard gastroscope was introduced transvaginally into the abdominal cavity under direct vision. A multi-channel laparoscopy port was successfully positioned across the vaginal wall. Operating exclusively through the transvaginal port, the kidney was dissected and removed through the vagina; the vaginal incision was then closed.

The procedure was successfully completed transvaginally. Operative time was 307 minutes, of which 124 minutes were dedicated to obtaining vaginal access and port placement, and the remaining 183 minutes were dedicated to adhesiolysis and nephrectomy. Estimated blood loss was 100mL. No intraoperative complications occurred.

The patient’s vaginal pack and Foley catheter were removed on postoperative day 1. She was ambulatory 16 hours following her operation. She tolerated a soft diet and was discharged 23 hours following the completion of her procedure without apparent sequelae. Mean Visual Analog Pain Scale score during the course of admission was 5.6/10 and was 1/10 on postoperative day 2. As is demonstrated in Figure 4, the patient exhibited a scarless appearance on postoperative day 1.

Key Point:
Based on this first human experience, we conclude that transvaginal NOTES is feasible and safe. Existing instrumentation is adequate but significant improvement is still needed. Additional study is required to better define the future role of transvaginal NOTES in urologic surgery.
Natural orifice transluminal endoscopic surgery (NOTES) is an emerging technique with significant experimental and clinical ongoing investigation. NOTES may further reduce morbidity and provide a scarless surgery. Transgastric and transvaginal approaches have been used to access the peritoneal cavity.

Herein we present our experience with transgastric and transvaginal NOTES renal cryoablation in the animal model, as an alternative to the laparoscopic approach, for anteriorly located renal tumors not accessible percutaneously.

In 2 female farm pigs, we performed 4 procedures of NOTES renal cryoablation. In each animal, NOTES was performed through the transgastric approach and the transvaginal approach for each kidney, respectively. In the first animal, we started with the left kidney with a transgastric approach. A dual-channel video gastroscope (Olympus, Tokyo, Japan) was used; the stomach wall was punctured using a needle-knife, a guide wire was passed into the abdominal cavity and the access dilated using a controlled radial expansion balloon. The bowel was mobilized medially and the Gerota’s fascia overlying the upper pole was dissected. Under direct endoscopic vision, a cryoablation probe was introduced percutaneously into the anterior upper pole of the kidney. The animal was then flipped to the right flank position and a transvaginal approach was used. For the second animal, we performed initially a transgastric right side cryoablation then a transvaginal left side cryoablation as described for the first animal. All procedures were performed successfully without any addition of laparoscopic port. The only visible scar was the site of percutaneous insertion of the Veress® needle and cryoprobe. No complications occurred during any procedure and surgical access and exposure of the anterior upper kidney pole was adequate with enough space dissected around the kidney to avoid accidental freeze of surrounding organs. Mean total operative time was 83 min (range 76 to 94). Operative time was longer for the transgastric approach versus the transvaginal approach (91±4.2 versus 74.5±2.1). Gastric closure was watertight in both cases. The cryoablation time was the same for all procedures (10 min and 8 min for the first and second cryoablation cycles, respectively). Mean cryoablation zone diameter was 3.7 cm (range 3.5 to 3.9 cm). Blood loss was less than 20 ml in all cases. There were no inadvertent injuries to kidney or surrounding bowel or other organs during dissection or during freezing cycles.

NOTES can provide adequate minimal surgical dissection for safe and effective percutaneous renal cryoablation under direct videoscopic monitoring at kidney locations otherwise not accessible percutaneously. Both transgastric and transvaginal approaches can be used effectively to perform renal cryoablation providing a minimally invasive scarless surgery.

**Key Points:**

Our initial experience with transgastric and transvaginal NOTES renal cryoablation in the animal model, as an alternative to the laparoscopic approach, for anteriorly located renal tumors not accessible percutaneously has been positive. Both transgastric and transvaginal approaches can be used effectively to perform renal cryoablation, providing a minimally invasive scarless surgery.
Laparoscopic Surgery Without Visible Scars: Experience with the First 100 Cases

Jihad Kaouk, MD, Robert Stein, MD, Courtenay Moore, MD, and Raymond Rackley, MD

In the past 2 years, the surgical community has witnessed an exciting foray into the burgeoning field of single-port laparoscopic or laparoendoscopic single site (LESS) surgery. Developed as an extension of standard laparoscopy that requires 3 to 6 small incisions, LESS seeks to minimize patient discomfort, shorten convalescence, and improve cosmesis by placing all instruments through a readily concealed 2cm incision mostly within the umbilicus. Initial series have been published that extol the safety, aesthetics, and superior pain profile of the single-port approach. However, questions remain regarding the comparative benefit of LESS, its applicability, its potentially lengthy learning curve, and technical limitations of existing instrumentation.

We present our initial experience with 100 patients who underwent LESS urologic surgery from September 2007 to February 2009. Specifically, 74 patients underwent LESS renal surgery (cryoablation, 8; partial nephrectomy, 15; metastectomy, 1; renal biopsy, 1; simple nephrectomy, 7; radical nephrectomy, 6; cyst decortication, 2; nephroureterectomy, 7; donor nephrectomy, 19; and dismembered pyeloplasty, 8) and 26 patients underwent LESS pelvic surgery (varicocelectomy, 3; radical prostatectomy, 6; radical cystectomy, 3; sacral colpopexy, 13; and ureteral reimplant, 1). Mean patient age was 54 years.

Mean operative time was 199 minutes. Estimated blood loss was 136 mL. No intraoperative complications occurred. Six patients required conversion to standard laparoscopy. Mean length of hospitalization was 3 days. Mean Visual Analog Pain Scale score at discharge was 1.5/10. At a mean follow-up of 11 months, 9 Clavien Grade II (transfusion, 7; urinary tract infection, 1; deep vein thrombosis, 1) and 2 Clavien Grade IIIb (recto-urethral fistula, 1; angioembolization, 1) surgical complications occurred.

Based on our initial experience that represents one of the largest experiences in this technique worldwide, LESS urologic surgery is safe, offers improved patient cosmesis and decreased pain, and can be performed with a modicum of laparoscopic skills. Its superiority compared to traditional laparoscopy is currently speculative. As such, a prospective, randomized trial is under way to better define its role.
### LESS Renal Surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Tumor Size (cm)</th>
<th>EBL (mL)</th>
<th>OR Time (min)</th>
<th>LOS (days)</th>
<th>VAPS</th>
<th>Comments</th>
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<td>Renal Cryotherapy (n = 8)</td>
<td>2.64</td>
<td>75</td>
<td>171</td>
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<td>Partial Nephrectomy (n = 15)</td>
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<td>422</td>
<td>196</td>
<td>4.5</td>
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<td>Transfusions – 4</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conversion – 2</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Margins Negative</td>
</tr>
<tr>
<td>Renal Biopsy (n = 1)</td>
<td>4.1</td>
<td>150</td>
<td>120</td>
<td>3</td>
<td>2/10</td>
<td>No Complications</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>Dx – Oncocytosis</td>
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<td>Simple Nephrectomy (n = 7)</td>
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<td>121</td>
<td>156</td>
<td>2.3</td>
<td>1/10</td>
<td>No Complications</td>
</tr>
<tr>
<td>Radical Nephrectomy (n = 6)</td>
<td>4.6</td>
<td>146</td>
<td>206</td>
<td>2.3</td>
<td>3.2/10</td>
<td>Transfusion/ICU Admission – 1</td>
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<td>Margins Negative</td>
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<td>Cyst Decortication (n = 2)</td>
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<td>135</td>
<td>1.5</td>
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<td>Metastectomy (n = 1)</td>
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<td>150</td>
<td>122</td>
<td>1</td>
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<td>No Complications</td>
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<td>Nephroureterectomy (n = 7)</td>
<td>2.73</td>
<td>396</td>
<td>198</td>
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<td>1.4/10</td>
<td>Conversion – 2</td>
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<td>197</td>
<td>199</td>
<td>3.3</td>
<td>1.9/10</td>
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### LESS Pelvic Surgery

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<tr>
<th>Procedure</th>
<th>Tumor Size (cm)</th>
<th>EBL (mL)</th>
<th>OR Time (min)</th>
<th>LOS (days)</th>
<th>VAPS</th>
<th>Comments</th>
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<td>250</td>
<td>270</td>
<td>27.1</td>
<td>2.3</td>
<td>1.2/10</td>
<td>Positive Margins – 3/Fistula – 1</td>
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<td>Radical Cystectomy (n = 3)</td>
<td>216</td>
<td>315</td>
<td>27.8</td>
<td>6.6</td>
<td>0/10</td>
<td>No complications/Margins Negative/LN yield – 16</td>
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<td>Sacral Colpopexy (n = 13)</td>
<td>46.9</td>
<td>182</td>
<td>26.7</td>
<td>1.6</td>
<td>1/10</td>
<td>No complications/No recurrences</td>
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<td>Varicocelectomy (n = 3)</td>
<td>6.5</td>
<td>60</td>
<td>21.3</td>
<td>0</td>
<td>0/10</td>
<td>No complications/No recurrences</td>
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<td>Ureteral Reimplant (n = 1)</td>
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<td>180</td>
<td>24</td>
<td>3</td>
<td>3/10</td>
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<tr>
<td>All Patients (n = 26)</td>
<td>115</td>
<td>200</td>
<td>26.8</td>
<td>2.2</td>
<td>0.9/10</td>
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Application of 2-mm Needlescopic Instruments in Urological Laparoscopic Surgery

Shih-Chieh Jeff Chueh, MD, PhD

Dr. Chueh recently joined the staff of the Glickman Urological & Kidney Institute. Prior to his appointment at Cleveland Clinic, Dr. Chueh practiced at National Taiwan University Hospital in Taipei. He now offers this care as part of the Glickman program at Charleston Area Medical Center in Charleston, W.Va.

Our endeavor to perform transperitoneal laparoscopic adrenalectomy solely with needlescopic working instruments (Figure 1) for presumptively benign adrenal tumors < 5 cm started in 2000, after Gagner, Yu, and Soble, et al reported some initial experience in a variety of surgery. Only one umbilical 12mm port for the telescope and 2 (for left adrenomas) or 3 (for right adenomas) subcostal 2mm working ports were used (Figure 2). Control of the adrenal vessels and hemostasis were achieved by a 2mm bipolar coagulator without any clipping.

Our initial 12 consecutive successful cases revealed the benefits of less pain, better cosmesis and faster recovery compared with those done by the conventional 5-12mm laparoscopic instruments. We continued to accumulate more cases and a larger series (112 patients) to further examine the safety and efficacy for most adrenal tumors < 5 cm. All 112 operations were completed without any mortality or re-operation. Mean operative time was 151 minutes, and mean blood loss was 30 mL. Only one patient required a blood transfusion and application of a hand-assisted device. Conversion to conventional laparoscopic instruments was necessary in another five patients (4.5%). The operative time of the latter 100 cases (mean 147 min) was significantly shorter than that of the initial 12 cases (183 min). Larger tumors, previous abdominal surgery, and pheochromocytoma were independent risk factors of a longer operative time. Except for one leiomyosarcoma, all the others were benign adrenal pathologies (57 aldosterone-producing adenomas, 23 Cushing’s adenomas, 12 pheochromocytomas, and 20 incidentalomas). Our experience indicates that the safety and effectiveness of laparoscopic adrenalectomy employing only needlescopic instruments for most adrenal tumors < 5 cm was feasible with acceptable operative time. The patients with previous upper midline or ipsilateral upper quadrant open surgery may not be suitable candidates for such a technique.

Experience of laparoscopic total adrenalectomy with only mini-instruments prompted interest in its application in laparoscopic partial adrenalectomy. For the treatment of aldosterone-producing adrenal adenomas (APAs) partial adrenalectomy offers definite benefits to patients with suspected bilateral APAs or an APA in a solitary adrenal gland. We described the feasibility of this novel technique

Key Point:

Needlescopic instruments (mini-instruments) offer virtually scarless wounds, excellent postoperative cosmetic effect, less pain and faster convalescence, although it is more challenging to master their proper usage. Needlescopic techniques have been successfully employed for adrenalectomy (112 cases), partial adrenalectomy (8 cases), and bilateral varicocelectomy (25 cases), renal cyst enroofing, localization (and excision) of descending testis, and lymphocele fenestration.

Figure 1.
Left: Comparison of the diameters of the needlescopic (in yellow loops) versus the conventional laparoscopic trocars and instruments.
of laparoscopic partial adrenalectomy for APAs solely using 2mm working instruments as a safe and effective treatment alternative for 6 unilateral and 2 bilateral partial adrenalectomies. Hemostasis and transection of adrenal tissues were performed using a 2mm mini-bipolar coagulator and 2mm scissors (Figure 3). All such operations were successfully performed with no intraoperative or postoperative complications. Blood loss was minimal, and the operative times were comparable to those of previous reports. All patients had low pain scores, required minimal amounts of narcotics postoperatively, and reported excellent cosmetic results for the wounds. The pathologic examinations confirmed complete excision of all adenomas with intact capsules. The plasma aldosterone concentrations and renin activities returned to normal ranges postoperatively in all patients.

At a mean follow-up of 25 months (range 13 to 48), 7 of the 8 were cured of hypertension, and one had hypertensive medications significantly reduced.

The potential of employing mini-instruments in a clipless purely needleoscopic bilateral varix ligation was also investigated. The positions of laparoscopic ports and surgical procedures were similar to those of the conventional 3-port laparoscopic technique, but all original 5- and 10mm trocars were replaced by 2mm mini-trocars (Figure 4). The internal spermatic veins proximal to the internal inguinal ring were isolated and coagulated for an adequate segment with a 2mm bipolar electrocoagulator and then transected in between. The mean amount of analgesics used, the maximal and mean postoperative pain scores, the postoperative hospital stay, and convalescence to normal activity were all significantly decreased in the needlescopic group of 25 patients compared to 25 matched controls. Our experience showed that needlescopic bilateral varix ligation not only is feasible and safe but also provides the same therapeutic efficacy of a conventional laparoscopic approach.
Nearly 74% of small kidney tumors are discovered incidentally, through imaging techniques, often while tumors are still small and confined to one organ. New minimally invasive techniques for treatment of kidney tumors are giving patients better, less radical treatment options, including cryotherapy of small renal masses.

Currently, many of these procedures are performed using CT-guided probes. This is not real-time guidance, which makes the preparation and setup for surgery a lengthy process. Moreover, because the guidance cannot be precise, the patient’s position must be manually adjusted, sometimes leading to undertreatment of a tumor.

The image-guided stereotactic concept has been successfully reported in numerous surgical applications including neurosurgery, orthopedics, deep brain biopsies, breast tumor biopsies, and ablation using laser fibers.

We have assembled a dedicated surgical team at the forefront of developing new minimally invasive ablative techniques for the treatment of renal tumors. Our team is studying the use of a stereotactic system for the percutaneous treatment of kidney tumor with probe ablation. To our knowledge, this is the first study of its kind in the literature.

Precise probe placement is essential for a successful ablation. We used a novel stereotactic surgical navigation system that may enhance precision during percutaneous probe placement while reducing radiation exposure compared to conventional CT-guided procedures. CT-Nav® (Koelis, France) is a stereotactic surgical navigation system used routinely in neurosurgery and orthopedic applications. The system consists of a tracking sensor, a needle guide targeting handle, a stereoscopic infrared camera, and a personal computer (Figure 1). An infrared tracking sensor is taped to the patient flank, then a CT scan is completed and the 3-D CT volume data is uploaded into the CT-Nav®. Using a point/area matching and registration protocol, the pre-placed tracking sensor is automatically recognized in the 3-D CT volume data. The infrared camera detects the tracking sensor and localizes it three-dimensionally. The tracking sensor is then used as a reference point. Any movement of the patient is detected by the movement of the tracking sensor, allowing the system to readjust the CT volume coordinates in real-time. The targeting handle is also detected and its position is correlated to the tracking sensor, thus allowing the CT-Nav to reconstruct a cross-section CT slice corresponding to the position and angle of the targeting handle (Figure 2). The tracking handle is then used to navigate and guide the needle percutaneously to the targeted tumor. The optimal trajectory is subsequently saved by the CT-Nav® system.

**Key Point:**

Based on our experience, stereotactic percutaneous cryoablation of renal tumors offers the potential for safe and precise needle placement while reducing radiation exposure compared to traditional CT guidance. A multicentric prospective randomized study is needed to confirm those potentials.
Ten patients with a total of 13 tumors successfully underwent cryoablation using the novel navigational system. Mean tumor size was 2.2 cm. Preoperative biopsy demonstrated renal cell carcinoma in 6 cases (tumors in 2 patients were benign; the remaining 2 biopsies were inconclusive). Mean operative time was 155 min. No intraoperative or postoperative complications were noted. Mean length of stay was 9.5 hours. A mean decrease in CT fluoroscopy duration of 18.3 seconds was noted for each cryoprobe placed. Mean targeting registration error was 4.2mm.

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### Oncological data

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<table>
<thead>
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<tr>
<td>Mean tumor size (cm)</td>
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<td>Preoperative cancer on biopsy</td>
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<td>Cryoablation at day 1 (cm)</td>
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<td>Cryoablation at 3 months (cm)</td>
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<td>Residual enhancement at 3 months (%)</td>
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<td>Cancer at 6-month biopsy (%)</td>
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</tr>
<tr>
<td>Re-treatment (%)</td>
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**Robotic Laparoendoscopic Single Site Surgery Using GelPort® as the Access Platform**

Robert J. Stein, MD, Wesley M. White, MD, Raj K. Goel, MD, Brian H. Irwin, MD, Georges-Pascal Haber, MD, Monish Aron, MD, and Jihad H. Kaouk, MD

The two greatest challenges with laparoendoscopic single site surgery (LESS) include clashing between the laparoscope and instruments and the loss of triangulation with limitation of instrument maneuverability. To overcome these obstacles, articulating instruments for greater spacing have been developed. Nevertheless, these instruments can be bulky and difficult to master, thus reducing ergonomics and efficiency for the surgeon.

The primary advantage of the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) for LESS is easier articulation through EndoWrist® instruments. Other benefits include 3-D visualization, motion scaling, and tremor filtration. We reported our initial experience with robotic LESS (R-LESS) using a multichannel single port (Triport®, Advanced Surgical Concepts, Dublin, Ireland) next to which one additional robotic port was placed through the same umbilical incision. This platform arrangement is usable, but limitations include less flexibility for customized placement of ports and interference with placement of ports in tandem through the single incision as the multichannel port has a rigid outer ring. The GelPort® system (Applied Medical, Rancho Santa Margarita, CA) provides a larger working platform that can be useful in all cases, but especially for patients requiring a 3- to 5cm specimen extraction incision.

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*continued on next page*
Since April 2008, we have performed 11 R-LESS cases including radical prostatectomy (n=1), partial nephrectomy (n=2), ureteroneocystostomy (n=1), radical nephrectomy (n=2), and dismembered pyeloplasty (n=5). For the 4 most recent procedures: radical nephrectomy, dismembered pyeloplasty (n=2), and partial nephrectomy for an 11cm right renal angiomyolipoma not amenable to angioembolization, the GelPort® was used as the surgical platform due to the subjective ease of use noted during the first such procedure.

The access procedure involves placement of the patient in modified flank position. A 2- to 5cm transumbilical incision is created either directly through the middle of the umbilicus or using a semi-circle incision concealed within the umbilicus. The GelPort® is then placed through the incision according to standard technique. For upper tract procedures, a 12mm trocar for the camera is placed in the most medial position. Eight millimeter robotic ports are then placed more laterally and near the edges of the cap. (Figure 1). An assistant 5- or 12mm port is positioned between the camera and robotic ports as needed (Figure 2).

In our early experience all 4 R-LESS procedures attempted with the GelPort® were completed successfully without need for placement of additional ports. Median operative time was 200 minutes and hospital stay was 1 to 2 days in all cases. The patient undergoing partial nephrectomy had 600cc estimated blood loss as the lesion was excised using harmonic scalpel without hilar clamping and was transfused one unit of packed red blood cells. Pathology revealed angiomyolipoma with negative margins.

The initial patient who underwent pyeloplasty had resolution of flank pain postoperatively. Differential renal function was maintained at 33% and drainage as determined by diuretic radionuclide scanning was improved. The final patient who also underwent pyeloplasty has not had postoperative imaging given the brevity of follow-up from surgery. There were no operative or wound complications in any case.

For references, please email the editor.

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Laparoendoscopic Single Site Pyeloplasty:
A Comparison to Standard Laparoscopic Technique

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Several groups have reported success using laparoscopic techniques compared to open surgery for treatment of UPJO with pyeloplasty. The morbidity of a laparoscopic approach is certainly decreased compared to an open incision. The question therefore raised is how a laparoendoscopic single site (LESS) approach compares to laparoscopy with regard to perioperative morbidity and successful treatment of UPJO. In this vain we sought to compare perioperative factors, success rates and quality of life variables between LESS and conventional laparoscopic pyeloplasty.

Since December 2007, 16 patients underwent successful LESS pyeloplasty. One patient during this time period was converted to standard laparoscopic technique due to technical limitations and failure to progress and is not included in the comparative analysis. The patients undergoing LESS pyeloplasty were compared to 16 matched patients undergo-
Our technique for LESS pyeloplasty begins with cystoscopy and ipsilateral retrograde pyelogram to confirm the diagnosis of UPJO followed by retrograde placement of a 4.7Fr x 28cm double-J ureteral stent. The patient is then placed in modified flank position and a 2cm incision is used for transumbilical open access and placement of the TriPort® (Advanced Surgical Concepts, Wickliffe, Ireland) access platform. A combination of standard and articulating laparoscopic instruments are then used to dissect the UPJ. The remainder of the procedure duplicates the standard laparoscopic procedure described above. An additional grasper through a 2mm access was variably used in some cases for dissection. The 2mm grasper was used in all cases to aid in suturing.

Preoperative variables between standard laparoscopic and LESS pyeloplasty groups were not significantly different except body mass index (BMI) was greater for the standard laparoscopic group (30±7 kg/m2 vs. 23±6 kg/m2, p=0.002). No difference was noted for intraoperative estimated blood loss between the 2 groups (87±38cc vs. 79±43cc, p=0.05). Operative time was longer for the LESS pyeloplasty group but the difference did not reach statistical significance (215±78min. vs. 183±29min., p=0.055).

No difference was noted between the 2 groups in terms of length of stay or postoperative narcotic analgesic requirements. No intraoperative or postoperative complications were noted for either group. All patients in both groups experienced clinical resolution of their symptoms. One patient in the standard laparoscopy group and 2 patients in the LESS group had T ½ >20min. (0.063% vs. 0.125%) on diuretic radionuclide scanning 3 months postoperatively. One of the patients in the LESS group with radiographic failure had the appearance of a widely patent UPJ on subsequent diagnostic ureteroscopy and, therefore, endopyelotomy was not performed. This patient and the additional patient from each group with radiographic failure are being observed clinically and radiographically.

Review of a 6-item questionnaire demonstrated equivalent convalescence between the 2 groups. (Table 1). LESS provides obvious aesthetic advantages over standard laparoscopic procedures. The present study suggests that other potential advantages, including decreased analgesic requirements, faster recovery, and quality-of-life benefits, do not exist for LESS compared to standard laparoscopic pyeloplasty. It must be kept in mind that this is a retrospective review with a relatively small study population, which includes our earliest experience with LESS reconstructive procedures. In addition, this series only involves patients undergoing pyeloplasty and our ability to extrapolate the results and conclusions of other procedures is still unknown. As experience with LESS increases, further prospective comparative trials are needed.

For references, please email the editor.

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Jihad H. Kaouk, MD, Sebastien Crouzet, MD, Georges-Pascal Haber, MD, Raj K. Goel, MD, and Wesley M. White, MD

Because all laparoscopic instruments are placed in parallel through the umbilicus, significant clashing of both the camera and other laparoscopic instruments can increase operative times and require significant laparoscopic skills. Competition of laparoscopic instruments for a limited space around the umbilicus may be improved by using a small robot as a camera holder. This eliminates the need for a camera holder assistant, thus allowing for a single-port single-surgeon surgery with potential improvement of surgical range of motion.

We present the initial experience with single-port robotic-assisted laparoscopic surgery in reconstructive urology performed by a single surgeon.

On 5 male farm pigs we performed 10 dismembered pyeloplasties and 10 partial nephrectomies followed by 10 radical nephrectomies. A multichannel single port was inserted through a 2 cm incision in the umbilicus. The scope was held using a novel low profile light endoscopic robot (LER) fixed to the OR table and controlled using voice-command or foot-control. We used articulated instruments with deflectable and 360° rotatable tips that provide 7 degrees of freedom (CambridgeEndo, Framingham, USA).

All 30 procedures were performed successfully by a single surgeon without addition of any ports or open conversion. No complications occurred during any procedure and no robotic unexpected movement or malfunction occurred. The robotic endoscope holder with foot control provided a stable image with easy movements, and minimal limitation of the scope range of motion occurred. Conflict between instruments and scope were minimized by the use of articulated instruments. The ring base of the robot gave enough space to access the additional 2 channels of the single port. Mean incision size after wound closure was 2.6 cm (range 2.4 to 3 cm). Mean operative time for dismembered pyeloplasty was 110 min (range 95 to 130 min), 120 min for partial nephrectomy (range 100 to 150 min) and 20 min for radical nephrectomy (15 to 30 min).

The combination of a robotic scope holder, a transumbilical single-port access and articulated laparoscopic instruments allow for a virtually scarless laparoscopic surgery performed by a single surgeon. The compact size of the robot helps to avoid clashing between instruments and camera and improves the limited space needed by the surgeon. Further improvements of the current robot and instruments used are needed to move single-port single surgeon to the clinical level.

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Technical Modifications of Robotic-Assisted Pyeloplasty in Children Resulting in Minimal Morbidity and Improved Efficacy

Jeffrey S. Palmer, MD, FACS, FAAP

Robotic-assisted laparoscopic pyeloplasty (RALP) is an evolving approach in the pediatric population for the treatment of ureteropelvic junction (UPJ) obstruction. Available robotic systems provide precision afforded by 3-D visualization and articulating instruments. We have refined and introduced innovative RALP techniques in the pediatric population.

Our RALP technique is a 3-port transperitoneal dismembered (Anderson-Hynes) pyeloplasty using the da Vinci® Surgical System. The primary 12 mm camera port is inserted at the umbilicus to minimize surgical scars. A 30-degree telescope is used to provide adequate visualization of the renal hilum. Retraction of the liver for right-sided pyeloplasty is not necessary as the UPJ can be dissected and further retracted below the level of the liver edge in most cases. Secondary ports are placed along the ipsilateral rectus muscle border. Transmesenteric approach is employed for the significantly dilated renal pelvis, and mobilization of the upper ureter and renal pelvis is performed meticulously with generous surrounding tissue to avoid devascularization injury of the mobilized ureter. If an anterior crossing vessel is present at the UPJ, ureteral transposition is performed. The UPJ is excised using cold scissors and spatulated at its lateral border. The renal pelvis is reduced if necessary. The main disadvantage for using the robot in the pediatric population is the small working space and proximity of the robotic arms that may limit their range of motion. All RALP procedures have been successfully completed without conversion to laparoscopy or to open pyeloplasty. There have not been any intraoperative or postoperative complications related to these techniques.

Conventional pyeloplasty may require a ureteral stent insertion that necessitates a second procedure under anesthesia for the child to have the stent removed. Kidney Internal Splint Stent (KISS), a percutaneous nephroureteral catheter, is commonly used postoperatively after open pyeloplasty in children in order to bridge the anastomosis and permit renal drainage. One advantage of this catheter in children over the double J stent is that it can be removed in the office without sedation or anesthesia. Also, the KISS can be cut to the appropriate size so as to only bridge the UPJ anastomosis without entering the bladder, thereby preventing urinary reflux across the anastomosis and bladder spasms. We report on the first series using the KISS in a robotic-assisted or laparoscopic pyeloplasty in children. The KISS is brought into the operative field through a working port, inserted into the renal pelvis/ureteral defect, brought through a small pyelotomy proximal to the anastomosis, and the ureteropelvic anastomosis is performed. The catheter is brought through and sutured to the skin, and then connected to a small collection bag.

Key Points:

Robotic-assisted procedures continue to evolve for the pediatric population. Our refinement and introduction of new RALP techniques minimize surgical morbidity with excellent surgical outcomes.

We are developing additional innovative techniques to further enhance the robotic-assisted surgical treatment of UPJ obstruction.

Left: Ureteropelvic junction (UPJ) obstruction with excision of obstruction.

Center: Ureter is spatulated on the lateral aspect. Sutures are placed both medially and laterally for a running anastomosis anteriorly and posteriorly.

Right: Completion of the anastomosis.
Guidelines for Management of the Clinical Stage 1 Renal Mass

With more frequent detection and rising incidence rates, clinical stage 1 (< 7.0 cm) solid, enhancing renal masses are now a common clinical scenario for urologists. Approximately 80% of these tumors are malignant and, of these, about 20-30% demonstrate potentially aggressive features. Management options range from observation to radical nephrectomy (RN). However, current practice is divergent and sometimes potentially discordant with what the existing literature supports. Consequently, the Practice Guidelines Committee of the American Urological Association (AUA) commissioned a panel to develop guidelines for the management of the clinical stage 1 renal mass for physicians who treat this condition. The panel chair was the late Andrew C. Novick, MD, and co-chair was Steven C. Campbell, MD, PhD. The guidelines were presented at the American Urological Association’s annual meeting in April by Dr. Campbell.

The panel based its recommendations on an extensive review of available professional literature, clinical experience and expert opinion. The guideline statements are graded as standard, recommendation or option based on the degree of flexibility in application.

The following guidelines regarding evaluation and counseling address all index patients with a clinical T1 renal mass:

**Evaluation**

Standards: A high-quality cross-sectional image study (CT or MRI). Percutaneous renal mass core biopsy should be performed when clinical or radiographic findings are suggestive of lymphoma, abscess or metastasis or in patients in whom the results will potentially affect management.

**Counseling**

Standards: Discuss the current understanding of clinical stage 1 renal masses, the relative risks of benign vs. malignant pathology and the potential role of active surveillance (AS). Review available treatment options and counsel the patient about the potential advantages of a nephron-sparing approach.

**Key Findings:**

- Nephron-sparing approaches should be considered in all patients with a clinical T1 renal mass, presuming adequate oncologic control can be achieved, based on an increased risk of chronic kidney disease (CKD) associated with radical nephrectomy (RN). CKD is directly correlated with morbidity and mortality.
- Active surveillance should be a primary consideration for patients with decreased life expectancy or who are particularly high-risk for surgery.
- Thermal ablation (cryoablation or radiofrequency ablation) is a treatment option for the high-risk surgical patient.
- Surgical excision by partial nephrectomy (PN) is a reference standard for the management of clinical T1 renal masses. PN is underutilized and has well-established longitudinal oncologic outcomes data comparable to RN.

To reflect commonly encountered clinical variations, the following treatment guidelines address specific patient profiles:

**Index Patient 1: Healthy with clinical T1a (<4 cm).**

Standards: Complete surgical excision by partial nephrectomy (PN) is a standard of care. Most tumors in this size range are amenable to PN. Radical nephrectomy (RN) is an alternate standard of care if PN is not technically feasible.

Options: Thermal ablation (TA), such as cryoablation or radiofrequency ablation, is a less-invasive treatment option but is associated with a substantially increased risk of local recurrence and surgical salvage may be difficult. Active surveillance (AS) is an option for patients wishing to avoid treatment and willing to assume oncologic risk.

**Index Patient 2: Major comorbidities/increased surgical risk and clinical T1a (<4 cm).**

Standards: Complete surgical excision by PN is a standard of care with increased surgical risk in this patient. It should be considered whenever preservation of renal function is a primary issue. RN is another standard of care with increased risks of surgical complications and CKD. A laparoscopic approach to RN can reduce blood loss and shorten recovery time.

Recommendations: TA is a less-invasive option in this high-risk surgical patient. AS should be a primary consideration in patients with decreased life expectancy or who are particularly high risk for surgery.
Index Patient 3: Healthy with clinical T1b (> 4 cm but <7 cm).

Standards: RN is associated with less perioperative morbidity than PN and remains a standard of care for patients with a normal contralateral kidney. A laparoscopic approach to RN should be considered. Complete surgical excision by PN is an alternative standard of care, particularly when renal function needs to be preserved.

Options: TA is a less effective treatment option and may represent suboptimal management for these healthy patients. AS may be an option for patients who want to avoid surgery and are willing to accept an increased risk of tumor progression compared to PN or RN.

Index Patient 4: Major comorbidities/increased surgical risk and clinical T1b (> 4 cm but <7 cm).

Standard: RN is a standard of care for patients with a normal contralateral kidney, although it can be associated with surgical morbidity and an increased risk of CKD.

Recommendations: PN is a recommended modality when renal function needs to be preserved, although it is associated with increased urologic morbidity, an important consideration in this high-risk patient. AS should be a primary consideration for patients with limited life expectancy or those who are particularly high-risk for surgery.

Option: TA is a treatment option which is less effective due to high risks of local recurrence and complications in this patient population, given larger tumor size.
Partial nephrectomy has been the procedure of choice for patients with poor renal function, tumors in solitary kidneys or bilateral renal tumors. The efficacy of partial nephrectomy in regard to cancer control and preservation of renal function has been well documented. The traditional size limitation for masses amenable to this approach has been 4 cm.

Indications for partial nephrectomy have been expanding over the last few years. Partial nephrectomy has become an elective procedure for patients with tumors less than 4 cm and a normal contralateral kidney. This has allowed the preservation of renal function and also avoids overtreatment of benign conditions that can arise more frequently in small renal masses. Preservation of renal function has led to improved quality of life with cancer control rates similar to radical nephrectomy.

The loss of a kidney cannot be viewed as an innocuous procedure. Patients who undergo radical nephrectomy can develop chronic renal disease. This seems to contradict the conventional wisdom that patients do well with only one kidney. However, this belief has been based upon the outcome of healthy patients who have undergone donor nephrectomies. These individuals are not comparable with patients who have renal surgery for renal masses. Renal donors undergo stringent screening to rule out diseases that may affect long-term renal function. Patients with renal masses are often older and more likely to have comorbidities such as hypertension or diabetes. Preservation of renal tissue in this population would carry an obvious benefit, thus leading to the consideration of partial nephrectomy in patients with tumors larger than 4 cm.

Partial nephrectomy for masses between 4 and 7 cm (T1b) can achieve tumor control similar to radical nephrectomy. Rates of distal or local recurrences have been similar to that of radical nephrectomy in patients undergoing partial nephrectomy for T1b tumors. Cancer-specific survival and metastasis-free survival also was shown to be similar between the 2 groups.

Key Point:

Partial nephrectomy is an integral tool in the management of renal cortical tumors. Renal tumors 4 cm or less should always be considered for renal preservation surgery. With proper patient selection, partial nephrectomy can also apply to patients with tumors between 4 and 7 cm. Partial nephrectomy for all T1 tumors can be highly successful and can offer curative treatment of renal cortical numbers to a larger group of patients while preserving long-term renal function.

We recently reviewed our experience at Cleveland Clinic Florida of patients who underwent partial nephrectomy for renal masses greater than 4 cm. In this group of 14 patients, the average age was 59.9 years (41-80 yrs). 13 patients had renal cell carcinoma and 1 had an oncocytoma, suggesting that even in the T1b stage some patients may be over-treated with radical nephrectomy if their pathology is benign. Mean tumor size was 4.98 cm (4.0-8.5 cm). 2 of the 14 patients had solitary kidneys. 9 of 14 patients had a GFR that returned to baseline (>60ml per min/1.73m squared) after partial nephrectomy, suggesting that removing larger tumors will not compromise function in the remaining portion of the kidney.

No major complications were noted except for acute tubular necrosis in 2, only one patient with solitary kidney requiring postop temporary dialysis). Creatinine levels were similar before and after surgery with mean preop creatinine at 1.2 mg/dl (0.8-1.8 mg/dl) and mean postop creatinine (after discharge) was 1.41 mg/dl (0.74-2.9 mg/dl). Mean ischemic time was 43 minutes (12min-75min) and mean estimated blood loss was 230cc (100-700cc). Margins were negative on all specimens. Follow-up to date has demonstrated no evidence of recurrences on imaging studies. One patient died of a second malignancy that developed after renal surgery. These results suggest that not only is partial nephrectomy for T1 numbers feasible, but it can be performed with minimal complications and with good preservation of renal function.

For references, please email the editor.
Neoadjuvant VEGF-targeted Therapy in Renal Cell Carcinoma

Brian I. Rini, MD, and Steven Campbell, MD, PhD

Recent therapeutic advances in metastatic renal cell carcinoma (RCC) have included agents targeted against vascular endothelial growth factor (VEGF). These agents targeting circulating VEGF ligand (e.g., bevacizumab) or the tyrosine kinase portion of the VEGF receptor (e.g., sunitinib, sorafenib) have dramatically altered the therapeutic landscape of this disease and have become standards of care. These agents were initially tested in patients with distant metastatic disease, most of whom had undergone primary tumor resection. One remarkable feature of all these agents is a high objective response rate of 10-40%, and approximately 70% of patients experience some degree of tumor burden reduction. Further, some reduction of primary tumor size has been observed in patients with primary tumor in place, which was unusual in the cytokine era. As such, a natural extension of the use of these agents is prior to nephrectomy for locally advanced disease in an attempt to downstage the primary tumor.

Locally advanced RCC presents challenges to both the urologist and medical oncologist. Local disease is often surgically difficult to resect entirely due to invasion of local organs, tumor size, bulky lymphadenopathy or involvement of critical structures such as mesenteric blood vessels. Further, such patients are at very high risk for recurrence without proven effective adjuvant therapy. A recently published Cleveland Clinic experience administered sunitinib 50 mg 4 weeks on with 2 weeks off therapy to 12 patients deemed unresectable alternating because of invasion into adjacent organs, proximity to vital structures, bulky regional lymph nodes or vascular invasion, with many patients possessing multiple such adverse features. Partial responses of the primary tumor were noted in 3 patients (25%). Primary tumor shrinkage was observed in 8 patients (67%) with an average decrease of primary tumor size by 24% (range, 2-46%). Three patients demonstrated tumor size reduction enough to facilitate resection with mean primary tumor shrinkage of 16% (range, 11-24%). Viable tumor was present in all pathological specimens after nephrectomy. No issues with wound healing, bleeding, or thromboembolic events were encountered.

A prospective trial of sunitinib in RCC patients with unresectable primary tumors (with or without distant metastases) is currently ongoing at Cleveland Clinic. Patients with histologically confirmed RCC with an unresectable primary tumor (with or without distant metastases) and no prior treatment are enrolled on this single-arm phase II trial.

Key Point:
We are currently studying sunitinib in renal cell carcinoma patients with unresectable primary tumors (with or without distant metastases). Patients receive 50 mg sunitinib continuous dosing in repeated 6-week cycles. Preliminary results in 18 patients treated to date have shown a reduction in some primary tumors enough to permit subsequent surgical resection. Continued investigation is needed.

Primary tumors are deemed unresectable by the surgeon due to various combinations of the following: large tumor size, bulky lymphadenopathy, proximity to vital structures, or high-level venous thrombosis. Patients receive 50 mg sunitinib continuous dosing in repeated 6-week cycles. Preliminary results in 18 patients treated to date have shown a reduction in some primary tumors substantial enough to permit subsequent surgical resection. A total of 71% of patients had a reduction in the primary RCC tumor, permitting resection in 3 patients who were otherwise unresectable. The median percent primary tumor shrinkage is 15.0% (range, 2.0 - 58.5%). Continued investigation is needed to identify the optimal neoadjuvant setting and approach, timing of surgical intervention and to further define safety considerations such as time off drug needed before and after surgery.

Renal Cell Carcinoma Review in The Lancet
Dr. Campbell and Dr. Rini, along with Bernard Escudier, MD, recently published the first major review of kidney cancer in the past few years in the March 2009 issue of The Lancet (Vol. 373, No. 9669, pages 1083-1096). The review is based largely on publications and abstract material from the past five years, along with older, highly regarded publications. Surgical and systemic approaches to treatment are explored.

For references, please email the editor.
Enrollment of patients in our Chronic Kidney Disease (CKD) Clinic and use of the electronic medical record (EMR) permitted establishment of a CKD database of the demographics, clinical parameters and outcome measures of these patients. In addition, the EMR-based database was used for identifying and enrolling patients in clinical research projects.

We are now embarking upon a more ambitious project to examine the role of the EMR in the identification and management of CKD patients throughout our health system. The development of a CKD Registry is the initial objective of a comprehensive program to develop an EMR-based disease management model for the care of patients with CKD. The other objectives for this comprehensive program are to: a) implement clinical decision tools (Physician Alerts) within the EMR based upon clinical guidelines in CKD management, b) measure the utility and impact on quality of care and cost of these CKD tools (Physician Alerts) upon management of CKD patients, and, c) determine the potential barriers of physician acceptance to these clinical decision tools (Physician Alerts).

The CKD Registry has recently identified nearly 40,000 patients with CKD who have received their medical care at Cleveland Clinic since January 2005. Patients with CKD were identified from the Cleveland Clinic EMR/Epic based upon: a) an eGFR < 60mL/min, (measured in outpatients at least twice in an interval > 3 months), or b) an ICD-9 Diagnostic Code for kidney disease such as diabetic nephropathy, polycystic kidney disease, glomerulonephritis, hypertensive nephrosclerosis, etc. Data elements within the CKD Registry include:

- Patient demographics
- Blood pressure, height, weight, BMI
- Comprehensive laboratory testing including GFR, anemia management, calcium, phosphorus, PTH, Vitamin D, lipids, etc.
- Medications
- Comorbid diseases—especially cardiovascular disease and its risk factors.

Key Points:

We are developing a Chronic Kidney Disease Registry from our electronic medical records and CKD Clinic. The information and observations learned from our CKD Registry should be hypothesis-generating for the development of our comprehensive CKD Model of Care Program.

Based upon our insights into the management of CKD, we plan to implement clinical decision tools within the EMR based upon clinical guidelines in CKD management. We have initiated a collaborative effort with our colleagues in Primary Care and Quantitative Health Sciences to develop an EMR-based tool which will be helpful and efficient for all involved in the care of CKD patients.

Our CKD Registry will also interface with the USRDS and the Social Security network. It is uniquely designed to examine the recognition and management of CKD in patients over the entire care spectrum ranging from the primary care environment, traditional nephrologic care, CKD Clinic, and renal replacement therapy with either dialysis or transplantation via the USRDS. Our CKD Registry will help us address the following issues regarding the scope of CKD and its management:

1. Prevalence of CKD by stage within Cleveland Clinic.
2. CKD recognition by physician and the healthcare team.
3. CKD progression with loss of GFR over time. The goal of this area will be to produce a “CKD progression tool” for use by physicians, healthcare teams, and patients in preparing for future CKD needs such as education, vascular access, or renal replacement therapy.
4. Assess “Processes of Care” by the physician regarding the ordering of appropriate assessment related to: hypertension, anemia, hyperlipidemia, PTH, etc.
5. Assess “Clinical Practice Measures Targets” related to the management of hypertension, anemia, hyperlipidemia, hyperparathyroidism, etc.
The Development of a Glomerulonephritis Board Can Help in the Treatment of Individual Cases as Well as in Developing Effective Treatment Regimens

Surafel Gebreselassie, MD

Considering the advancement in the diagnosis and treatment of glomerular disease, we believed that a Glomerulonephritis Board at Cleveland Clinic would bring together key medical specialists who could collectively examine specific pathologic findings of complex glomerulonephritis cases, review current treatment approaches and devise the most effective treatment regimen for salvaging functional renal parenchyma. The Glomerulonephritis Board (GN Board) would function much like a Tumor Board functions. In addition each specimen would be paired with clinical case data and biobanked information which could provide valuable insight into disease risk and mechanisms for the future.

In the past 5 years more than 700 patients underwent kidney biopsy at Cleveland Clinic to evaluate for glomerular diseases. And, a number of kidney biopsies performed outside Cleveland Clinic were submitted to our pathology department for review. While there is a database of individual diagnoses, there is less clarity as to treatment approaches and individual treatment outcomes. The GN Board will review individual cases from within Cleveland Clinic and offer an opportunity for outside nephrologists and patients to submit specimens for evaluation. Once the specimens were linked to clinical data, the board would then suggest treatment recommendations based on structural findings on biopsy and up-to-date findings from treatment trials.

This GN Board approach to the diagnosis and treatment of glomerulonephritis requires a team of physicians/experts representing nephrology, pathology, vasculitis, rheumatology/immunology and genetics who are committed to better understanding the structural changes from parenchymal injury and assessing known clinical trials results. The GN Board will provide an opportunity to examine the utilization of newer agents for specific cases in a more controlled fashion. Tracking responses to renal injury treatment over time with a link to biobanked material will facilitate future opportunities for predicting response to therapy and progressive ongoing injury despite treatment.

Patients will not generally participate in GN Board presentations, but there are plans to invite patients in selected cases. Feedback from the GN Board would be communicated back to the referring nephrologists or physician outlining the board’s opinion and treatment recommendations. All treatment recommendations would represent agents and strategies described in clinical trials throughout the world. Also the board will seek ongoing access to participation in specific NIH treatment trials and other impact trials deemed critical to the understanding and treatment of glomerulonephritis.
Sankar D. Navaneethan, MD, MPH

Although the number of chronic kidney disease patients is increasing at an alarming rate (about 13% of Americans have some form of kidney disease), the treatment options are still limited. The number of randomized controlled trials among all medical subspecialties is lowest in nephrology. Until these trials are conducted, systematic reviews and meta-analysis conducted on topics in which clinical trials might take longer to complete or might be impossible can help clinicians improve quality of care.

Systematic reviews, which are different from traditional reviews, summarize the available evidence in an unbiased way. The major advantage of systematic reviews/meta-analysis is the ability to pool data from similar studies and analyze both benefits and risks associated with a particular treatment option while enhancing the precision of point estimates. This is especially important when controversy exists about a particular treatment option, such as whether to use statins in kidney disease patients, or whether higher hemoglobin levels are better for kidney disease patients.

We have conducted and published several systematic reviews and meta-analyses that would influence the treatment provided to kidney disease patients. These include the role of statins in kidney disease patients, sodium bicarbonate for preventing contrast-induced nephropathy, aldosterone antagonists for preventing progression of chronic kidney disease, and phosphate binders for chronic kidney disease. We are also conducting several other systematic reviews of both observational and clinical trials in nephrology, the results of which would be published in the near future.

Apart from leading the conduct of systematic reviews, we also collaborate with other centers that pioneer in such kind of research. This includes the Cochrane Renal group in Sydney, Australia, and the Mario Negri Sud Consortium in Italy. Further, we also train several researchers from various parts of the country (University of Rochester, Southern Illinois University, Indian Health Service) in the conduct of such systematic reviews so that the quality of care delivered to our kidney disease patients can improve.

There is a general consensus that untreated anemia in chronic kidney disease (CKD) probably contributes to the large cardiovascular burden in this population. Anemia is aggressively treated with erythropoietic stimulating agents (ESA) and parenteral iron. However, the issue of how best to treat anemia in CKD has come to the forefront, with the results of recent randomized control trials showing that hemoglobin normalization, by utilizing erythropoietic stimulating agents (ESA), can result in increased morbidity and mortality. The optimal target of hemoglobin is still hotly debated.

The overall scope of our laboratory continues to be to improve our understanding of the molecular mechanism involved in anemia of CKD and utilize this knowledge to design better and more physiological treatments that could have a positive impact in CKD patients.

By utilizing a well-described mouse model of CKD that develops anemia and responds to ESAs we have found that CKD anemia lowers hepatic hepcidin expression, the main regulator of circulating iron, and that ESA decrease hepcidin even further. We speculate the existence of a circulating negative hepcidin regulator in CKD serum. A potential candidate is erythroblast expression of growth differentiation factor 15 (GDF15), a member of the transforming growth factor- superfamily, that is increased in thalassemia (ineffective erythropoiesis) and has been shown to suppress hepatocytes hepcidin mRNA expression. However its role in CKD is not known. Our preliminary data suggest that we can eliminate the decreased hepcidin expression induced by CKD mouse serum in an in vitro system by immunodepleting the serum with anti GDF15 antibody. These results suggest a potential role of GDF15 in CKD that has not been described. Further characterization and understanding of these observations are in progress.

In addition, we have also shown that increasing doses of parenteral iron result in upregulation of hepatic hepcidin expression in CKD mice that is associated with a diminished ESA response when compared to mice treated with ESA only. We speculate that parenteral iron, as given, interferes with the necessary decrease in hepcidin expression required for ESA response.

Our future plan includes continued testing of different iron regimens on the iron regulatory proteins that we are studying to identify the optimal dose required for a robust erythropoietic response.
The New Centers for Medicare and Medicaid Services Conditions for Coverage Regulations

Rachel Fissell, MD, and Robert Heyka, MD

In 2008, Centers for Medicare and Medicaid Services (CMS) published the first major revised conditions for coverage (CFC) for dialysis patients since 1976. The guidelines outline proper practices in dialysis care, and are aimed at improving the quality of care for the nearly 336,000 Medicare beneficiaries with end-stage renal disease (ESRD) who receive dialysis treatment at the more than 4,700 Medicare-approved renal dialysis facilities in the United States. The new regulations took effect on October 14, 2008.

Several factors led to reform of the previous conditions of coverage:

• The economics of provision of dialysis have changed since the first conditions of coverage.
• There are many more nurse practitioners working in dialysis units than even 10 years ago.
• There is a greater sense of the importance of pre-ESRD care, particularly with regard to preparing patients for, and achieving, optimal vascular access prior to starting hemodialysis.
• Finally, investigators, organizations, and companies all over the world as well as in the United States have put much time, effort and funds into learning how to optimize outcomes for ESRD patients.

There are several areas related to the care of ESRD patients for which there is national and international consensus. The conditions of coverage of ESRD patients attempt to address these changes in the economics of dialysis, as well as increase knowledge in the nephrology community about which practice patterns are associated with the best clinical outcomes. The updated conditions of coverage provide a framework for incorporating performance measures into payment.

Several elements of the process of caring for dialysis patients are emphasized more strongly than in the previous conditions of coverage, including patient involvement, the role of the interdisciplinary team, and the active involvement of the medical director.

Three notable components of the new conditions of coverage are:

• An interdisciplinary team consisting of the patient (or someone designated to stand in for the patient), a social worker, physician, nurse and nutritionist must provide each patient with an individualized and comprehensive assessment of needs.
• The interdisciplinary team must develop a plan that includes measurable and expected outcomes, and estimated timetables to achieve those outcomes.
• The dialysis facility must develop, implement and maintain an effective data-driven quality assessment and performance improvement program, and constantly evaluate that program in terms of improving health outcomes and preventing and reducing medical errors.

The onus of implementing the program falls on the shoulders of the medical director of the dialysis center.

In theory, the regulations address goals that every physician and healthcare worker have–providing the best care possible to our dialysis patients. However, concerns exist. Documentation requirements seem to be increased under the new regulations. The increased time each team must spend fulfilling documentation requirements may have the unintended consequence of decreasing the time each member of the team can spend seeing patients and working on clinical issues with the patients. There is also concern about the process of linking performance measures with payment decisions by CMS. Part of this concern is related to the fact that rounding nephrologists and medical directors may have a reduced payment as a consequence of an outcome over which they may feel they have little to no control.

Overall, the previous conditions of coverage were due for a revision. As CMS, hospitals, and the large dialysis organizations such as Fresenius and FMC, move forward with the new conditions of coverage, we can hope that the changes improve the quality of care delivered to our dialysis patients.
Sevag Demirjian, MD

Despite ongoing discoveries, the outcome for patients who develop renal failure requiring dialysis remains at 50%. Though there have been a number of clinical trials addressing the issue of dialysis dose and type (continuous vs. intermittent), no individual disruptive technology or approach has fully altered the natural course for the patient who develops acute kidney injury (AKI) in the ICU. Future efforts at identifying the high risk patient, creative approaches to preventing injury and protocols aimed at repairing the kidney following an insult are being initiated here. Current studies are examining the use of sRNA compounds to prevent injury, along with a series of biomarkers for early detection of kidney injury in postoperative and ICU settings. While showing great promise, these markers have not been validated against hard clinical endpoints.

The large patient volume at Cleveland Clinic combined with state-of-the art electronic data capture has enabled our researchers to better understand risk factors, characteristics and complications associated with AKI and its treatment. We also are able to better phenotype our patients at high risk for renal complications. Subsequently, we can offer individualized care and investigational therapy opportunities for these patients. RENAL RES-Q clinic (Renal Risk Evaluation for Surgery at the Q building (Glickman Tower)), capitalizes on meticulous pre-intervention evaluation of these high-risk patients, detailed counseling and timely fine-tuning of their modifiable risk factors. Moreover, for those interested, serum and urine samples will be collected to improve predictive ability via biomarkers, and opportunities will be provided for participation in clinical trials.

Two recent large multicenter trials renal replacement dosage in acute kidney injury showed very high mortality rates in critically ill patients with AKI. In contrast to earlier smaller trials, neither trial showed a clear-cut benefit from increased dose of renal replacement therapy. This has prompted our nephrologists to refocus our attention on detailed technical aspects of renal replacement in the ICU. We hypothesize that apparently insignificant details of dialysis prescription in the ICU may influence patient survival by mechanisms that renal replacement therapy (RRT) dose alone may not capture. We are probing the effects of RRT on drug dosing, middle molecule clearance, and nutritional health of critically ill patients.

As our understanding of critical illness and acute kidney injury evolves, we must progress from a one-size-fits-all approach to renal replacement in the ICU, and tailor goals and prescription to each patient. We are incorporating various techniques to both adequately and efficiently provide renal replacement therapy to ICU patients utilizing multiple different dialysis machines and RRT options. Safe and cost-effective methods for accomplishing the dialysis procedure without systemic anticoagulation are rapidly replacing unfractionated heparin as the standard of care in dialysis, and we are implementing regional anticoagulation techniques for dialysis in our ICUs.
Bioartificial Kidney
Making Milestones

William Fissell, MD

A pioneering implantable artificial kidney developed jointly by teams of researchers at Cleveland Clinic, the University of California San Francisco, and the University of Michigan is on track to meet project milestones in a pilot and feasibility study funded by the NIH. The device is a hybrid of high-tech nano-scale silicon membranes and living kidney cells designed to support patients with renal failure without the need for external machines or dialysate. The project is in the second year of the feasibility study, intended to stress-test key technologies needed for a full-scale device that would serve as a third alternative to dialysis and transplantation.

We are working to develop the novel membranes essential to success of the implantable artificial kidney and coordinating membrane testing and bioreactor development. A second-phase proposal will be submitted to the NIH in late winter. This scale-up phase of the project will take the bioartificial kidney from components on a lab bench to a clinical trial in patients.

Clinical experience with extended daily dialysis suggests that a total dose of dialysis almost four times as much as is routinely provided today can improve nutrition, quality of life, cardiac disease, and even reproductive health in dialysis patients. At the same time, the numbers of patients starting dialysis each year continues to rise. About 400,000 patients in the United States depend on dialysis to live, and 80,000 patients are on the kidney transplant waitlist. These two pressures – a need for more therapy and more people who need it – conflicts with the financial need for cost-containment in healthcare. Dialysis patients cost Medicare about 10 times as much as the average Medicare patient, and the Medicare Trust Fund is projected to become insolvent in 10 years – well within the lifetimes of some patients on dialysis today. Therefore, alternatives to reduce cost associated with renal failure are desperately needed.

This technology provides a third path for patients with renal failure – an implantable hybrid device combining high-efficiency filters with living cells. The device, based on silicon nanotechnology, overcomes fundamental barriers to implanting dialysis – the size of the dialyzer and pumps, and the need for dialysate. The high-efficiency hemofilter is powered by the patient’s own blood pressure, eliminating the need for blood pumps. Derived from technology developed by David Humes, MD, and his team at the University of Michigan, the bioreactor of human kidney cells recycles the ultrafiltrate and concentrates it into urine, which can be directed to the patient’s own bladder.
The Hybrid In-Hospital Dialysis Unit: Current and Future Challenges

Martin Lascano, MD

The provision of in-hospital dialysis services over the next decade will necessitate a rethinking of the unit infrastructure, coordination of resource allocation, application of newer dialysis techniques, attention to data management and quality targets, and the continuous development of dialysis personnel. The in-hospital unit in actuality is a hybrid unit, caring mostly for hospitalized end-stage renal disease (ESRD) and acute kidney injury (AKI) patients who require dialysis, but also serving a significant number of ESRD and AKI outpatients.

Our in-hospital dialysis unit relocated to a state-of-the-art facility on the 6th floor of the Glickman Tower last year. The new location provided the opportunity to expand from 12 to 21 beds in response to the increasing number of patients who are transferred to Cleveland Clinic for complex issues or who develop AKI during their hospitalization. The number of treatments during the last 5 years averaged 12,950 a year and is expected to grow. Nearly 4,800 (37%) treatments are performed in the specialized in-hospital dialysis unit; the remainder in the ICU. The average acuity score for patients dialyzed in the in-hospital unit is 3.47.

Because hospitalization outcomes and length of stay are keenly linked to the quality of each dialysis treatment, the electronic medical record (EMR), in addition to a knowledgeable staff, is critical to our understanding of the patient’s condition and in the effective communication between the medical team, actual dialysis treatment site and the nursing floor team. During the past 6 months we developed a system wherein all dialysis orders are placed directly into the EMR. In the next 12 months, a linkage will be completed connecting the actual dialysis machine to the EMR for automated individual dialysis treatment data transfer. This will automate data transfer for all events that occur during the treatment and assist with quality data management in the future, a critical component for improving overall patient outcomes.

The standard outpatient dialysis prescription may not be tolerated by all ESRD patients, requiring further evaluation to determine the optimal dialysis treatment design critical to ensuring optimal treatment tolerance and laboratory results. Our unit will provide patients who experience difficulty with standard OPD dialysis treatments an opportunity to be evaluated with diagnostic dialysis protocols bringing together nephrologists, cardiology, nursing and additional specialty areas in an integrated approach aimed at improving an individual’s tolerance of the dialysis procedure without experiencing those complications which add to the morbidity of the procedure and interfere with quality of life. In addition, newer approaches to measuring body composition and volume will be tested in those dialysis patients who have experienced complications related to ineffective volume regulation with dialysis; hypervolemia can lead to increased morbidity, hospitalization rates and shortened patient survival.

Exploring technology for ultrapure water

There is an increasing body of information supporting the view that standard dialysis water may increase cytokine production, which can potentially stimulate inflammation/oxidative stress and add to the decrease in observed dialysis outcomes. Several studies have examined such parameters as serum advanced oxidation protein products (AOPP), malondialdehyde (MDA), glutathione peroxidase (GSH-Px), myeloperoxidase (MPO), albumin (Alb), C-reactive protein (CRP), neopterin, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-6, attempting to better characterize the level of inflammation change that may occur with conversion to ultrapure water.

While studies are ongoing to determine the exact impact of currently utilized water treatments on outcomes, we continue to explore newer technologies capable of producing ultrapure water in our hospital unit. The current technology utilizes automated hot water disinfection of the reverse osmosis membranes and distribution loop and a 0.05 pyrogen filter; this technology achieves the current AAMI standards for bacteria and endotoxin control (bacteria (CFU/M): <200/>50 action level and endotoxin (EU/ml)<2/>1 action level). We believe that future systems utilizing reverse osmosis/electrode ionization will be required to set a new standard that would provide patients with pharmaceutical quality water, critical for achieving “true” ultrapure water.
Developing a nocturnal dialysis program

Over the last year, there have been a number of reports on the advantages in patient outcome with daily home dialysis or nocturnal home dialysis. And yet not all patients that may benefit from this technique have the resources to undertake home dialysis. Yet, these studies have demonstrated that total treatment time plays a key role in determining outcome for the home patient and, most likely, the complex hospitalized patient. As we continue to examine the best approach to providing therapy, we will begin to develop a nocturnal in-center program for patients who necessitate more aggressive intervention and/or slower blood flow rates for optimal middle molecule clearance. While the issue of preemptive dialysis for the CKD patient not previously on dialysis or at end-stage is still controversial, we are examining the appropriateness of preemptive dialysis in certain patients with the intent of avoiding acute/chronic postoperative renal failure.

Decreasing infection from intravascular catheters

Infectious complications stemming from the use of intravascular catheters for hemodialysis treatments add significant morbidity and mortality to the hospitalized patient. Considering this significant risk we have initiated a protocol in the last 2 months that utilizes an antimicrobial locking solution in all catheters used for hemodialysis, with the primary objective of decreasing the infection risk. During the next 2 years we will continue to collect data to determine the impact this approach will have on infection risk for the HD patient.

Redefining Hypertension for Tomorrow: Target Levels

Mohammed A. Rafey, MD, MS

During the last 45 years, Cleveland Clinic has been in the forefront of defining mechanisms responsible for hypertension. While there has been a resounding increase in the recognition of hypertension as a risk factor for cardiovascular disease and stroke, less than 40% of patients are actually achieving acceptable levels of control. We continue to examine what the target blood pressure (BP) for an individual patient should be, and the correct approach to measuring it.

The commonly used threshold BP level of less than 140/90 mmHg was initially derived from the actuaries of the insurance industry and there is sufficient evidence to demonstrate that lowering BP to this level offers cardiovascular and renal protection. It is also clear from clinical trials that a lower BP goal of less than 130/80 mmHg is preferable in individuals with diabetes mellitus or chronic kidney disease. While these goal blood pressure levels offer a general threshold to direct antihypertensive therapy, it remains undecided whether a more intense lowering of blood pressure offers additional benefit. Most clinical trials in hypertension thus far have not been designed to evaluate the effect of intense BP lowering.

The best evidence so far for a threshold BP above which there is an increased risk in cardiovascular mortality was provided by a meta-analysis published in The Lancet in 2002. This meta-analysis included 61 prospective observational studies of blood pressure and mortality with one million adults with no previous vascular disease recorded at baseline. Results indicated that an increased risk for cardiovascular mortality begins at a BP level above 115/75 mmHg. Based on these data, JNC VII opted to create the new category ‘pre-hypertension’ including individuals with BP level in the range of 120-139/80-89 mmHg.

Debate exists whether (1) an individual’s raw BP readings should solely be utilized for classification into various stages of hypertension or (2) a more comprehensive evaluation including risk factors in addition to baseline blood pressure assessment should be done, or a combination of the above. This approach is evidence-based and readily acceptable for individuals with co-morbid cardiovascular and renal disease in whom intense BP control has been shown to be beneficial. A similar approach is less understood and debatable when applied to healthy individuals who present with BP levels in the pre-hypertension range.

The existing European hypertension guidelines attempt to address this undecided clinical question by stratifying individuals based on both known risk factors and early markers of subclinical target organ damage (e.g., objective measures of arterial stiffness and carotid wall thickening) to guide hypertension therapy.

The problem in including subclinical target organ damage markers lies in the fact that there are limited data and no large outcome studies on the presence of these markers in...
healthy individuals causing an increase in cardiovascular or renal events. It is plausible that modifying these early risk factors will have a beneficial effect in reducing cardiovascular and renal outcomes, but there is no evidence yet to demonstrate that this is true.

The concept of ‘pre-hypertension’ introduced in JNC 7 was based on data on the lifetime risk of hypertension and an increased risk for cardiovascular complications associated with levels of blood pressure previously considered to be normal. These data were derived from the general population, which also included individuals who were at higher risk due to comorbid conditions. It is now time to clearly define the role of BP elevation in the pre-hypertension range in healthy individuals.

In a study presented at the AHA Scientific Sessions 2008, we evaluated a relatively healthy group of healthy individuals with blood pressure less than 140/90 mmHg. In this study, we evaluated cardiovascular and renal risk parameters after stratification into two groups based on a systolic BP level cut-off of 115 mmHg. Interestingly in this study, although all parameters were within normal range for both groups, the group with BP level greater than 115 mmHg had a significantly higher BMI, worse lipid panel parameters, higher CRP, elevated renal hemodynamic parameters and higher fasting blood glucose levels as well as higher glucose levels at all stages of the oral glucose tolerance test. These results demonstrate that cardiovascular and metabolic disarray begins much earlier in healthy individuals and that systolic BP level may be a useful surrogate marker. Conclusions drawn from these data may help guide management of healthy individuals with blood pressure in the pre-hypertension range.

The pre-hypertension state probably begins at a lower systolic blood pressure of 115 mmHg instead of the currently recognized threshold of 120 mmHg. Non-pharmacological, multi-pronged interventions based on healthy diet and exercise may be more effective in prevention of this subclinical metabolic disarray and progressive target organ damage rather than treatment of elevated BP with anti-hypertensive therapy alone. Large, prospective clinical trials are needed to further explore this interesting finding and hypothesis.

For references, please email the editor.

### Current Research into Hypertension

Those BP instruments that have traditionally been utilized to assess the patient’s actual blood pressure may give way to newer approaches being evaluated here. As we attempt to determine an individual’s optimal BP, we have begun to assess the benefit of devices such as 24-hour ambulatory blood pressure monitor (ABPM), the BpTRU™, which measures more accurate blood pressure readings in the office setting and Sphygmacor, a device that measures central blood pressure. There is increasing evidence that suggests that ABPM more closely predicts target organ damage than do clinic BP measurements. In addition, a significant percentage of patients with progressive chronic kidney injury have nocturnal rather than daytime hypertension; instruments which may identify patients at risk would be helpful. Moreover while the peripheral BP measurement has been the trusted approach to designate individuals with so-called elevated BP we now are learning that the key pressure to monitor is the central aortic augmentation pressure and the pulse wave velocity. Certain patients may require significantly lower peripheral BPs to achieve an acceptable central BP; this phenomenon may be more important in females vs. males.

Although there is a valuable role for monitoring BP in the home, most patients do not consistently measure their BP nor does the model of hypertension care link the healthcare team with the patient at home to monitor, recognize poor control and act on it in a timely fashion. We are testing a system leveraging Microsoft HealthVault™ to capture BP readings taken at home, linked to the patient’s computer and then transmitted to a server, which notifies the physician by email at regular intervals of BP readings from an individual patient. In addition, we are assessing the transmission of data automatically from a home BP device directly to the individual’s cell phone, then to a server, which is maintained by a member of the healthcare team. While each of these models necessitates the patient actually measuring BP at home, we are evaluating a more advanced technology that leverages a sensor device implanted in a vessel to transmit data to an external receiver then is automatically transmitted to a server for review.

While the genetics of hypertension remain a complex uncertain area, we are searching for a specific gene polymorphism which may control nocturnal hypertension in the Black patient with CKD and hypertension. If this project is successful, we will be able to identify those individuals with the greatest risk for progressive kidney injury from uncontrolled BP elevations at night.
A history of ongoing data collection has provided the basis for a rational approach to drug therapy in complicated patients with resistant hypertension.

Our hemodynamic laboratory is a unique facility that provides valuable information (neurohormone measurements, cardiac hemodynamics, cardio-pulmonary transit time, and blood volume, etc.) critical to understanding the etiologies for drug resistance. These data are utilized to structure successful therapeutic regimens linking pharmacologic effect with the individualized hypertension physiology. Our accumulated understanding of those hemodynamic mechanisms that sustain the uncontrolled hypertension state have provided the basis for a rational approach to antihypertensive therapy selection in the most complex patients despite a long history of poor control and multiple different medication trials.

In 1970, an Endocrine Hypertension Research Laboratory was established within the Clinical Section of the Research Division here, headed by Emmanuel Bravo, MD. This led to the development of rapid, sensitive and specific assay techniques for the measurement of plasma renin activity, plasma and urinary aldosterone, plasma cortisol and plasma catecholamines and their urinary metabolites. Today, these measurements are performed in a special section of our clinical laboratories and are the standard of care for resistant hypertension and endocrine-related hypertension protocols employed at here.

The availability and expertise in the use of these diagnostic biochemical tools has allowed precise and prompt diagnosis of endocrine-related hypertension. We are continuing to examine what the target blood pressure level should be and how blood pressure should be measured. As the target level for hypertension control changes and we learn more about the appropriate ways of measuring blood pressure, employing newer tools such as BpTRU™, pulse wave velocity, central aortic augmentation pressure, will help in identifying patients with true endocrine-related hypertension, which is pivotal in optimizing long-term patient outcome.

The integrated approach to patient assessment in the Glickman Urological & Kidney Institute, where medical physicians, researchers and surgeons work in the same location, has defined a unique approach to a healthcare model that we believe can have a tremendous impact on the assessment and appropriate treatment of patients with resistant hypertension.

**Resistant Endocrine Hypertension: A Legacy of Experience**

A. CT of a pheochromocytoma
B. MRI of a pheochromocytoma
C. MIBG uptake of a pheochromocytoma

Pathological picture of a pheochromocytoma
Courtenay Moore, MD

With the expanding use of laparoscopic techniques in female reconstructive surgery, there has been an increasing interest in applying minimally invasive approaches to pelvic organ prolapse repair and uterine preservation procedures. These approaches have the potential to combine the success, versatility and durability of traditional open abdominal repairs with the minimal invasiveness and faster recovery afforded by vaginal approaches. Since its introduction in 1991, laparoscopic sacrocolpopexy has undergone many modifications to decrease complication rates and improve cure rates. Given the challenges of laparoscopy, the robotic sacrocolpopexy was introduced as a way to improve visualization while facilitating suturing. In comparison to the open abdominal approach, both laparoscopic and robotic-assisted laparoscopic sacrocolpopexy have decreased hospital stay, decreased narcotic use, hastened return to normal activity, and improved cosmesis.

In an effort to even further decrease postoperative pain while further improving cosmeses, we have developed a less invasive approach to pelvic organ prolapse (POP) utilizing a single port as opposed to the traditional 4 or 5 ports used in laparoscopic and robotic sacrocolpopexy respectively. With improved technology and surgeon experience, laparoscopic surgery through a single incision has become possible. Single-port surgery has been used for oncologic renal, prostate and reconstructive surgery. Over the last year, pelvic organ prolapse surgery has been added to this growing list of applications.

To date a total of 11 women with stage 3 or greater POP have undergone a laparoscopic sacrocolpopinerealpexy using a single laparoscopic port. With the patient in the lithotomy position, the genitalia and abdomen are prepped and draped. After placing a Foley catheter, a 2cm peri-umbilical skin incision is made. Under direct visualization, Hasan technique is used to incise the rectus fascia and enter the peritoneal cavity. Four 2-0 vicryl sutures are placed into the fascia. The single port is introduced through the peri-umbilical incision. Pneumoperitoneum is created using CO2. The patient is then placed in steep Trendelenberg. The mesentery of the sigmoid is grasped using a bowel grasper and a 0-Ethibond suture is then placed through the mesentery. The suture is then passed through to the abdominal wall caudal to the anterior iliac spine and secured with a hemostat. This allows mobilization of the sigmoid colon, exposing the deep pelvis. In patients undergoing a uterine-sparing procedure, a figure-of-eight 0-vicryl suture is placed in the uterine fundus and passed through the abdominal wall using the Carter Thompson to retract the uterus. The sacral promontory is identified and the posterior peritoneum is incised caudal to the sacral promontory. Using angled trocar needles, two 1.5cm wide by 12 cm long pieces of polypropylene mesh are passed lateral to the vaginal walls from the perineum through the uterosacral ligaments and grasped laparoscopically. Vaginal passage allows not only apical but paravaginal support along the full length of the vagina. The mesh is then pulled through the ligaments and secured to the vaginal vault at 3 and 9 o’clock using 2-0vicryl sutures. The free ends of the mesh are then tacked to the anterior longitudinal ligament of the sacral promontory using with either two 0-Ethibond sutures or the Endo-Tac device. The posterior retroperitoneum is then closed over the mesh using a running 2-0 vicryl suture. This approach offers women an almost scar-free approach to the correction of pelvic organ prolapse.

In order to decrease operative times, we are now applying single port technology to robotic surgery. This technique combines the improved cosmesis of single port surgery with the dexterity of the da Vinci robot and decreased operative time.

Key Point:
We have developed a less invasive approach to pelvic organ prolapse utilizing a single port. This approach offers women almost scar-free correction of pelvic organ prolapse.

With advancement in technology we are able to perform major pelvic reconstructive surgery through a single port rather than 5 ports.

Robotic Sacrocolpopexy with 5 ports
Electrostimulation after Delivery Injury to Treat Urinary Incontinence

Margot S. Damaser, PhD

Between 20 and 50% of all women in the United States report frequent and/or bothersome urinary incontinence. An important element of continence is the contraction strength of the external urethral sphincter (EUS), the striated muscle component of the urethra, which is innervated by the pudendal nerve. During vaginal delivery of children, the tissues, muscles and organs of the pelvic floor including the EUS are compressed and injured. In addition, the pudendal nerve can be trapped and injured. These two injuries are both strongly correlated with later development of stress urinary incontinence.

After nerve injury, neurotrophins and their receptors are produced by the muscle and neuron and facilitate regrowth of the nerve and reinnervation of the muscle. However, the same neurotrophins are decreased in injured muscles because they inhibit repair of the muscle and neuromuscular junctions after muscular injury. Thus, it is likely that injury to the EUS inhibits regeneration of the pudendal nerve. Clinical studies have demonstrated pudendal nerve dysfunction years after childbirth at a time point when a peripheral nerve injury should be fully recovered.

Electrical stimulation of the nerve proximal to the site of nerve injury has been demonstrated to increase expression of neurotrophins in the neuron and promote nerve regrowth. This method could potentially be used to facilitate recovery after delivery by promoting nerve regrowth and reinnervation without muscular inhibition because the muscle is damaged simultaneously.

Hai-Hong Jiang, MD, PhD, of the Glickman Urological & Kidney Institute and the Biomedical Engineering Department of the Cleveland Clinic Lerner Research Institute uses electrical stimulation of the pudendal nerve proximal to the crush after simulated childbirth injury in laboratory animals to determine if this upregulates neurotrophins in Onuf’s nucleus, whose axons control the sphincter via the pudendal nerve. He expects that electrostimulation of the pudendal nerve will upregulate neurotrophins in Onuf’s nucleus, improving recovery after simulated childbirth injury, a dual injury to both the pudendal nerve and the sphincter. Dr. Jiang has been awarded a research fellowship from the AUA Foundation for this promising research. His long-term goals are to optimize and develop electrical stimulation treatment as a preventive paradigm for stress urinary incontinence due to childbirth injury. This study will enable clinicians and researchers to further clarify how the stress urinary incontinence develops after vaginal delivery as well as to test a potential treatment.

**Key Points:**

Electrical stimulation of the nerve proximal to the site of nerve injury has been demonstrated to increase expression of neurotrophins in the neuron and promote nerve regrowth. This method could potentially facilitate recovery from injury after childbirth and prevent later development of stress urinary incontinence.

Schematic of the labeled location for chronic stimulation, where the pudendal nerve crosses the ischial spine.
Bladder Neck Coaptation as a Predictor of Successful Injection for Female Stress Incontinence

Gamal M. Ghoniem, MD, FACS

Urethral bulking agents for female sphincteric incontinence have been used for decades. Results of these procedures are usually reported as cure, improvement or failure. However, to date there are no standard definitions of these terms and no standard, widely accepted clinical tool for assessing outcome after anti-incontinence therapy.

Although urethral bulking agent (UBA) injection is monitored cystoscopically, there is no study to elucidate the value of visual urethral / bladder neck coaptation measuring the surface area preoperatively, postoperatively and one year after the last injection.

Our aim of this study was to correlate the degree of bladder neck coaptation in stress urinary incontinence (SUI) patients with intrinsic sphincter deficiency (ISD) before and after r UBA.

Thirty females were involved in this study with one-year follow-up. Twelve patients had polydimethylsiloxane (solid silicone elastomer - Macroplastique® Implants, Uroplasty, Inc, Minnetonka, Minn., USA) and 18 underwent a bovine-collagen (Contigen®, Bard Urological, Covington, Ga., USA) injection. Evaluation of the surface area of the opened bladder neck was made in all the cases before and after injection, and at 12 months of last injection. This evaluation was made by computer analysis of a cystoscopic picture taken 1 cm distal to bladder neck by using ImageJ (image processing and analysis in Java) free software from the NIH. The percentage of surface area reduction (Figure 1) was then correlated with the Stamey’s grade, pad weight, number of pads changed and number of incontinence episodes on voiding diary and urodynamic evaluation done before and at 12-month interval after last UBA. (Table 1).

Our findings showed that the mean age was 67 +/- 9.7 years with average incontinence duration of 10 years; 81% had prior treatment, 19% had prior incontinence surgery; 72% had history of hysterectomy. At 12 months all the patients had significant surface area reduction postoperatively: 0.23 inches (6 %) as compared to the preoperative measurement 0.85 inches (24 %) (p value < 0.001). Patients improving > one Stamey’s grade were 93% (28/30). The one hour-pad decrease was 10 ml from base line 18 ml (p<0.001). The QoL score improved significantly from 68 to 82 (p<0.001). Ninety percent of the patients leaked urine pre-injection according to the voiding diary, which improved significantly post-injection, and more then 53 % were dry (p<0.001), (Table 1). There was a positive correlation found between the post-injection surface area with the Stamey’s grade (p=0.068) and the number of episodes in the voiding diary (p=0.039). The

valsalva leak point pressure (VLPP) showed inverse relation with the post-operative surface area (Figure 2).

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Table 1.

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<th>Pre- injection (mean +/- SD)</th>
<th>At 12-month post-injection (mean +/- SD)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Pad test (ml)</td>
<td>18 +/- 19</td>
<td>10 +/- 13</td>
<td>0.001</td>
</tr>
<tr>
<td>Stamey’s grade</td>
<td>2 +/- 0.4</td>
<td>1 +/- 0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of pads change</td>
<td>2.1 +/- 1.3</td>
<td>0.8 +/- 1</td>
<td>0.001</td>
</tr>
<tr>
<td>Episodes of leakage</td>
<td>4.5 +/- 1.8</td>
<td>0.93 +/- 1.1</td>
<td>0.001</td>
</tr>
<tr>
<td>QoL questionnaire score</td>
<td>68 +/- 22</td>
<td>83 +/- 25</td>
<td>0.001</td>
</tr>
<tr>
<td>VLPP (cm H_2O)</td>
<td>62.6 +/- 16</td>
<td>96 +/- 45</td>
<td>0.001</td>
</tr>
<tr>
<td>Surface area (percentage)</td>
<td>23.7 +/- 0.6</td>
<td>6.6 +/- 6.7</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Figure 2.

\[
s_{area\_12m} = 13.00 + -0.07 \times VLPP_{post} \\
R-Square = 0.20
\]
Urine cytokine assays have been studied in various bladder and kidney disorders. Stretching of the bladder wall as in filling may stimulate the urothelium to release Ach, ATP, nitrous oxide and urothelial derived inhibition factor. One or more of these substances can activate sensory nerve endings in the lamina propria and urothelium where M2 and M3 receptors are present, leading to urgency. We hypothesized that overactive bladder can produce inflammatory cytokines as a result of afferent neural plasticity or from urothelial dysfunction. The objective of our study was to detect abnormal cytokine levels in urine of patients with overactive bladder (OAB) compared to normal.

Our prospective, single blind study included 20 healthy women (control) and 20 women suffering from overactive bladder (group II). Urine samples were centrifuged and mixed with protease inhibitor solution, pH 7.4 to prevent protein degradation, frozen, and stored at -80°C. Urinary total proteins were quantified using BCA protein micro assay kit in accord with manufacturer's instructions. Differential expression profile analysis of cytokines in urine samples of normal and OAB were performed using a human cytokine protein chip. The levels of each cytokine were expressed and compared as mean +/- SE in normal subjects and OAB patients. Each urine sample was tested for 120 cytokines.

Among the expression of 120 cytokines studied in the present study, the majority of the cytokines showed the same expression in the OAB as compared with the control. The chemokines that were found to have two-fold or more positive expression were Monocyte chemoattractant protein 1 (MCP-1), Monocyte chemo-attractant protein 2 (MCP-2), Monocyte chemo-attractant protein 3 (MCP-3), and Eotaxin-3. The pro-inflammatoty cytokines showing two-fold or more positive expression were tumor necrosis factor beta (TNF-β), granulocyte colony stimulating factor (GCSF) and epidermal growth factor receptor (EGF-R), (Figure 2). A few of the cytokines were down regulated like IL-5, IL-6, IL-7 and GM-CSF. It was striking to note that the expression of β-Nerve growth factor (β-NGF) was low.

These findings for the first time demonstrate the production of the most potent chemokine MCP-1 along with other chemokines and proinflammatory cytokines in patients with overactive bladder.
Lack of Pathologic Down-Staging with Neoadjuvant Chemotherapy for Muscle-Invasive Urothelial Carcinoma of the Bladder: A Contemporary Series

Christopher J. Weight, MD, Jorge A. Garcia, MD, Donna E. Hansel, MD, PhD, Amr F. Fergany, MD, Steven C. Campbell, MD, PhD, Michael C. Gong, MD, PhD, J. Stephen Jones, MD, Eric A. Klein, MD, Robert Dreicer, MD, and Andrew J. Stephenson, MD

Neoadjuvant chemotherapy (NC) before open radical cystectomy (RC) is considered by many to be the standard of care for muscle-invasive bladder cancer. The post-cystectomy survival benefit associated with the combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) neoadjuvant chemotherapy for muscle-invasive bladder cancer has been most evident in patients who achieve a pathologic complete response (pCR).

Over the past decade, the combination of gemcitabine and cisplatin (GC) has supplanted MVAC as the standard regimen for advanced bladder cancer due to an improved toxicity profile without substantial differences in overall or progression-free survival. Based on this evidence, GC is often substituted for MVAC for patients receiving NC before RC, despite the lack of evidence indicating a similar benefit in this setting. The logic of improved toxicity is not justification for the use of neoadjuvant GC given the lack of evidence that neoadjuvant MVAC precludes or delays RC in a substantial number of patients.

We obtained patient information from a prospective database and analyzed the pathologic responses to NC and post-cystectomy survival and compared them with published clinical trials.

From January 2006 to November 2007, 117 patients underwent open RC for muscle-invasive bladder cancer at Cleveland Clinic. Of those 117, 29 (25%) received NC. Clinical stage at the time of diagnosis in the NC cohort was T2 in 23 (79%) and T3-4a in 6 (21%) patients. A total of 20 (69%) patients received the combination of gemcitabine and cisplatin (GC), 4 (14%) received MVAC, and 5 (17%) received other regimens. The median interval from the time of diagnosis of muscle-invasive bladder cancer to RC was 208 days (interquartile range, 149 days - 327 days) in the NC cohort.

Overall, only 2 patients (7%; 95% confidence interval [95% CI], 0 patient - 17 patients) in the NC cohort achieved a pCR, both of whom received GC (+/-paclitaxel) compared with 8 (9%; 95% CI, 3 patients - 15 patients) who were pT0 in the immediate RC cohort (P<.001). Both the NC and immediate RC cohorts were comparable with regard to pathologic stage, soft tissue surgical margins, number of lymph nodes removed, and lymph node density. Overall, 62% (95% CI, 43 patients - 81 patients) versus 60% (95% CI, 50 patients - 70 patients) of patients had non-organ-confined cancer (pT3-4 or pN1-2) in the NC and immediate RC cohorts, respectively (P=.4). Of the 20 NC patients with clinical stage T2N0, 1 (5%; 95% CI, 0 patients - 15 patients) achieved a pCR and 11 (55%; 95% CI, 31 patients - 79 patients) had non-organ-confined residual cancer. Comparing MVAC and GC with other chemotherapy regimens, there was a trend toward improved pathologic stage with MVAC and GC (non-organ-confined cancer, 44% vs. 66%) that did not reach statistical significance (P=.3).

Few RC patients with advanced disease in our recent experience achieved a pCR with NC and most experienced rapid disease progression. These poor outcomes may be related to the use of non-MVAC-based regimens or excessive delays in performing RC. A delay in RC has been previously reported to be associated with advanced pathologic stage and diminished post-cystectomy survival. Given that our patients are frequently referred from locations remote to Cleveland Clinic, NC is often administered under the care of patients’ local oncologists. Subdividing patients into those that received NC at our institution (n=6) versus other centers (n=23), a significant delay in the interval from diagnosis of muscle-invasive bladder cancer to RC was observed for the latter group (155 vs. 222 days; P<.046), and these patients also tended to have higher pathologic stage (non-organ-confined cancer, 33% vs. 56%; P=.4).

In the absence of supportive data for GC in the neoadjuvant setting, MVAC remains the preferred regimen. Excessive delays in performing RC may negate the benefit of NC.


For references, please email the editor.

Key Point:
The combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) remains the preferred regimen of neoadjuvant chemotherapy for muscle-invasive bladder cancer due to an absence of supportive data for gemcitabine and cisplatin (GC).
Studying the Effects of Smoke on Bladder Cancer Treatment

William Larchian, MD

Anecdotal reports tell us that smokers and people who are routinely exposed to second-hand smoke do not fare as well with immunotherapy for bladder cancer as other patients. Although they seem to have higher rates of recurrence and progression, a direct association between smoking and bladder cancer treatment has never been proven.

Our laboratory has established a bladder cancer mouse model that will allow us to test the effects of smoke on current treatment regimens used in humans, as well as novel treatments that may be able to overcome the effect of smoking. We have demonstrated increased cure rates in mice with bladder cancer undergoing intravesical gene therapy with immunocytokines such as IL-2 and B7.1, which yielded prolonged immunological memory that protected mice from tumor re-challenge.

This approach may be limited by the propensity of a high level of IL-2 to stimulate expansion and proliferation of immunosuppressive regulatory T cells (T reg). Studies have also noted the similar immunosuppressive activity of smoking. Recent studies demonstrate that the anti-angiogenic tyrosine kinase inhibitor sunitinib malate can attenuate the induction of T reg cell proliferation by IL-2.

Our lab team recently received a $325,000 grant from the Flight Attendants Medical Research Institute (FAMRI) to study the relationship between smoking and responsiveness to bladder cancer treatment. This group was created from a settlement with tobacco companies over flight attendant exposure to second-hand smoke in their work. The money is used to fund research into a variety of health effects related to smoking.

Key Point:

Preliminary findings of our study show that animals in the sunitinib treated group demonstrated significantly lower tumor growth rates and tumor volumes compared to the control group. Once the optimal combination of IL-2 and sunitinib is determined, the regimen will be combined with two different doses of B7.1 gene therapy and compared to B7.1 therapy alone in treating MBT-2 tumor-bearing mice.

We then will test the best treatments against secondhand smoke exposure by measuring the effects on the immune response.

We have identified several specific aims for this research. The first is to scientifically determine if animals that are exposed to smoke develop more bladder tumors than animals that are not exposed to smoke. Also, we are interested in seeing how the two groups vary in their response to intravesical treatment with BCG immunotherapy.

Our second aim is to compare the effects of intravesical liposome-mediated IL-2 gene therapy and the antiangiogenic role of sunitinib malate with the effects of combined treatments on survival of C3H mice with MBT-2 tumors. We presented our preliminary findings at the annual American Urological Association meeting in May 2009. Animals with orthotopic bladder cancer were randomized on day 14 following tumor implantation to receive either 40mg/kg/day of oral sunitinib or saline. Treatment was continued for 7 days. Assessment was performed on day 25. Animals in the sunitinib treated group demonstrated significantly lower tumor growth rates and tumor volumes compared to the control group (20 mm³ vs 56 mm³ p=0.03 t-test). Control group had higher stage disease with extravesical disease, hydronephrosis, and lymphadenopathy. Quantified VEGFR expression was significantly decreased in the treatment group compared to the control group.

When the optimal combination of IL-2 and sunitinib is determined, the regimen will be combined with two different doses of B7.1 gene therapy and compared to B7.1 therapy alone in treating MBT-2 tumor-bearing mice in our third aim.

For aims two and three, survival and treatment efficacy will be assessed by measuring urine levels of IL-2, interferon-gamma (immunostimulatory cytokines) and IL-10 and TGF-beta1 (immunosuppressive cytokines).

In aim four, we will test the best treatments from aims two and three against secondhand smoke exposure by measuring the effects on the immune response.

This project will serve to define the detrimental effect of
cigarette smoke exposure on intravesical treatment for bladder cancer and serve a translational basis for a human clinical trial combining sunitinib malate with IL-2 + B7.1 gene therapy for bladder cancer.

Our lab team includes Warren Heston, PhD, lab director; Amit Patel, MD, and Thomas Powell, PhD. We see this project as a unique opportunity to categorize and identify immune responses in bladder cancer. Our next step will be to develop a human protocol, as early as next year, to follow patients through bladder cancer treatment and quantify the different results achieved by smokers versus nonsmokers. No treatment interventions will occur in this phase.

For references, please email the editor.
Urethral Reconstruction in Older Men Results in High Patient Satisfaction and Excellent Urinary Function

Kenneth W. Angermeier, MD, and Hadley Wood, MD

While urethral strictures can develop secondary to a number of causes, iatrogenic injury is more prominent in older men and may include endoscopic interventions, treatments for prostate cancer, or prolonged catheterization. Owing to its proven long-term durability compared with internal urethrotomy, urethral reconstruction is considered the gold standard for younger men who develop a refractory urethral stricture. However, urethral reconstruction is often considered to be too risky for older patients, and they are therefore more often managed with repeated internal urethrotomy or urethral dilation, perineal urethrostomy, or suprapubic catheter diversion.

In order to better assess the role of definitive surgical treatment of refractory urethral strictures in older men, we identified men 60 years of age and older who had undergone urethral reconstruction at Cleveland Clinic over the last 12 years. Our goal was to assess patient satisfaction, functional outcomes, and morbidity in this cohort of patients. Medical charts were reviewed to document preoperative factors, operative details, and postoperative complications. Patients were then contacted by telephone and asked five questions pertaining to urinary function and quality of life.

Forty-five men with a mean age of 67.7 years (60-79) were identified; however 16 were excluded for a variety of reasons, most commonly inability to be contacted. Among the respondents, the population was obese [mean BMI=29.0 (21.7-37.9)] with significant co-morbidities [mean Charlson index: 4.11 (2-8)]. Etiology of urethral stricture was unknown (33%), trauma (20%), iatrogenic (40%), and hypospadias (2.5%). Eighty-six percent of the patients had undergone multiple prior endoscopic interventions and 3 (10%) had undergone prior urethroplasty. Most strictures were located in the bulbous urethra (14), followed by the bulbomembranous (7) and distal/penile urethra (2). Surgical repairs included excision/primary anastomosis (EPA), dorsal or ventral buccal mucosa grafts (BMG) + excision of stricture and roof-strip anastomosis, or dartos-based genital island flaps (Table 1). Six patients (21%) had multiple, discontinuous strictures, necessitating either extremely long or multiple simultaneous urethral repairs. Average length of BMG was 6.6 cm (3-15 cm). Twenty-six of the patients underwent single-stage urethroplasty, with the remaining 3 patients undergoing staged reconstruction. Post-operative evaluation included a voiding urethrogram 3 weeks after surgery (Figure 1), followed by office cystoscopy in all individuals 6 and 12 months postoperatively and as needed based on symptomatology thereafter.

Figure 1. (a) 77 year-old male – Excision of urethral stricture and associated urethral stent at bulbomembranous junction; (b) Postoperative VCUG demonstrating patent reconstruction and contrast within chronically dilated prostatic ducts.

Key Point:
A recent study completed here shows that urethroplasty in men 60 years of age and older is feasible, safe and results in a high degree of patient satisfaction.
Failure of treatment was strictly defined as any necessary intervention or self-dilation following reconstruction. With a mean duration of follow-up of 52 months (4-142), the success rate was 90%. Three patients (10%) met the criteria for failure and have undergone DVIU. One of these three is self-dilating every 7-10 days. No significant intraoperative or perioperative complications were encountered. Three patients reported minor problems postoperatively. There were no buccal donor site complications.

Patients were recently contacted and asked five questions pertaining to the durability/quality of their urethral reconstruction and their overall satisfaction with the procedure (Table 2). Only two patients had seen another urologist for a urinary problem since their reconstruction; both for relatively minor problems. While the average urinary stream strength rating was 7.59, most patients rated their urinary stream strength between 8 and 10. A few patients (notably the failures) rated their urinary stream strength as low. Most patients either reported 0 or one pad-per-day leakage (average 0.71), again with the notable exception of the three failures. Most telling, however, is that all of the men (including the failures) except for one reported that they would undergo repeat urethroplasty rather than opting for an easier operation (i.e., perineal urethrostomy). Finally, patients overwhelmingly denied that their urinary function had a negative impact on their overall quality of life. On a scale from 1 to 10 with 1 being “complete negative impact” and 10 being “no negative impact whatsoever,” the average score was 8.31.

Our series represents a heterogeneous group of patients with extremely complex urethral stricture disease. A number of these men had previously undergone prostate surgery (radical prostatectomy or TURP) or pelvic radiation, which increases their baseline risk for voiding dysfunction. Moreover, these patients were older with significant co-morbidity profiles, also increasing their risk for open surgery. The repairs were frequently extensive, with an average graft/flap length of nearly 7 cm, and several strictures which were multiple and discontinuous, thereby increasing the technical difficulty. Despite all of these factors, however, we experienced only three (10%) failures, two of whom have been stabilized after DVIU. No intraoperative or perioperative morbidity was encountered in this group of patients. Patients reported high satisfaction with quality of life as it relates to urinary function and minimal incontinence.

<table>
<thead>
<tr>
<th>Table 1. Types of urethral reconstructions</th>
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<tbody>
<tr>
<td>Excision and primary anastomosis</td>
</tr>
<tr>
<td>Dorsal excision and anastomosis with ventral buccal graft onlay</td>
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<tr>
<td>Dorsal buccal graft onlay</td>
</tr>
<tr>
<td>Ventral buccal graft onlay</td>
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<td>Island flap</td>
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<th>Table 2. Results to telephone-administered questionnaire</th>
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<tbody>
<tr>
<td>Question</td>
</tr>
<tr>
<td>Have you seen any other physician for complications related</td>
</tr>
<tr>
<td>to your urinary tract?</td>
</tr>
<tr>
<td>Yes-2 (bladder stone, urge incontinence)</td>
</tr>
<tr>
<td>No-27</td>
</tr>
<tr>
<td>Rate the strength and quality of your urinary stream (1=worst)</td>
</tr>
<tr>
<td>7.59 (3-10)</td>
</tr>
<tr>
<td>Characterize your urinary continence over a 24-hour period:</td>
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<tr>
<td>0, 1, 2, &gt;3 pads/condom cath/diaper</td>
</tr>
<tr>
<td>0.69 (0-3)</td>
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<tr>
<td>Knowing what you know now, if you were given the option of</td>
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<tr>
<td>having had a simpler operation that would result in you</td>
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<tr>
<td>having to sit to void and void through a small hole under</td>
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<tr>
<td>your scrotum, would you select the simpler option or repeat</td>
</tr>
<tr>
<td>the urethral reconstruction?</td>
</tr>
<tr>
<td>Same-28</td>
</tr>
<tr>
<td>Other-1</td>
</tr>
<tr>
<td>Rate how much your urinary function negatively impacts</td>
</tr>
<tr>
<td>on your general wellbeing and quality of life (1=total neg</td>
</tr>
<tr>
<td>impact)-10(no neg impact))</td>
</tr>
<tr>
<td>8.31 (3-10)</td>
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Functional and Quality of Life Outcomes in Patients Undergoing Transperineal Repair with Gracilis Muscle Interposition for Complex Rectourethral Fistula

Kenneth W. Angermeier, MD

Although relatively uncommon, rectourethral fistulas (RUF) remain a challenge for the urological surgeon. While surgical treatment for an uncomplicated RUF is fairly well established, no single procedure has gained widespread acceptance for treatment of complex RUF, such as those occurring after radiotherapy or previous attempts at repair. In these situations, the interposition of vascularized tissue between the closed ends of the fistula appears to be an important component of a successful repair. The gracilis muscle is an excellent choice for a perineal interposition flap because it is readily mobilized, well-vascularized, and obviates the need for intra-abdominal exploration. In order to assess surgical and quality of life outcomes, we reviewed our patients who have undergone repair of complex RUF using a transperineal approach with gracilis muscle interposition (GMI) with the intent of preserving both bowel and bladder function.

We identified 13 consecutive patients with complex RUF who underwent transperineal repair with GMI between 2004 and 2007. Careful preoperative evaluation, including intraoperative cystoscopy and proctoscopy at the time of fecal/urinary diversion, was employed to identify these patients who were all felt to be reasonable candidates for attempted preservation of both bowel and bladder function. Hospital charts were reviewed for preoperative, intraoperative, perioperative and postoperative factors. Patients were all sent an overall health questionnaire as well as validated quality of life instruments (Fecal Incontinence Quality of Life questionnaire and ICS Male Short Form questionnaire). Median age at the time of treatment was 61.8 years (35.9-74.5). Etiology of RUF included: prostate cancer treatment (12) and history of imperforate anus (1). Prior treatment for prostate cancer included radical prostatectomy (RP) (4); brachytherapy (BT) (3); external beam radiation (EBRT) + BT (3); cryoablation (1); and EBRT + cryoablation (1). Five patients underwent unsuccessful RUF repair prior to referral. All patients underwent pre-operative fecal diversion, 10 with a diverting loop ileostomy and three with loop or end colostomy.

No intraoperative or immediate postoperative complications were encountered. Median hospital stay was five days (3-7). A VCUG was obtained after six weeks and in all cases the suprapubic catheter was removed at that time. Median time to reversal of fecal diversion was 17.5 weeks (12-44) after confirmation of rectal integrity with a contrast enema. Median follow-up after stoma closure was 2.5 months (1-39), and there was no recurrence of fistula in 12/13 patients (92%). The patient who failed developed a recurrent RUF after takedown of his fecal diversion, and had previously received combined EBRT + BT. He subsequently was managed with a permanent colostomy and successful urethral reconstruction using buccal mucosa bolstered by the opposite gracilis muscle.

Long-term complications occurred in three patients. One patient developed a bladder neck contracture that was dilated at the time of ileostomy reversal. A second patient, who had been treated with EBRT + salvage cryoablation for prostate cancer, developed urinary incontinence after completion of his repair. An initial artificial urinary sphincter required removal due to infection, and a second was complicated by erosion and infection. He then underwent bladder neck closure and continent bladder augmentation with appendicovesicostomy. He has done well with good fecal and urinary function for three years. The third patient, who had also been treated with EBRT + BT, developed a fistula in ano which was treated with fistulotomy and prolonged fecal diversion of 44 months. He subsequently underwent reversal of his ileostomy and is currently continent of both urine and stool.

Urinary outcomes were measured using the ICS Male Short Form questionnaire. One patient was excluded because he had undergone continent bladder augmentation. “Voiding” domain results were positive overall. Obstructive symptoms were minimal, with diminished strength of stream being the most problematic complaint. Urge and incontinence domains fared poorer than the obstructive domain with 50% of the patients complaining of urgency some or most of the time, urge incontinence some/most of the time in 42%, and stress incontinence some/most/all of the time in 58.4%. Overall, 23% of patients reported that they were completely continent and voiding per urethra, with 15% partially continent relying on pads. Most
patients reported daytime voiding every two or three hours, and nighttime voiding one to three times. Interestingly, a minority of patients (17%) characterized their urinary symptoms as having a lot of impact on their overall quality of life (Figure 2).

Fecal outcomes were measured using the Fecal Incontinence Quality of Life questionnaire. One patient was excluded because he had undergone permanent fecal diversion. Fecal outcomes were generally better than urinary outcomes. “Lifestyle” domains measured patients’ behavioral modification with regard to going out in public, and the “Depression/Self-Perception” domain questioned patients about the impact that fecal function has on the patient’s mental perception of self. In these domains, a majority of patients reported no or little impact. In the “Embarrassment” domain, patients reported minimal or no complaints as well. “Coping” outcomes were measured by asking patients specific behaviors that they have adapted to cope with fecal symptoms. Again, these outcomes were generally positive but suggest that patients may have some fecal urgency, with more patients reporting that “the possibility of an accident is always on my mind.” In terms of “Overall Health” with respect to fecal function, only one patient reported “fair” and none reported “poor” (Figure 3). Fifty-four percent of patients reported complete fecal continence.

We feel that the perineal approach for RUF repair with GMI is particularly applicable to patients with a history of failed previous repair, radiation or co-existing stricture disease because it avoids an intra-abdominal incision and affords excellent visualization of the fistula and surrounding tissues. In addition, this approach provides good access for the repair of an associated membranoprostatic urethral stricture if necessary. Our results demonstrate low morbidity, with most patients discharged to home on the 4th or 5th postoperative day (range 3-7 days), and a low rate of postoperative complications and fistula recurrence. In addition, most patients demonstrated satisfactory preservation of urinary and bowel function, with the notable exception of a few individuals at high risk for external urethral sphincter or bladder dysfunction due to prior prostate surgery or pelvic radiation. Fecal outcome measures demonstrate minimal impact of fecal function on all domains with the exception of some urge-related symptoms. These findings, we believe, are more likely attributable to the prior surgeries and interventions that the patient had endured leading up to development of the fistula.
Peyronie’s Disease: An Update On The Role of Diagnostics

Lawrence S. Hakim, MD, FACS

Peyronie’s disease (PD), often associated with erectile dysfunction (ED), is also an important medical problem occurring in up to 9% of all men. Improved clinical diagnostic techniques – including the diagnostic algorithm – have been developed, allowing for the successful treatment of both ED and PD.

To achieve the restoration of a straight, rigid erection, a number of effective procedures can be used, including intracavernosal injection therapy, surgical plication, or plaque incision and grafting. For patients who have poor erectile function, insertion of a penile implant with subsequent repair of any residual curvature is an excellent treatment option for restoring both normal sexual function and a straight erection.

As in any form of sexual dysfunction, the initial evaluation of the male with PD begins with a sexual, psychosocial and medical history. It is critical to make an accurate diagnosis prior to treatment, and such factors as plaque size and length of time present, stability and location, penile curvature, stretch and baseline erectile function should be determined prior to instituting any form of intervention. The presence of penile injury or trauma, as well as systemic vascular disease, should be assessed. Both patient and partner sexual issues should be addressed.

Once a complete history has been obtained, a thorough physical examination and routine laboratory tests are in order. Assessment of the penile plaque, if present, is of foremost importance. In most cases, a clearly palpable penile plaque will be identified on physical examination, and may be the reason for the patient’s concern (i.e., cancer scare). PD may present with decreased penile stretch or deformity with no specific, palpable plaque. Evaluation of penile length, stretch and sensation are important. In certain cases, neurologic, hormonal and psychologic testing may be useful.

Evaluation of the penile curvature or deformity in the erect state is imperative. This is usually assessed following intracorporeal injection of vaso-active agents, such as prostaglandin, phentolamine, papaverine, or some mixture of these drugs (i.e., Trimix). Addition of high-resolution duplex Doppler ultrasonography is useful in helping to assess penile hemodynamics, anatomy and erectile function with a simple, noninvasive office-based test.

When assessing the plaque in the erect state, factors including the size, degree of penile curvature, direction of curvature (dorsal, ventral, lateral or some combination), and location are critical. Other noninvasive erectile function tests may include penile biothesiometry to evaluate sensation preoperatively. Anatomic changes, such as an “hourglass-deformity,” should be documented in the erect state as well. The severity of the deformity, as well as the associated erectile function and storage ability are critical factors.

Key Points:

A diagnostic algorithm and improved clinical diagnostic techniques can assist in the successful treatment of both erectile dysfunction and Peyronie’s disease.

One mechanism of Peyronie’s disease-associated ED is secondary to hemodynamic changes in the corpora cavernosa. Decreased compliance of the penile fibroelastic frame induced by Peyronie’s plaques may result in an inability to expand the trabeculae against the tunica albuginea and compress the subtunical venules. The clinical consequence of such hemodynamic alterations in the “trapping” mechanism is excessive outflow of lacunar blood through the subtunical venules, leading to decreased penile rigidity and a diminished ability to sustain an erection. Objective evaluation of penile hemodynamics is critical, as any therapeutic intervention for Peyronie’s disease may have some adverse impact upon erectile function. Hence, documentation of the baseline erectile function is imperative, both from a medical and medico-legal perspective.

While the evaluation process should be individualized for each patient, a simple, diagnostic algorithm for the evaluation of all patients with Peyronie’s disease is described in the table.

Peyronie’s Disease: Diagnostic Algorithm

Patient and Partner History:
- Medical, sexual and psychosocial history
- History of penile trauma and pain, ejaculatory or orgasmic dysfunction
- Length of time and stability of plaque/deformity/curvature
- Prior therapies (including herbal/vitamins)
- Endocrinologic and laboratory evaluation

Physical Examination:
- Palpable penile plaque (location, size, severity)
- Penile stretch, length, sensation, pain

Vascular Evaluation in the Erect State:
- Office intracavernosal injection test
- Assess penile curvature (location, plaque size, severity)
- Presence of hourglass deformity or narrowing (location, size, severity)
- Penile duplex Doppler ultrasonography
- Dynamic infusion pharmacocavernosography and cavernosography *

Neurologic Evaluation*:
- Biothesiometry
- Vibration perception sensitivity testing

(* performed in selected patients)
Increasing Penile Length at Time of Penile Prosthesis Implantation

Drogo K. Montague, MD, and Kenneth W. Angermeier, MD

Penile prosthesis implantation is suitable treatment for men with ED when first- and second-line treatment options fail or are otherwise unsatisfactory. Three-piece inflatable penile prostheses, which are widely used in penile prosthesis implantation in the United States, come closest to the ideal of producing normal penile flaccidity and erection. Nevertheless, even in first-time penile prosthesis recipients with normal anatomy, many report that their prosthetic erection is shorter than their former natural erection. Part of this is due to lack of glans tumescence.

Another factor, however, is the absence of length expansion with most inflatable penile prostheses. The tunica albuginea of the corpora cavernosa has both inner circular elastic fibers allowing penile girth expansion with erection and outer longitudinal elastic fibers allowing penile length expansion. The ideal penile prosthesis, like the normal corporal cavernosa, would produce both penile girth and length expansion with the prosthetic erection.

The first prosthesis to do this was the AMS 700 Ultrex Inflatable Penile Prosthesis™ (American Medical Systems, Minnetonka, MN), which was introduced in 1989. Early experience with these girth and length expanding cylinders showed 1 to 5 cm (mean 1.9) of length increase with inflation. This increase in penile length, however, came at the expense of both decreased cylinder survival and S-shaped penile deformities. Later Ultrex cylinder design improvements (1993) resulted in increased Ultrex cylinder survival, making it equivalent to that of other three piece inflatable implants. The S-shaped cylinder deformities, which are caused by placement of oversized cylinders, can be avoided by using a proper cylinder sizing technique.

When the AMS 700 MS Inflatable Penile Prosthesis™ with the new momentary squeeze pump was introduced in 2007, the Ultrex cylinders were renamed LGX. We regularly began using Ultrex cylinders in 1989 and today we continue using girth and length expanding AMS 700 LGX cylinders to provide our penile prosthesis recipients, when appropriate, with the most natural prosthetic erection available.

Key Points:

A diagnostic algorithm and improved clinical diagnostic techniques can assist in the successful treatment of both erectile dysfunction and Peyronie’s disease.

Figure 1. Ultrex recipient with deflated cylinders. Length is 11.5 cm.

Figure 2. The same patient with the cylinders inflated. The length is now 14 cm.
Prediction in Transplantation

David Goldfarb, MD

In an era characterized by a shortage of transplantable organs, living donation has become important. The number of available living donors has increased dramatically in the past 10 years. The number of suitable living donors has expanded with the inclusion of donors who are genetically unrelated to the recipients, as well as through paired living kidney donation. A transplant candidate may now have several potential living donors, and clinicians must identify which donor would yield the most optimal post-transplant graft function and long-term outcome.

We were struck by the lack of tools to assess or predict such outcomes. The quality of the donated organ is a well-established factor that influences graft fate after deceased donor kidney transplantation. The factors contributing to quality include donor age, gender, ethnicity, body mass index (BMI), body surface area (BSA), the presence of donor diseases (e.g., hypertension), cause of brain death, renal function prior to procurement and cold ischemia time. In contrast, the renal allografts for living donor transplantation are derived from healthy donors and are subjected to minimal cold ischemia. Therefore, donor variables that define nephron mass become more important. These include donor age, gender, and measurements of body size such as height, weight, BMI or BSA. In addition, variables that relate to immunological, recipient, and procurement factors such as HLA mismatch, recipient size, cause of renal failure, donor operation, and immunosuppression regimens have been shown to play a part in determining graft function and survival. Following transplantation, the presence of delayed graft function, acute rejection episodes and the level of allograft function at 6 months are the important factors affecting long term graft survival.

We used information from the United Network for Organ Sharing (UNOS) to generate nomograms that would predict transplant renal function at 1-year, and 5-year graft survival. These two tools were based on information known at the time of transplantation. A third nomogram was developed to predict 5-year graft survival based upon additional variables that occurred during the first 6 months after transplantation.

The information from 20,085 donor-recipient pairs operated between 2000-2003 were used. Pre-transplant recipient variables included: age, gender, BMI (kg/m2), race, cause of renal failure, induction therapy, use of mycophenolate mofetil (MMF), sirolimus, and/or calcineurin inhibitors. Pre-transplant donor predictors included: BMI (kg/m2), creatinine (mg/dL), HLA mismatch, age, gender, race, donor/recipient relationship and type of procurement procedure (open versus laparoscopic). For the 6-month post-transplant prediction of 5-year graft survival, all of the pre-transplant donor and recipient predictors were the same as noted above. Additional predictors for this nomogram included delayed graft function, any treated rejection episode in 6 months and the 6-month eGFR (ml/min/1.73 m2).

The nomogram developed to predict 1-year eGFR showed modest correlation by internal validation, and worked best for an eGFR between 50-70 ml/min/1.73m2. The 5-year graft survival nomogram based on pre-transplant variables had a concordance index of 0.71 (see the accompanying figure). This is comparable performance to many tools used for predicting cancer outcomes in urological oncology. The dynamic nomogram, predicting 5-year graft survival with additional measures from the first six months post-transplant, performed even better than the pre-transplant nomogram, with an improved concordance index of 0.78.

Nomograms can reconcile the multitude of donor and recipient parameters that impact on transplant outcome and permit transplant physicians to better counsel their patients. In the context of multiple suitable donors, clinicians can select the donor-recipient pair for transplantation that maximizes expected function and survival of the allograft. In the absence of multiple donors, the availability of objective prognostic information may better guide individualization of post-transplant care. For example, closer follow-up, targeted immunosuppressive tailoring, or more aggressive treatment of modifiable risk factors can be implemented for patients at greater risk based on nomogram calculations.
Instructions: The first row (Points) is the point assignment for each variable. Rows 2 to 19 represent variables included in the model. For each donor-recipient pair, each variable is assigned a point value (uppermost scale; Points). A vertical line is made between the appropriate variable value and the Points line. The assigned points for all the variables are summed, and the total is found in row 20 (Total Points). Once the total is located, a vertical line is made between Total Points and the final row 21 (5-Year Graft Survival Probability).


Diagonal line represents performance of ideal nomogram in which predicted outcome corresponds perfectly with actual ones. Line with vertical boxes represents performance of constructed nomogram. Vertical boxes indicate 95% confidence intervals based on bootstrapping analysis. Concordance Index of this nomogram was 0.71.
Kidney Function in Living Kidney Donors

Emilio Poggio, MD

Kidney transplantation is the best available treatment for patients who suffer end-stage renal disease (ESRD). However, the main limitation to universal access to transplantation is organ shortage. There are approximately 85,000 patients with ESRD awaiting kidney transplantation in the United States, but only about 13,000 patients were transplanted in 2008 (UNOS.org). Therefore, the current demand for kidney transplants is about 6 times higher than what it is offered, with the average patient waiting for 4 to 5 years before receiving a deceased donor organ. While 55% of the organs came from deceased donors in 2008, the remaining kidneys were donated by living donors. In fact, more than 90,000 living donors have donated a kidney since 1998, according to the United Network for Organ Sharing. Living donation not only offers better long-term outcomes, but also allows for timed donation, avoiding long waiting times that are detrimental to patients.

A common concern of the healthcare practitioner as well as the prospective donors and recipients relates to the long-term safety of organ donation. Fortunately, when a proper evaluation is undertaken to rule out medical and renal abnormalities, the long-term outcomes of former kidney donors suggest that these subjects enjoy better quality of life and live as long as the general population. The rates of renal disease are also the same as or lower than those observed in the general population. Nevertheless, a careful pre-donation evaluation with a special emphasis on kidney function and a post-donation follow-up are needed to continue to protect this altruistic population.

At the same time, the classification of kidney disease as defined by the National Kidney Foundation (NKF) is strongly based on the level of kidney function. Moreover, the current classification states that when the glomerular filtration rate (GFR) of a subject is below 60 ml/min/1.73m², that subject has kidney disease, irrespective of cause. This classification does not take into consideration the physiological age and gender-related decline in kidney function. Living kidney donors are usually considered candidates to donate a kidney as long as their GFR is greater than 80 ml/min/1.73m², generally irrespective of gender and age. That is, a GFR of 85 ml/min/1.73 m² would allow donation in a 25-year-old male or a 60-year-old female indistinctively.

While controversial, the application of the NKF guidelines to define kidney disease in former kidney donors would suggest that a former kidney donor, by virtue of having donated 50% of the kidney mass, would qualify as having this disease assuming that their post-donation estimated GFR falls below that threshold. There is about 20 to 30% regain of kidney function as part of the compensation achieved by the remaining kidney following donation. Because of the importance of understanding the normal range of GFR based on age and gender and its implication to kidney donation and kidney disease, we recently reported on the Cleveland Clinic experience of kidney function measurements obtained as part of the pre-donation evaluation from 1972 to 2005. We reported the normal reference values of GFR derived from more than 1,000 former kidney donors evaluated at our institution using a “gold standard” method to assess kidney function. We clearly showed that normal values of GFR decline as we aged and, therefore, may pose a risk when used as classification for kidney disease.

Key Point:

It is critical to continue to place very careful attention on kidney function in living donors when deciding on candidacy for donation. Normal values of GFR decline as we age and, therefore, may pose a risk when used as classification for kidney disease.
Lifestyle Modification Program Shows Promise for Prostate Cancer Patients

Elizabeth Ricanati, MD, and J. Stephen Jones, MD, FACS

This spring, Cleveland Clinic expanded the disease states targeted in its Lifestyle 180SM program to include prostate cancer under active surveillance. Lifestyle 180 addresses chronic disease in an attainable, practical and engaging way through a structured systematic approach to nutrition, physical activity and stress management.

The Preventive Medicine Research Institute has recently demonstrated that men with prostate cancer in active surveillance who adopted lifestyle modification were able to delay conventional treatment and possibly lower rising PSA levels. We expect our Lifestyle 180 program to afford at least similar results.

The program has an immersion phase and an after-care phase. Initially, participants attend two sessions a week for six weeks. Each four-hour session includes one of the following: an exercise class; a nutrition class taught by a chef and dietician; and a stress management class taught by a yoga instructor and a behavioral health specialist. The sessions are conducted in small groups, averaging 10 to 16 participants. The after-care phase includes four components: on-site classes five times during the year (at one, three, six, nine and 12 months), drop-in additional weekly classes, a weekly email newsletter and a “buddy system,” which allows participants to reach out to someone in the group, or be available for another person.

The prostate cancer program is a new offering. Thus far all groups have been targeted for individuals with risk factors for heart disease (e.g., hypertension, hyperlipidemia, obesity and diabetes). Preliminary data from the program has demonstrated reductions in biometric data, laboratory data and improvement in quality of life. Participants have had reductions in weight, waist circumference and blood pressure; their LDL cholesterol, C-reactive protein and fasting glucose measures have improved. Participants report improved sleep, decreased pain and overall increased satisfaction. Finally, up to one third of participants so far have been able to either avoid starting a prescription medication, reduce the dose of a prescription medication or discontinue taking a prescription medication. As the program continues, we expect even more improvement.

The Novick Center for Clinical and Translational Research Manages High Volume of Research within the Institute

The newly established Novick Center for Clinical and Translational Research was created based on an idea by the late former Institute Chairman Andrew Novick, MD. The center’s role within the Glickman Urological & Kidney Institute is to facilitate interaction between researchers and clinicians across the departments of nephrology and urology. It also seeks to promote clinical and translational research and help assure compliance with all federal and institutional regulations.

Center Director Daniel Shoskes, MD, a urologist, says that because the institute is so large, the center allows for the necessary and efficient pooling of resources. The institute currently has $25 million in research funding.

Nephrologist Emilio Poggio, MD, serves as Associate Director. He and Dr. Shoskes have organized a staff that includes coordinators and database managers, statisticians, grant writers, and two managers. Staff members work closely with the Lerner Research Institute to be sure regulations and mandates are followed and to review every existing and future clinical study for soundness, budget and resources required.

Dr. Shoskes says fundraising also will be a focus for the center, as there is more work that can be done than present resources will allow.
The Department of Urology has applied for and received permission to expand the Residency Program from four residents per year to five—an exciting development that will allow for further improvement of the residents’ educational experiences. Recruitment this past year was highly successful with the Residency matching 5 outstanding candidates who will begin training in July of 2009. All 5 were ranked in the top tier and are highly qualified for this challenging field. The applicant pool for urology remains very deep with outstanding candidates as urology continues to be one of the most desirable surgical subspecialties in the field of medicine in 2009. Recent innovations have reenergized the field and many medical students are attracted to the unique combination of endoscopic, minimally invasive, and traditional open surgical interventions that urology offers, as well as the challenges of caring for an older patient population. The paradigm of long-term care and strong patient-physician relationships that is ingrained in this field also remains a drawing point.

Expansion of the residency program will take four to five years to roll out, and it will offer a number of distinct educational advantages. It will provide an opportunity to develop new resident experiences including plans for a rotation focused on prostate cancer and robotic surgery headed by Eric Klein, MD, Chair of the Glickman Urological & Kidney Institute, another focused on other minimally invasive surgical interventions led by the head of the section of MIS, Jihad Kaouk, MD, and an outpatient rotation, which will be centered at one of our regional hospitals and outpatient facilities with an upper level and a younger resident integrally involved in these community based practices. All of these new rotations will allow for more intensive resident participation in learning areas that are vitally important in 2009. Expansion also will facilitate ongoing efforts to maintain balance in surgical training, between OR and clinic experiences, and efforts to develop a strong knowledge base and research/academic pursuits.

Supply and demand in the field of urology has become unbalanced, and with an aging population there will be a great need for more urologists for the future. As there has been only one new urology training program startup in the past two decades, expansion of resident complement by the more well-established programs is needed to address this deficiency. The Department of Urology is particularly well-suited for this given its steady growth during the past several years, the great wealth and diversity of surgical cases and challenging patient consults that are seen on a daily basis. Efforts to manage growth of the department here and its impact on the residency program in as positive of a manner as possible are ongoing, with a strong emphasis on maintaining a healthy education/service balance.
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Urology & Kidney Disease News is a publication of the Cleveland Clinic Glickman Urological & Kidney Institute.

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The Glickman Urological & Kidney Institute is one of 26 institutes at Cleveland Clinic that group multiple specialties together to provide collaborative, patient-centered care. The institute is a world leader in treating complex urologic and kidney conditions in adults and children. Our physicians have pioneered medical advances including partial nephrectomy, laparoscopic and robotic urologic surgery, and the biartificial kidney, while serving tens of thousands of patients annually. Cleveland Clinic is a nonprofit, multispecialty academic medical center. Founded in 1921, it is dedicated to providing quality specialized care and includes an outpatient clinic, a hospital with more than 1,000 staffed beds, an education institute and a research institute.

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