Urology & Kidney Disease News

Glickman Urological & Kidney Institute
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On the Cover
A single multichannel port inserted into the umbilicus allows for the deployment of specially designed curved laparoscopic instruments. To date, surgeons in the Glickman Urological & Kidney Institute have performed 90 such single-port surgeries, now known as Laparo-Endoscopic Single-Site (LESS) Surgery. (See articles, pages 23-25.)

A thin flat-sheet membrane with highly uniform slit-shaped pores, (close-up below) is used in the development of an implantable bioartificial kidney currently being evaluated for feasibility through a $3.2 million NIH grant. The implantable kidney could replace maintenance dialysis. (See article, page 33.)

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Institute Chairman’s Report

Andrew C. Novick, MD  
Chairman, Cleveland Clinic  
Glickman Urological & Kidney Institute

The Glickman Urological & Kidney Institute recently completed its first full year of operation. At Cleveland Clinic, we are moving toward a new paradigm in which clinical areas are organized around organ and disease systems, rather than individual specialties, with the aim of enhancing both patient care and academic collaboration. The Glickman Urological & Kidney Institute was the second institute to be created around this new model and represents a coalescence of urologists, kidney and pancreas transplant surgeons, nephrologists, hypertension specialists, dialysis physicians and scientists working in these areas. This consolidation of disciplines allows us to better serve patients in the prevention, diagnosis and treatment of kidney disease while continuing to provide high-quality care and develop innovative approaches in all aspects of urology. This model is unique in United States medicine and, in our view, represents the future of healthcare in this country.

Our institute soon will be relocated to the Glickman Tower, a new 12-story facility being constructed on the main Cleveland Clinic campus, which will comprise more than 200,000 square feet of space for clinical and academic activities. Construction of the tower is nearing completion and it is scheduled to open in October 2008. The Glickman Tower has been carefully designed to provide patients with state-of-the-art care in urologic and kidney disease, 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.

The Glickman Urological & Kidney Institute and the Glickman Tower are named after Carl and Babs Glickman. Mr. Glickman is a Cleveland-based businessman who developed end-stage kidney failure several years ago. In 2002, at the age of 75, he underwent a successful kidney transplant within our program. The Glickmans elected to express their appreciation through philanthropic support for the urology program at Cleveland Clinic. This led to the Urological Institute being named in their honor and, ultimately, a new facility to house the institute, termed the Glickman Tower. Mr. Glickman serves as chairman of the Glickman Urological & Kidney Institute National Leadership Board, which comprises 54 prominent individuals from across the United States.

The Glickman Urological & Kidney Institute presently houses four clinical departments and two multidisciplinary core centers. In Cleveland, two urology departments have been established: a Department of Urology, chaired by Inderbir Gill, MD, comprising main campus faculty; and a Department of Regional Urology, chaired by J. Stephen Jones, MD, comprising faculty who are predominantly based in outreach locations. The institute also houses the Department of Nephrology and Hypertension, chaired by Martin Schreiber, MD, and the Department of Urology at the Cleveland Clinic in Florida.

We have established a new Center for Quality Patient Care to promote excellence in healthcare quality, outcomes quality and outcomes measurement. This is a multidisciplinary group led by Chris Hebert, MD, who serves as Center Director. The immediate goal is to make optimal use of currently available data for outcomes measurement and to ensure compliance with patient safety and regulatory requirements. An intermediate-term goal is to create innovative and effective methods of capturing new patient data as well as managing, analyzing, and publishing information on health outcomes. Integral to this goal will be realization of the full potential of our electronic medical record in creating a robust clinical data warehouse.

We also have established a new Center for Research and Innovation to support translational and funded clinical research within the institute. This is a multidisciplinary group comprising basic scientists and clinician-investigators from all departments, and a search process is under way for the Center Director position. The specific goals of the center are to foster new research initiatives in the form of individual projects, program projects or center grants; to assist in securing funding for such initiatives through peer-reviewed agencies and/or industry; and to develop educational programs within the center. These educational initiatives will include administration of the NIH-funded T32 urology basic training program, courses on research methodology, monthly scientific seminars, and visiting scientists programs.

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 2007, we performed 21,347 urological operations. Our departments of Urology and Regional Urology recorded a total of 88,732 outpatient visits, while our Department of Nephrology and Hypertension recorded 21,635 outpatient visits.
Our urology and nephrology faculty members share a passion for discovery and a deep commitment to providing the best possible clinical and investigative training for our residents and postgraduate fellows. During 2007, our faculty edited three major textbooks and authored 274 scientific publications in peer-reviewed medical journals. The institute currently houses 13 scientist staff members who are conducting translational laboratory research studies in kidney cancer, prostate cancer, kidney transplant biology, male infertility, female pelvic floor disorders, extracorporeal renal therapy, and minimally invasive surgical therapy. These activities are presently supported by $29.9 million of extramural peer-reviewed research funding.

Our urology and nephrology programs continue to achieve a high level of national recognition for their aggregate activities. This year, our urology program was ranked again among the top 2 programs in the United States in the annual survey conducted by U.S. News & World Report. This is the 9th consecutive year that our program has been ranked among the top 2 in the country. Also this year, the kidney disease program was ranked among the top 4 programs in the United States in the U.S. News & World Report survey.

This is indeed an exciting time for our urology and nephrology faculty and trainees within the Glickman Urological & Kidney Institute. We are proud of our past accomplishments, energized by our ongoing activities and passionate about our future. Going forward, our paramount objectives remain to provide the highest quality of care for patients with routine or complex nephro-urological disorders, to nurture the future leaders of our specialties, and to continue to define the state of the art in urological and kidney disease through credible clinical scientific and translational research contributions. We are pleased to share current activities with our colleagues and friends in this inaugural issue of Urology & Kidney Disease News.

Andrew C. Novick, MD
Department Chairmen’s Reports

Inderbir S. Gill, MD, MCh
Chairman, Department of Urology

Building on our institute’s foundation of excellence in patient care and innovation, Department of Urology staff continuously strive to provide leading edge, innovative clinical care across all urologic sub-specialties.

The Department comprises 32 clinical and research faculty, and over 40 residents and post-graduate fellows. With a focus on distinct sub-specialties in a milieu of rigorous scientific investigation, our staff authored more than 200 scientific publications in 2007. Significant advancements were made in a variety of research initiatives, including identifying the role of the XMRV virus in prostate cancer, expanding the use of laparoscopic partial nephrectomy for complex tumors while decreasing ischemia time, developing single-port laparoscopy, and flexible robotic ureteroscopy. Ongoing and future areas of interest include focal, targeted ablation of select organ-confined prostate and kidney cancers, use of stem cells in female incontinence, and augmented reality, to name just a few.

Going forward, our entire urology program is reorganizing into additional centers, which are each focused on subspecialty areas with clearly-defined programs of excellence. We believe such interdisciplinary synergy will expedite new discoveries.

These exciting initiatives take on fresh momentum with the expanded facilities provided by the newly constructed Glickman Tower. This 12-story state-of-the-art building on Cleveland Clinic’s main campus will double our capacity and consolidate all urological and nephrological services in one location, thus delivering the most high-tech urologic care, all centered on a “patients-first” approach.

The Department of Urology, supported by our institute’s solid history of leading-edge research, innovation and patient care, enthusiastically embarks upon a new era in healthcare at Cleveland Clinic – an era of new physical surroundings, a sophisticated patient-centered structure, and a vigorous drive for cutting-edge advancements in urologic care. It is a true privilege to be a vibrant part of such a futuristic environment.

J. Stephen Jones, MD, FACS
Chairman, Department of Regional Urology

The success of our inaugural year underscores the vision expressed in establishing the Department of Regional Urology as a distinct clinical and academic department. Based on the fact that most Cleveland Clinic urologists perform at least part of their patient care outside the main campus, this department was created to focus on and support these clinical and academic activities. Our 20 regional locations, encompassing 11 hospital practices, cover a three-state area across parts of Ohio (including Cleveland), West Virginia and Indiana. The majority of clinical volume for a number of programs, including brachytherapy, cryotherapy, male infertility, non-muscle-invasive bladder cancer, urolithiasis, BPH, and female incontinence, occurs in these locations, assuring that patients benefit from Cleveland Clinic care in the optimal setting.

When I received the distinct privilege of the chairmanship of the Department of Regional Urology in 2007, it was clear that this was a special—unprecedented—opportunity. The department began with 26 urologists, most of whom are fellowship-trained, and all of whom base their career focus on achieving and maintaining the highest levels of excellence. Upon that firmly established clinical foundation we continue to build a novel academic enterprise offering care in every urological subspecialty. Partnering with colleagues in the Department of Urology allows our physicians to lead the field in innovative care delivery and discovery in both translational and clinical outcomes research. The academic productivity of the Department of Regional Urology is among the highest in the country regarding the number of peer-reviewed publications, book chapters, and major presentations at major urologic meetings in the United States and internationally.

Exciting challenges lie ahead as we begin our second year. We are expanding our tertiary care services in the region that already serve as active access points to the Glickman Urological & Kidney Institute for patients from Ohio, Indiana, Michigan, Pennsylvania, New York, Kentucky and West Virginia. Expanding the residency program within the department is a major part of this initiative. Finally, plans are in place for two new urological oncologists to join our ranks by the end of 2008.

All these changes are occurring in order to offer innovative ambulatory and hospital-based urological care within accessible locations to patients throughout the region and beyond. We are confident these developments are only the early stages of an exciting future.
In 2007 and 2008, the Department of Nephrology and Hypertension has focused on delivering superior outcomes for our patients, and on leading research projects critical to our understanding of renal disease and hypertension. The department faculty firmly believes nothing is unimaginable and anything is likely provided that we combine the very best talent, carry out impactful scientific projects and achieve the very best outcomes for our patients.

Research activities in the department are focused on developing the bioartificial kidney, investigating novel immune monitoring techniques or biomarkers for predicting long term allograft survival in transplantation, characterizing endothelial dysfunction and hyperlipidemia in transplantation, understanding risk factors and early predictors for acute kidney injury, utilizing a chronic kidney disease animal model to study hepcidin and the EPO receptor, and unraveling the genetic controls of nocturnal and resistant hypertension.

The GFR laboratory has been redesigned as a Center for Innovations in Assessing Renal Function and the site for the departmental gene biobank. The department remains active in the NIH studies: CRIC, HALT-ADPKD, and CTOT. William Fissell, MD, Director of the Center for Extracorporeal Therapy, was a co-investigator with Shuvo Roy, PhD, on the $3.4 million NIH Quantum project grant award, dedicated to the design and implementation of the next generation renal therapy to replace dialysis. Qing Yu Wu, MD, PhD, recently was awarded an RO1 NIH grant to examine the role of corin in pre-eclampsia.

Our department has published 45 articles, 18 book chapters and submitted 20 abstracts in the past year. We continue to link innovative research with high-quality clinical outcomes. In our quest to lead in nephrology and hypertension, the department continuously tracks quality and outcomes measurements and publishes our results for outpatient hemodialysis, ICU nephrology, chronic kidney disease, anemia management, hypertension, polycystic kidney disease, and transplantation. We are excited about the new faculty joining the department in 2008 and the clinical practice and research opportunities during the coming year.
Andrew C. Novick, MD, Receives AUA’s Highest Honor

Andrew C. Novick, MD, Chairman of the Glickman Urological & Kidney Institute, received the Ramon Guiteras Award, the American Urological Association’s highest honor, in May.

Dr. Novick was presented with the award for his outstanding contributions to the art and science of urology during the AUA’s 2008 annual meeting in Orlando, Fla.

Receipt of the Ramon Guiteras Award, combined with the many other career-achievement awards he’s received to date, makes Dr. Novick the most honored practicing urologist today.

“I am truly honored to receive this prestigious award,” Dr. Novick said. “The opportunity to contribute to the advancement of knowledge within urology has been deeply satisfying for me, and it is humbling to be recognized in this way by my peers.”

Inderbir S. Gill, MD, MCh,
Awarded St. Paul’s Medal

Inderbir S. Gill, MD, MCh, Chairman of the Department of Urology, was awarded the St. Paul’s Medal for his outstanding contributions to the field of urology by the British Association of Urological Surgeons (BAUS) at their 61st annual meeting in Manchester, England. Dr. Gill was the unanimous choice for the medal, which is the highest award presented by the BAUS. Dr. Gill is the second Cleveland Clinic urologist to receive this honor. Andrew C. Novick, MD, received this award in 2004.

Eric A. Klein, MD, Begins Work as Editor-in-Chief of UROLOGY®

Eric A. Klein, MD, head of urologic oncology, assumed responsibilities as Editor-in-Chief of UROLOGY® in January. He says that 15 years ago he discovered a strong sense of purpose in his professional life when he fully understood the impact one published paper could have on other physicians. This, in turn, could provide major benefits to patients.

“I now find myself in a position to magnify the effect of observations that others have made by dint of editorship of the Gold Journal,” Dr. Klein says.

Beginning with his first issue, some of the design and organization of the publication have been updated, and new sections emphasizing Ambulatory and Office Urology, Laparoscopy and Robotics, and Technology and Engineering have been added. Plans for expanding the journal’s Web presence are in the works as well, according to Dr. Klein.
Staff Awards and Appointments

Charles S. Modlin, Jr., MD, director of the Minority Men’s Health Center, has been appointed to the Ohio Commission on Minority Health by Gov. Ted Strickland. This is the first state commission on minority health and seeks to eliminate health disparities in minority populations.

Kenneth W. Angermeier, MD, has been named president-elect of the Society of Genitourinary Reconstructive Surgeons.

Inderbir S. Gill, MD, MCh, is president of the Urologic Society for Transplantation and Renal Surgery for 2008-2009.

William E. Braun, MD, was named the Kidney Foundation of Ohio’s Man of the Year in February.

Stuart M. Flechner, MD, FACS, has joined the editorial board of Clinical Transplantation.

Operative Urology at the Cleveland Clinic, a comprehensive urologic surgery atlas published in 2006, was named an essential purchase by Doody’s Review Service. Andrew C. Novick, MD, served as senior editor of the publication, with J. Stephen Jones, MD, FACS, as associate editor. Inderbir S. Gill, MD, MCh, Eric Klein, MD, Raymond Rackley, MD, and Jonathan Ross, MD, were assistant editors.

The book was the only Humana Press title to receive this prestigious designation, and also won the Illustrated Medical Book Award from the Association of Medical Illustrators. Medical Illustrators from Cleveland Clinic’s Center for Medical Art and Photography provided more than 700 illustrations for the book.

Resident and Fellow Awards

Robert Abouassaly, MD, was named UCSF CapSURE™ scholar for 2007-2008.

Robert Abouassaly, MD, received the George and Grace Crile Traveling Fellowship Award in May.

John Kefer, MD, received the 2008 SLS Outstanding Laparoendoscopic Resident Surgeon award.

John Kefer, MD, won first prize for resident competition at the annual Ohio Urological Society meeting in April.

Brian Lane, MD, received the Traveling Fellowship Award, North Central Section of the AUA, October 2007.

Brian Lane, MD, was named 2008 AUA Foundation Research Scholars Program recipient for post-graduate training in urologic oncology.

Una Lee, MD, received the travel award from the Society of Urodynamics and Female Urology in February.

Ping Liew, MD, won a best abstract award for her abstract entitled “Achievement of Recommended Blood Pressure Goals in Chronic Kidney Disease Improves Arterial Stiffness” at the European Renal Association/European Dialysis and Transplant Association Meeting in Stockholm, Sweden, in May.

Matthew Simmons, MD, received the 2007 SLS Outstanding Laparoendoscopic Resident Surgeon award.

Lynn Woo, MD, received the Silbar Award, North Central Section of the American Urologic Association, October 2007.

Hadley Wood, MD, received the Bruce Hubbard Stewart Award for Humanistic Medicine in May.
New Staff The Glickman Urological & Kidney Institute welcomes the following new staff members:

Urology

**Monish Aron, MD**, a laparoscopic and robotic surgeon, received his medical degree from Sarojini Najdu Medical College, Agra University, in Agra, India. He went through residency training at S.N. Medical College, in Agra, India, and the All India Institute of Medical Sciences, in New Delhi. Dr. Aron has fellowship training from Royal Melbourne Hospital, in Melbourne, Australia, and Cleveland Clinic.

**Alvin C. Wee, MD**, received his medical degree from the University of Santo Tomas College of Medicine and Surgery, in Manila, Philippines. He completed his internship at Santo Tomas University Hospital in Manila, and his residency at University of the Philippines-Philippine General Hospital, Manila, and St. Vincent Charity Hospital in Cleveland. He recently completed a fellowship in renal/pancreas transplant at Cleveland Clinic.

Cleveland Clinic Excels in Latest *U.S. News* Rankings

Urology ranked No. 2 in the nation; Kidney disease ranked No. 4

The Cleveland Clinic Glickman Urological & Kidney Institute’s urology program was ranked among the top 2 programs in the United States for the 9th consecutive year by *U.S. News & World Report*. The institute’s kidney disease program ranked 4th in the nation.

The 2008 “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 all 16 specialties surveyed by the magazine. Ten of its specialties were listed among the top 10 in the United States and all of the Clinic’s specialties placed in the nation’s top 25. For details, visit clevelandclinic.org.
Nephrology

Saud Butt, MD, received his medical degree from the Medical College of Ohio in Toledo. He completed postgraduate training at MetroHealth Medical Center/Case Western Reserve University in Cleveland, and recently completed a fellowship at Cleveland Clinic.

Surafel Gebreselassie, MD, earned his medical degree at Jimma University in Jimma, Ethiopia. He completed all of his postgraduate training at Wayne State University/Detroit Medical Center.

Sorana Hila, MD, earned her medical degree at the University of Medicine & Pharmacy in Tirgu Mures, Romania. She completed her postgraduate training, including a research fellowship, at Cleveland Clinic.

Titte Srinivas, MD, earned his medical degree from Jawaharial Institute of Post Graduate Medical Education and Research in Pondicherry, India. He completed an internship and residency in internal medicine at Montefiore Medical Center in Bronx, NY, as well as a nephrology fellowship at Saint Luke’s Roosevelt Hospital Center in New York.

Online Access to Your Patient’s Treatment Progress: DrConnect

DrConnect is a complimentary service for referring physicians that allows them to follow their patient’s treatment progress while at Cleveland Clinic. By providing physicians with real-time information about their patient’s treatment progress, DrConnect is propelling physicians into the future of healthcare, a world in which their patients’ detailed medical information is always just a click away.

clevelandclinic.org/drconnect

Outcomes Data Available

The latest edition of outcomes data from the Cleveland Clinic Glickman Urological & Kidney Institute is available. Our outcomes booklet also offers summary reviews of medical and surgical trends and approaches. Charts, graphs and data illustrate the scope and volume of procedures performed each year.

To view outcomes booklets for the Glickman Urological & Kidney Institute as well as many other Cleveland Clinic medical and surgical disciplines, visit clevelandclinic.org/quality.
Upcoming Preceptorships

October 2008

4th Annual National Urology Resident Preceptorship in Adult and Pediatric Reconstructive Urologic Surgery

One of a series of invitation-only preceptorships presented by the Cleveland Clinic Glickman Urological and Kidney Institute. Designed exclusively for residents nominated by the respective program directors of accredited urology residency programs. Consists of didactic lectures and discussed video sessions.

May 2009

8th Annual National Urology Resident Preceptorship Program in Female Pelvic and Reconstructive Surgery

One of a series of invitation-only preceptorships presented by the Cleveland Clinic Glickman Urological and Kidney Institute. Designed exclusively for (3rd year of 5-year program or 4th year of 6-year program) residents nominated by the respective program directors of accredited urology residency programs. Consists of didactic lectures and discussed video sessions.

Researchers Share Innovations at Uremia Therapy Workshop

Twenty-five researchers came together at an invitation-only workshop at Cleveland Clinic in May to showcase and discuss advances in artificial kidney research. Engineers, biologists, clinicians and opinion leaders in the dialysis industry shared insights on the growing problem of end-stage renal disease and expensive dialysis treatment. The three-day workshop featured sessions on clinical data, the biology of uremia, engineering components of uremia therapy, and integrating new technology into therapy.

William H. Fissell, MD, was part of the workshop steering committee for a research team working with a NIH grant to design a next-generation renal therapy to replace dialysis (see article, page 33).

Please check our websites for more details on these programs as they become available: clevelandclinic.org/urology clevelandclinic.org/nephrology
Upcoming Conferences

September 5-6, 2008
International Reproductive Medicine Symposium
*Directors: Edmund S. Sabanegh Jr., MD, and Ashok Agarwal, PhD, HCLD*
Cleveland Clinic Lerner Research Institute
This course will provide an update on the most current, state-of-the-art diagnostic and treatment options for the management of infertility. The lectures will focus on a multidisciplinary approach to both the male and female factor management. Another International Reproductive Medicine Symposium will be held in September 2009.

September 12-14, 2008
1st International Pediatric Urology Preceptorship
*Director: Jeffrey S. Palmer, MD, FAAP, FACS*
InterContinental Hotel and Bank of America Conference Center
This program is designed for general urologists, pediatric urologists, urologists-in-training and allied healthcare professionals who are involved with the care of children with urologic conditions. The 2nd International Pediatric Urology Preceptorship will be held in September 2009.

October 4-7, 2008
Nephrology Update 2008
*Directors: Brian Stephany, MD, and Robert Heyka, MD*
Ritz Carlton, Cleveland, Ohio
This course will provide an intensive update on the latest developments and controversial issues in the pathogenesis and treatment of kidney diseases, hypertension, end-stage renal failure, critical care nephrology and other related conditions. It will feature lectures, in-depth problem-solving sessions and interactive forums.

November 13, 2008
8th Annual Multidisciplinary Genitourinary Oncology Course
*Directors: Robert Dreicer, MD, and Eric A. Klein, MD*
InterContinental Hotel and Bank of America Conference Center
This course is designed to provide a topical, clinically-based overview of many of the current therapy dilemmas faced by clinicians managing GU neoplasms, with an emphasis on the opportunities for multidisciplinary management.

March 5-7, 2009
4th Annual Ambulatory Urology Symposium
*Director: J. Stephen Jones, MD, FACS*
This course is intended to update urologists on ambulatory urology from both a practical and medical standpoint. The focus will be to target the two-track system that urology continues to develop and focus on. This year’s symposium will focus on socioeconomic issues facing the field today.

Cleveland Clinic
Celebrating 75 Years of Excellence in
CONTINUING MEDICAL EDUCATION

The Cleveland Clinic Center for Continuing Education is one of the nation’s largest academic accredited institutions and is proud to celebrate 75 years in continuing medical education. Please visit clevelandclinicmeded.com for a listing of live meetings, web casts and enduring material.
Focal Ablation World Summit: Prostate and Kidney Cancer

April 2-4, 2009

Outpatient focal tumor ablation has enormous potential. Join Cleveland Clinic's Glickman Urological & Kidney Institute in a forum for in-depth discussion and idea exchange regarding the emerging field of focal therapy for genitourinary cancer. The Focal Ablation World Summit will be held at the InterContinental Hotel & Bank of America Conference Center in Cleveland, April 2-4, 2009.

Events include live surgery demonstrations, hands-on workshops, panel discussions and moderated free papers.

Key topics for the summit:

Pathologic basis for focal therapy

Imaging basis for focal therapy

Technical advances and clinical implications for cryotherapy, radiofrequency ablation, phototherapy, high-intensity focused ultrasound, nanotechnology, brachytherapy, radiosurgery/stereotactic therapy, robotics and image-guided surgery.

For more information on the Focal Ablation World Summit, visit cfcme.org/ablation09.

Clinical and research abstracts for original work will be accepted until Feb. 1, 2009.

Summit Director:
Inderbir S. Gill, MD, MCh

Summit Co-Director:
J. Stephen Jones, MD, FACS

Keynote Speakers:
Andrew C. Novick, MD
Peter Scardino, MD

Cleveland Clinic Faculty:
Monish Aron, MD
Mihir M. Desai, MD
Robert Dreicer, MD
Georges-Pascal Haber, MD
Jihad Kaouk, MD
Eric A. Klein, MD
Vinod Labhasetwar, PhD
Erick Remer, MD
Brian Rini, MD
Andrew J. Stephenson, MD

Invited Guest Faculty:
Jelle Barentsz, MD
John Baust, PhD
Arie Beldegrun, MD
David Bostwick, MD, MBA
Jeffrey Cadeddu, MD
Christian Chaussy, MD
Jeffrey Cohen, MD
David Crawford, MD
Jean de la Rosette, MD
Franz Debruyne, MD
James Eastham, MD
Dave Ellis, MD
Mark Emberton, MD
John Fitzpatrick, MD
Masoom Haider, MD
Aaron Katz, MD
Lou Kavoussi, MD
Pilar Laguna, MD
Jamie Landman, MD
Mark Litwin, MD
Michael Marberger, MD
Francesco Montorsi, MD
Gary Onik, MD
David Penson, MD
Louis Pisters, MD
Thomas Polascik, MD
Philippe Puech, MD
Daniel Rukstalis, MD
Katsuto Shinohara, MD
Daniel Stiavano, MD
Osamu Ukimura, MD
Arnauld Villers, MD
Thomas Wheeler, MD
Minimally Invasive Urologic Technology the Focus of 6th Annual Cleveland Clinic Innovation Summit

Cleveland Clinic will host its 6th annual Medical Innovation Summit this year, highlighting minimally invasive urologic and gynecologic technology. The summit, November 10 to 12, is an international gathering of healthcare, business and media leaders for the purpose of examining trends in medical innovation. Previous summits have focused on cardiovascular and neurological technology.

The 2008 Medical Innovation Summit will feature live broadcasts of laparoscopic partial nephrectomies, performed by Inderbir Gill, MD, Chairman of the Department of Urology, and Mihir Desai, MD, and a single-port operation, performed by Jihad Kaouk, MD. Andrew Novick, MD, Chairman of the Glickman Urological & Kidney Institute, will moderate the surgeries. Sandip Vasavada, MD, and Matthew Barber, MD, both of the Center for Female Pelvic Medicine and Reconstructive Surgery, will perform live operations as well.

Dr. Novick, along with Bruce Lytle, MD, Chairman of Cleveland Clinic’s Heart & Vascular Institute, will join a panel of industry leaders to discuss extending clinical excellence.

J. Stephen Jones, MD, FACS, Chairman of the Department of Regional Urology, will lead a discussion on focal and image-guided therapy for localized prostate cancer. Other topics for panel discussions and presentations include natural orifice translumenal endoscopic surgery (NOTES), advances in laparoscopic and robotic surgery, IT and digitization in healthcare, emerging markets and reproductive health.

Cleveland Clinic clinicians and researchers will announce and discuss their third annual selection of the “Top 10” medical innovations they expect to have a significant impact in 2009.

To register or find out more about the Medical Innovation Summit, including the agenda and list of speakers and panelists, please visit clevelandclinic.org/innovations/summit.
Based on the multifocal nature of prostate cancer and an inability to limit the treatment effect to a portion of the gland, the traditional approach has been to target the entire gland.

We have offered focal cryotherapy on a very limited basis since 2005 for men with low-risk disease who understand the implications of all options.

Reluctance is largely based on the fact that most index prostate tumors are accompanied by smaller “satellite” lesions, and approximately 80% of men with prostate cancer have bilateral disease.

However, Villers showed that 80% of secondary tumors are less than 0.5cc, the lower threshold for detection using current MRI technology, which is a common criterion for depiction of clinical insignificance. Most cancers now are detected earlier and are, therefore, markedly smaller and earlier in their course. Even in the setting of multifocal disease, Hall found that the index tumor accurately predicted clinical behavior in more than 90% of patients, so small synchronous tumors may truly be “clinically insignificant,” and limiting treatment to the area of tumors large enough to identify using MRI and emerging technologies becomes appealing.

There is no consensus on what “focal” means. Some advocates attempt to treat only areas of known cancer. Others administer hemispheric treatment of the involved side, while some centers treat the entire gland with the exception of the area of the contralateral neurovascular bundle. The most common approach at Cleveland Clinic is the latter, which we have found preserves potency in most men and is associated with low risk of side effects compared to whole-gland therapy using cryotherapy or radiation therapy options.

Patients undergoing focal therapy at Cleveland Clinic compose a very highly selected group of men with small, unilateral primary tumors. All men undergo a repeat 20 core saturation biopsy in the office under periprostatic block to confirm that they truly have limited disease, and those found to have contralateral atypia or prostatic intrapathelial neoplasia are excluded.

All men are informed of all other management options. We have found that most men who choose focal therapy are those who would be excellent candidates for active surveillance with delayed curative intent, who are hesitant to leave their cancers untreated. This offers them an acceptable intervention with limited morbidity even if potency is not a priority. The other group that finds focal therapy appealing is comprised of men who prioritize potency above cure. All patients are informed that the gold standard for treatment is whole-gland therapy and that normal preoperative potency is maintained in approximately 80% of men. We recommend a saturation biopsy be performed several months after focal therapy to assess for complete response. Persistence of significant disease is typically retreated with focal or whole-gland cryotherapy, radiation therapy, or radical prostatectomy if identified on subsequent biopsy.

Long-term data are limited for focal cryotherapy, but an abstract presented at the 2008 American Urological Association annual meeting reported outcomes in 341 men treated with focal therapy whose data are recorded and tracked in the industry-sponsored COLD Registry. Biochemical disease-free survival, according to the ASTRO criteria, was 83% at 18 months, and 74% of men were potent 36 months after treatment.

Focal cryotherapy is in its early stages. We continue to pursue refinements in diagnostic techniques for identifying men who will benefit with limited risk of disease persistence. We seek improvements in technique to minimize risks of side effects while ablating all identifiable malignancy.

For references, please email the editor.
Prostate Mono Brachytherapy (I-125) is an Effective Treatment Option for Low Intermediate Risk Gleason 7 (3+4) Prostate Cancer

Craig D. Zippe, MD, J. Stephen Jones, MD, FACS, Geetu Pahlajani, MD, Arul Mahadevan, MD, and Jay Ciezki, MD

Prostate mono brachytherapy (PMB) is an accepted treatment option for Gleason 6 cancer. Its popularity has increased as more 10-year data are being reported regarding its efficacy in Gleason 6 cancers. Short- and long-term data demonstrate biochemical progression-free survival rate ranging from 81-98%; results that compare favorably to radical surgery.

While excellent results are reported with Gleason 6 cancers, controversy exists regarding the management of Gleason 7 tumors because of its heterogeneous nature. The American Brachytherapy Society (ABS) recommends Gleason 7 cancer as a cut point for the addition of external beam radiation when using permanent prostate brachytherapy. However, Potters, et al, in 2003 were the first to report that PMB can be an acceptable treatment for patients with Gleason pattern 3+4. We have observed that younger patients with Gleason 7 tumors with concerns of erectile dysfunction often elect to undergo PMB. In exploring the efficacy of this treatment option, we did a retrospective analysis of our database. Our hypothesis was that PMB was an accepted treatment option for selected low intermediate risk Gleason 7 cancers.

We identified 61 patients from our database (1997-2003), who had a minimum follow-up of 4 years and who underwent PMB for a Gleason 7 cancer. We compared them to 56 patients with Gleason 6 cancer from the author’s personal series in the same time period. We subdivided the Gleason 7 cancers into Gleason 7 (3+4) and Gleason 7 (4+3). In our Gleason 7 group, we found 48 patients had Gleason 3+4 cancer and 13 had Gleason 4+3 cancer. The mean age of the patients with Gleason 6 cancer was 65 years; with Gleason 7 (3+4) - 68.2 years; with Gleason 7 (4+3) - 71 years. The mean baseline PSAs were comparable; Gleason 6 - 6.67; Gleason 7 (3+4) - 6.78; Gleason 7 (4+3) - 6.4. In the Gleason 6 group, the mean PSA at 4 years was 0.18±0.20 with a 3.5% biochemical failure rate (ASTRO). In the Gleason 7 (3+4) group, the mean PSA at 4 years was 0.16±0.17 (p=0.56 vs GS 6) with a 6.2% biochemical failure rate. In the Gleason 7 (4+3) group, the mean PSA at 4 years was 0.70±0.74 (p=0.07 vs GS 6) with a 23% biochemical failure rate (see Table). Overall, the 4-year nadir PSA value for the Gleason 7 cancers (0.30) was not different from the nadir PSA value of the Gleason 6 cancers (0.18) (p=0.78). There were 3 failures in the Gleason 7 (3+4) group, 3 failures in Gleason 7 (4+3) group and 2 failures in Gleason 6 - all 8 failures occurring between 2 and 3 years. The small number of biochemical failures prevented statistical analysis.

Our intermediate data indicate that prostate mono brachytherapy is an acceptable treatment option for low intermediate risk Gleason 7 cancers. At 4 years, our biochemical cure rate for Gleason 7 (3+4) cancer (94%) was comparable to our cure rate for Gleason 6 (3+3) cancer (97%). Preliminary data would suggest that patients with Gleason (4+3) have a worse biochemical failure rate than those with Gleason 6 (3+3) and Gleason 7 (3+4). This data should impact positively on our selection criteria for prostate mono brachytherapy, such that low intermediate risk Gleason 7 (3+4) cancers can be routinely recommended.

For references, please email the editor.

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<th>GS 6 (n=56)</th>
<th>GS 7 (3+4)(n=48)</th>
<th>GS 7 (4+3)(n=13)</th>
<th>GS 7 TOTAL (n=61)</th>
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<td>4 YR MEAN PSA</td>
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<td>0.70±0.74</td>
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<td>BIOCHEMICAL FAILURE (%)</td>
<td>3.5%</td>
<td>6.3%</td>
<td>23%</td>
<td>9.8%</td>
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*p=0.56 (NS) for GS 7(3+4) vs GS 6; †p=0.076 for GS 7(4+3) vs GS 6; ‡p=0.78 for Total GS 7 vs GS 6
Update on Drug Therapy for Benign Prostatic Enlargement

Gaurang Shah, MD, and Khaled Fareed, MD

There has recently been renewed interest in studying the relationship between men with lower urinary tract symptoms (LUTS), bladder outlet obstruction (BOO) and benign prostatic enlargement (BPE). BPE is the most common cause of LUTS in the aging male. LUTS can be either storage, voiding or post void symptoms. Storage symptoms are typically more bothersome and could be attributed to overactive bladder (OAB); while voiding symptoms are more prevalent in men with BOO. OAB could be caused by BPE or bladder aging, among other causes.

Prior to 1990, watchful waiting and surgery, were the available treatment options for BPE. In the 1990s, Alpha Blockers (ABs) and 5-Alpha Reductase Inhibitors (5-ARIs) were introduced. ABs address the dynamic component of BOO, and therefore, afford rapid symptom relief. 5-ARIs have been shown to decrease disease progression and decrease prostatic growth by altering testosterone-dependent growth factors. The growing recognition of OAB symptoms in men has led to use of antimuscarinics (anti-Ms) along with ABs. In a small subgroup of men with LUTS and sexual dysfunction, the phase II trials have shown beneficial effects of PDE-5 inhibitors and ABs. Cleveland Clinic investigators are currently evaluating approaches to medical management of LUTS in order to determine the correct agent or combination in specific clinical scenarios.

Drug therapy could be classified into:

1. ABs
2. 5-ARIs
3. Combination therapy
   - ABs and 5-ARIs
   - ABs and anti-Ms
   - ABs and PDEIs

ABs

The Alpha-1A receptor is most dominant in prostate and bladder neck. Alpha-1B receptor is present in the blood vessels. ABs act on the Alpha-1A receptor causing relaxation of bladder neck area and prostate.

Currently, doxazosin, terazosin, tamsulosin and alfuzosin are in use in the United States. Of these, Doxazosin and terazosin require dose-titration to minimize the side effects of the dizziness and postural hypotension. Efficacy of alpha blockers is comparable. Their main difference is in the treatment-related adverse events (TEAE), and discontinuation rates. Doxazosin and terazosin are less selective and therefore are more prone to cause cardiovascular events. Tamsulosin may cause anejaculation or retrograde ejaculation.

Data from the MTOPS and ALTESS studies showed that symptomatic relief observed in the short and intermediate terms was maintained long term.

5-ARIs

There are two types of 5 alpha reductase isozymes. Finasteride inhibits only type 2 isozyme. Dutasteride is a dual inhibitor. Both decrease intraprostatic dihydrotestosterone (DHT) by 80 to 90%, leading to reduction in the size of the prostate by 15-25%. 5-ARIs improve BPE related symptoms slowly compared to ABs. They reduce the risk of acute urinary retention and/or risk of BPH-related surgery by 50%.

Combination Therapy

ABs and 5-ARIs:

The recognition that ABs provide early symptomatic relief and 5-ARIs reduce the risk of disease progression led to the idea of combination therapy.

In 2003, the results from the MTOPS trial showed benefit of combination therapy (doxazosin and finasteride) compared to both single therapies. The treatment provided improvements of 4.9, 5.6, 6.6 and 7.4 points in the placebo, finasteride, doxazosin and combination group respectively. Urine flow rate improvements were 2.8, 3.2, 4.0 and 5.1 ml/sec. for the four treatment groups respectively. Intuitively, side effects were greater in the combination arm; therefore, it is reserved for patients with the highest risk for progression as indicated by baseline parameters (e.g., prostate size larger than 40 g, PSA > 1.5 ng/mL).
Prostate Cancer Specific Mortality in the PSA Era

Andrew J. Stephenson, MD

Relative to other solid tumors, localized prostate cancer is characterized by an exceptionally protracted natural history. In population-based cohorts of patients treated without curative intent and before the introduction of opportunistic screening for prostate-specific antigen (PSA), the 10-year prostate cancer specific mortality (PCSM) ranged from 15-25%. After radical prostatectomy, the 10-year PCSM was 15% in a recent randomized trial comparing radical prostatectomy and watchful waiting in an unscreened cohort of men. The natural history of prostate cancer in screened populations is poorly defined, but may be substantially more favorable given that the diagnostic lead time associated with PSA screening is estimated to be 11 years.

Given this natural history, PSA-defined prostate cancer recurrence is widely used as an endpoint to assess treatment success. Models that predict PSA recurrence are the primary tools for counseling patients, making clinical decisions, and stratifying patients in clinical trials. A prostate cancer nomogram is currently the most widely used, disease-specific prediction tool in oncology. However, PSA recurrence is not a surrogate for PCSM. Within 15 years of PSA recurrence, men are as likely to die from competing causes as they are from prostate cancer.

Treatment decision-making for localized prostate cancer and the powering of clinical trials for clinically significant endpoints require accurate estimations of PCSM that account for the stage migration induced by PSA screening. To this end, investigators from Cleveland Clinic pooled data

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<th>% Patients with AE</th>
<th>% Patients discontinued due to AE</th>
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<tr>
<td></td>
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<tr>
<td>Terazosin (N=2084)</td>
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<tr>
<td>Doxazosin (N=156)</td>
<td>35</td>
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<td>Tamsulosin (N=295)</td>
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ABs and anti-M Agents

Storage symptoms associated with OAB are often more bothersome to the patient than are voiding symptoms. Recent reports show the safety and efficacy of toltolodine and oxybutynin to an existing regimen with ABs in men with symptoms of OAB. A recent study showed significant benefit from combination therapy of ABs and anti-M agents. Despite traditional teaching, the incidence of urinary retention appears to be low in this group, and there has been little if any evidence that anti-M agents create risk of urinary retention in men with or without BPO.

ABs and PDE-5 inhibitors

Kaplan reported improvement in IPSS, flow rate and erectile function after combination of ABs (alfuzosin 10 mg) and PDEI (sildenafil 25 mg) compared to either drug alone. McVary and Roehrborn demonstrated that LUTS secondary to BPH significantly improved in men using tadalafil.

Limitation of Drug Therapy

Medical therapy of BPE may be reaching a glass ceiling. Typically there is a 3- to 7-point improvement in IPSS on a single or combination therapy. Patients who are dissatisfied with efficacy and/or side effects can opt for minimally invasive surgical treatment or conventional surgical treatment. As a result, ongoing studies at Cleveland Clinic and elsewhere seek to improve upon current standard regimens. ■

For references, please email the editor.
Prostate Cancer Specific Mortality in the PSA Era continued from page 19

A nomogram to predict the 15-year risk of PCSM based on PSA, biopsy Gleason grade, clinical stage and adjusted for year of surgery had an accuracy of 82% and the nomogram predictions closely approximated the observed outcome. Considering all 11,649 patients in both cohorts with complete data, only 1,980 (17%) had a predicted 15-year PCSM greater than 5% and 467 (4%) had a probability greater than 30%. Considering the 7,403 patients treated since 1998, 296 (4%) had a probability of PCSM greater than 5%, and only 37 (0.5%) had a predicted risk greater than 30%. The addition of preoperative PSA velocity and body mass index did little to enhance the predictive accuracy of the nomogram.

This favorable prognosis of contemporary patients with localized prostate cancer treated by radical prostatectomy may be related to the effectiveness of radical prostatectomy or the low lethality of screen-detected cancers within 15 years of treatment. The study provides useful information to patients and physicians to guide treatment decision-making for localized prostate cancer and will help to guide the use of neoadjuvant or adjuvant treatments.

The notable finding of this study was a relatively low risk of PCSM within 15 years of radical prostatectomy, even among patients with adverse clinical features. For example, the risk of death from prostate cancer overall within 10 years of radical prostatectomy was 4%, which is substantially lower than that reported in unscreened populations. For patients classified as low- (PSA < 10 ng/mL, Gleason 2-6, clinical stage T1c-T2a), intermediate- (PSA 10-20 ng/mL, Gleason 7, clinical stage T2b), and high-risk (PSA > 20 ng/mL, Gleason 8-10, clinical stage T2c-T3), the 15-year PCSM was 2%, 10%, and 19%, respectively. In all subsets of patients, the risk of death from prostate cancer was substantially less than the risk of death from competing causes.
Fifty Percent of Patients with Biopsy Gleason Score 6 Prostate Cancer in Contemporary Practice are Upgraded At Radical Prostatectomy: Clinical Implications

Fei Dong, MD, J. Stephen Jones, MD, FACS, Andrew J. Stephenson, MD, Cristina Magi-Galluzzi, MD, PhD, Alwyn M. Reuther, MPH, and Eric A. Klein, MD

In patients with prostate cancer, Gleason score (GS) is an important predictor of outcome that is used in conjunction with clinical stage and serum PSA to guide clinical decision making. In particular, patients with high-grade disease (GS > 7) are at higher risk for extraprostatic extension, nodal metastases and biochemical recurrence and may, therefore, be poor candidates for active surveillance or omission of pelvic lymphadenectomy at the time of radical prostatectomy (RP). However, the GS assigned at diagnostic biopsy correlates poorly with the GS assigned following RP with concordance in only 28% to 68% of patients. The discrepancy is particularly important in patients with low-grade disease at biopsy (GS < 6 or less) who are at risk for postoperative upgrading. We recently investigated clinical and biopsy predictors of clinically significant upgrading in a contemporary population of patients with GS 6 on biopsy.

A total of 268 patients who underwent biopsy and radical prostatectomy between October 1999 and January 2007 were included in the study. Pretreatment characteristics were used to identify predictors of pathological upgrading. Upgrading significance was established by comparing radical prostatectomy pathology between cases that were and were not upgraded. A total of 134 patients (50%) were upgraded postoperatively to GS > 7. Preoperative prostate specific antigen > 5.0 ng/ml (p = 0.036), prostate weight < 60 gm or less (p = 0.004) and more cancer volume at biopsy, defined by cancer involving > 5% of the biopsy tissue (p = 0.002), > 1 biopsy core (p = 0.001) or > 10% of any core (p = 0.014), were associated with pathological upgrading. The number of cores taken at biopsy did not predict for tumor upgrading. Upgraded patients were more likely to have adverse pathological features (extraprostatic extension [EPE] or positive margins, p = 0.001 and 0.001, respectively), and more likely to suffer PSA recurrence (Figure).

These findings have important clinical implications. The higher likelihood of EPE suggests that men with high-volume Gleason 6 tumors should be considered to have intermediate rather than low-risk disease with appropriate modifications in therapeutic approach, including performing pelvic lymphadenectomy and avoidance of intrafascial dissection at RP, planning a larger target volume for brachytherapy that includes a wider margin than usual, and the avoidance of focal therapies that are not designed to treat EPE. The data also suggest that tumor volume should be added to preoperative predictive nomograms as an important variable that impacts the likelihood of cure.

This study was published in the Journal of Urology 179:896-900, 2008.

Key Points:
A recent study of 268 men who underwent biopsy and radical prostatectomy indicates that men with high-volume Gleason 6 tumors are likely to have upgrading on final prostatectomy pathology, and should be considered to have intermediate rather than low-risk disease. Appropriate modifications should be made in therapeutic approach.

Tumor volume should be added to preoperative predictive nomograms as an important variable that impacts the likelihood of cure.
Proteolytic enzymes, also called proteases, function to split other proteins in order to activate them, as in blood clotting, or to degrade them, as in food digestion. Most proteases are secreted soluble proteins. Recently, a new class of trypsin-like proteases has been identified that is anchored on the cell surface through an integral transmembrane domain. These membrane proteases participate in a variety of biological processes. We study two such proteases that are involved in hypertension and prostate cancer.

Hepsin is a cell surface protease that shares a similar topological structure with corin. (See page 39.) The hepsin gene was first identified in the liver. Recent studies have shown that hepsin plays an important role in prostate cancer. In microarray analyses, hepsin is one of the most consistently up-regulated genes in human prostate cancer. We found that hepsin protein expression was highly elevated in advanced prostate cancers and bone metastasis. In transgenic mouse models, high levels of hepsin expression promoted prostate cancer progression. Conversely, we showed that anti-hepsin antibodies inhibited prostate cancer cell invasion in culture. Elevated levels of hepsin also are found in advanced renal, ovarian and breast cancers. These data indicate that hepsin may contribute to cancer invasion and progression. Currently, we are investigating if hepsin can be used as a biomarker and therapeutic target for the diagnosis and treatment of prostate cancer.
A multidisciplinary consortium of 28 surgeons from the United States and internationally convened for a one-day closed-door brainstorming meeting at Cleveland Clinic July 7. The consortium’s goal was to establish an approach to responsibly advance the rapidly growing field of single-portal laparoscopic surgery.

The group of surgeons – from the fields of urology, obstetrics and gynecology, and bariatric, general, and colorectal surgery – focused on charting a course forward regarding innovations in surgical techniques, instrumentation, technology, collection of data and collaboration with other societies.

The following decisions emerged from the meeting:

**Terminology**

There exists understandable confusion regarding terminology in this emerging field. Given its potential for rapid growth, consensus on terminology is of immediate importance. In order to select the most appropriate name/designation for this field, the consortium felt that the selected name should indicate and encompass the following broad criteria: (a) single entry portal, (b) location: abdomen, pelvis, thorax, (c) laparoscopic, endoscopic or robotic surgery, (d) umbilical or extra-umbilical, (e) extraluminal or transluminal (percutaneous single-portal access) surgery, and (f) have a broad reach so as to be inclusive, not exclusive.

The consortium concluded that the term Laparo-Endoscopic Single-Site Surgery (LESS) most accurately conveys the broad philosophical and practical aspects of the field. Also, the Laparo-Endoscopic Single-Site Surgery Consortium for Assessment and Research (LESSCAR) was created. This group is created similarly to Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR), which seeks to further the field of NOTES surgery.

**Web-Based Secure Database Registry**

All clinical LESS cases would be prospectively entered into an international database open to all LESSCAR members and associated organizations. This IRB-approved database will incorporate necessary checks and balances to ensure data accuracy, which will form the basis for future clinical research studies.

**Liaison with Other Surgical Societies**

LESSCAR will seek to collaborate with various established professional surgical societies with a view to advancing the field. An effort will be made to coordinate research and increase awareness of developments in LESS procedures with other established major leadership surgical societies. As the clinical applications of LESS expand, LESSCAR will facilitate introduction of various specialties to the new techniques and technology.

**Annual Meetings**

LESSCAR will schedule meetings in conjunction with other professional organizations who may benefit from an exchange of knowledge on the subject.

**White Paper**

Details of the inaugural meeting of LESSCAR are in the process of being published in a comprehensive white paper. A semi-annual LESS newsletter is also planned.

**Training Courses**

“Hands-on” LESS training dry lab and live animal courses, specific to each specialty, are being planned.
Single-Port Laparoscopic and Robotic Surgery: A Scarless Approach

Jihad Kaouk, MD, Mihir M. Desai, MD, Robert Stein, MD, Raymond R. Rackley, MD, Courtenay K. Moore, MD, Jeffrey Palmer, MD, and Inderbir S. Gill, MD, MCh

Laparoscopic surgery substantially reduces abdominal wall trauma compared to open surgery. This translates into less postoperative pain, faster recovery, fewer wound complications and improved cosmetic outcomes. Current laparoscopic techniques call for 3 to 6 small skin incisions, depending on the complexity of the procedure.

A single-port device with multichannel access has been developed recently. This new FDA-registered device has a unique multichannel port through which specially designed curved laparoscopic instruments are deployed. This approach may allow many common laparoscopic procedures to be performed entirely through the patient’s umbilicus and enable essentially scarless abdominal surgery with further reduced wound morbidity. Importantly, this method allows a surgeon to “convert” the one-port trans-umbilical procedure to a conventional laparoscopic procedure at any point during the operation, if necessary, by adding one or more conventional laparoscopic port(s), thus preserving existing standards of care.

The multichannel port is inserted through a 1.5 cm semicircular incision at the inner edge of the umbilicus for transperitoneal surgery. We also performed retroperitoneal single-port kidney procedures (n=6). During the retroperitoneal approach, the multichannel port is inserted at the tip of the 12th rib.

To date, we have performed 90 single-port laparoscopic procedures for various indications. In some cases, through the pre-existing Veress needle access, 2-mm needlescopic instruments were used selectively. Data were collected prospectively into an IRB-approved database.

Results: Upper tract procedures (n=68): renal biopsy, cyst decortication (n=4), cryotherapy (n=11), pyeloplasty (n=14); including B/L single-session (n=4), ileal ureter (n=2), psoas hitch uretero-neocystostomy (n=3), nephrectomy (n=23); simple, n=8; radical, n=6; donor, n=9) and partial nephrectomy (n=11).

Key Point:

The recently developed single-port with multichannel access approach to urologic surgery may allow many common laparoscopic and robotic procedures to be performed entirely through the patient’s umbilicus and enable essentially scarless abdominal surgery. To date, we have performed 90 single-port laparoscopic procedures for various indications.

Umbilical incision 3 weeks after single-port nephrectomy.

Pelvic procedures (n=22): varicocelectomy (n=3), sacrocolpopexy (n=11), radical prostatectomy (n=5) and radical cystectomy, extended lymphadenectomy (n=3).

Data (range): OR time (120-360 minutes), EBL (20-550ml), and hospital stay (0-22 days). Nephron-sparing procedures: tumor size (1-6cm), ischemia time (0-29min). Donor nephrectomy: median warm ischemia time = 4.7min. Complications (n=4): corneal abrasion (n=1), retained J-stent fragment (n=1), bleed requiring angio-infarction (n=1) and rectourethral fistula (1). Conversion to standard laparoscopy for failure to progress (n=5): prostatectomy (2), adrenalectomy (1), pyeloplasty (1) and partial nephrectomy (1).

This initial experience with urologic single-port laparoscopy is encouraging. Complex procedures were successfully performed. The umbilicus presents a versatile access platform to various abdominal and pelvic surgical quadrants.
Robotic application is likely to further facilitate single-port laparoscopy. Our initial experience with a single-port robotic transumbilical surgery using the da Vinci® robot provided better ergonomics and precision during radical prostatectomy, partial nephrectomy, ureteral reimplanta
tion, radical nephrectomy and pyeloplasty without complications.

Robotic Surgery Through Natural Body Orifices: Initial Laboratory Experience

Jihad Kaouk, MD

Minimally invasive surgery has gained wide acceptance in urology because it is performed through small incisions that afford less pain, rapid recovery and improved cosme-
sis. To further minimize minimally invasive surgery, single-port laparoscopy has been introduced recently, using a multi-channel laparoscopic port that allow simultaneous introduction of a laparoscope and instruments through the same port. In addition, natural orifice transluminal endo-
scopic surgery (NOTES) using vaginal or gastric access has been investigated in the laboratory with no urologic clinical applications to date.

Surgical robots currently assist during intracorporeal sutur-
ing and knot tying because of their articulated instruments with wrist motion. We used the da Vinci® (Intuitive

Illustration of a single-port partial nephrectomy. Although all instruments are inserted in parallel through the umbilical port, flexible instruments allow adequate range of motion.

Illustration of a urethral vesical anastamosis during a single-port radical prostatectomy.

For references, please email the editor or Dr. Kaouk at kaoukj@ccf.org.

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Key Point:

We used a robotic application to perform natural orifice translumenal endoscopic surgery (NOTES) by combining both the transvaginal and transumbilical approaches simultaneously to provide a virtually scarless surgery. All 30 robotic NOTES procedures were performed successfully with no intraoperative complications.

Surgical) robot system to perform NOTES surgery by combi-
ing both the transvaginal and transumbilical approaches simultaneously to provide a virtually scarless surgery.

The study protocol was approved by our Institutional Animal Care and Use Committee. In 10 female pigs, we performed 10 pyeloplasties, 10 partial nephrectomies and

continued on next page
Robotic Surgery Through Natural Body Orifices continued from page 25

10 radical nephrectomies. A single port with 3-cannula was inserted into a 2.5 cm umbilical skin incision. Subsequently, a vaginal port was placed through the vagina under laparoscopic monitoring. The robot telescope and the first robotic arm were placed through the umbilical single port, and the second robotic arm was placed through the vagina.

For dismembered pyeloplasty, the ureteropelvic junction was transected and the ureter was spatulated. Using robotic needle drivers, the anastomosis was performed with two 5-0 running sutures. Radical nephrectomy was performed after completing the pyeloplasty on the same kidney then extracted transvaginally.

The animal was flipped to the opposite lateral flank position for partial nephrectomy. Renal hilum was controlled with bulldog clamps and partial nephrectomy was performed using cold scissors. Renorrhaphy was performed using robotic needle drivers with sutures cinched over a surgical bolster.

All 30 robotic NOTES procedures were performed successfully. Mean operative time was 154 minutes and mean estimated total blood loss was 72 cc. Mean warm ischemia time in the partial nephrectomy group was 25.4 min. There were no intraoperative complications. There were no robotic system failures during the entire experiment.

In our study, we inserted a robotic arm through a vaginal port. Vaginal access allowed a full range of motion for the robotic arm. It minimized clashing between robotic instruments and made it possible for a surgeon to manipulate an instrument going through the vagina and another instrument through the umbilicus at the same time in a manner impossible to do with conventional laparoscopic approach.

Although the NOTES approach has the potential for a less morbid and scarless surgery, incorporating robotics into NOTES will enhance intracorporeal suturing especially through the challenging transluminal natural orifice approach. Further development of robots specific to NOTES would enhance efforts toward clinical applications of natural orifice surgery.

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### Surgical Outcomes

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
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<tr>
<td>Number of porcine/Total number of procedures</td>
<td>10/30</td>
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<tr>
<td>Mean size of umbilical incision cm (range)</td>
<td>2.55 (2.4 – 2.9)</td>
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<tr>
<td>Mean operative time min (range)</td>
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<tr>
<td>Preparation (n = 10)</td>
<td>20.4 (16 – 30)</td>
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<tr>
<td>Pyeloplasty (n = 10)</td>
<td>41.7 (37 – 50)</td>
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<tr>
<td>Suturing time</td>
<td>24.3 (19 – 28)</td>
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<td>Partial nephrectomy (n = 10)</td>
<td>59.5 (52 – 70)</td>
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<tr>
<td>Warm ischemia time</td>
<td>25.4 (22 – 30)</td>
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<tr>
<td>Radical nephrectomy (n = 10)</td>
<td>32.1 (27 – 45)</td>
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<tr>
<td>Total surgery time per animal</td>
<td>153.7 (136 – 285)</td>
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<tr>
<td>Mean estimated blood loss cc (range)</td>
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<tr>
<td>Pyeloplasty (n = 10)</td>
<td>19.5 (10 – 35)</td>
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<tr>
<td>Partial nephrectomy (n = 10)</td>
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<td>Radical nephrectomy (n = 10)</td>
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<td>Total surgery</td>
<td>72.3 (55 – 95)</td>
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<td>Complications</td>
<td>None</td>
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Single-Port Transvesical Enucleation of the Prostate (STEP): A Novel Method for Treating Large Volume Prostate Enlargement

Mihir M. Desai, MD, Monish Aron, MD, David Canes, MD, Khaled Fareed, MD, Daniel Shoskes, MD, James Ulchaker, MD, and Inderbir S. Gill, MD, MCh

Laparoscopic and robotic simple prostatectomy have been reported with encouraging results as an alternative to open simple prostatectomy in select patients with lower urinary tract symptoms (LUTS) due to large volume prostatomegaly. More recently, the introduction of novel single-port devices has enabled performance of many laparoscopic ablative and reconstructive procedures in a virtually scarless fashion through a solitary intracorporeal incision. We recently reported our initial experience with single-port transvesical enucleation of the prostate (STEP) performed through a solitary suprapubic incision via a single-access port inserted directly into the bladder in 3 patients with symptomatic BPH. Our novel technique may provide an efficient and safe method of removing the entire prostate adenoma in patients with large volume BPH where transurethral procedures may be less effective and more time consuming. Additionally, we feel that our novel approach is likely to have less blood loss and quicker recovery compared to open simple prostatectomy.

STEP was performed in 3 patients with large volume (187 grams, 93 grams, 92 grams) BPH. A novel single-port device (r-Port®, Advanced Surgical Concepts) was introduced percutaneously into the bladder through a 2.5 cm skin, fascial and bladder incision under cystoscopic guidance. After establishing pneumo-vesicum, the adenoma was enucleated in its entirety transvesically under laparoscopic visualization using standard and articulating laparoscopic instrumentation. The adenoma was extracted through the solitary skin and bladder incision after bivalving the prostate lobes within the bladder.

Our novel technique was technically feasible in all 3 cases. Operative time was 6 hours, 1.5 hours, and 2.5 hours and blood loss was 900 cc, 250 cc, and 350 cc, respectively. In case No. 1, a patient who had previously undergone open suprapubic surgery, a bowel injury occurred at the time of r-Port® insertion; the injury was recognized and repaired intraoperatively without sequelae. Urethral Foley catheter was removed on day 4 and all patients were voiding spontaneously with minimal post-void residual with full continence.

Key Point:
We recently reported our initial experience with single-port transvesical enucleation of the prostate (STEP) performed through a solitary suprapubic incision via a single-access port inserted directly into the bladder in 3 patients with symptomatic BPH. Our novel technique may provide an efficient and safe method of removing the entire prostate adenoma in patients with large volume BPH where transurethral procedures may be less effective and more time consuming.

We believe that our novel transvesical technique of simple prostatectomy using a single-port device may have a role in the surgical treatment of moderate to large size BPH. Further refinement in technique and instrumentation is ongoing at our institution.

More recently, we have developed the technique of transvesical radical prostatectomy and are carefully exploring its application in carefully selected patients with prostate cancer.

For references, please email the editor.

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Retrograde uretero-renoscopy is routinely used for a variety of diagnostic and therapeutic applications involving the upper urinary tract. The increasing use of flexible uretero-renoscopy for retrograde intra-renal surgery is the result of advancements in flexible ureteroscope technology, Holmium-YAG laser lithotripsy, and ureteroscope accessories such as wires, baskets, and access sheaths. Significant technologic developments with flexible ureteroscopy include better deflection, improved optics, increased durability, and miniaturization. Recently, a novel robotic catheter system (Sensei™, Hansen Medical) has been developed for intra-cardiac electrophysiologic applications. This robotic catheter system may enhance the capabilities of conventional flexible uretero-renoscopy by providing a stable, easily maneuverable, and ergonomically superior platform. We modified software and catheter-guide configurations from the original system designed for cardiac applications and initially assessed the technical feasibility of performing retrograde uretero-renoscopy in the acute swine model.

Subsequent to our animal study, we performed the initial clinical trial using the flexible robotic system in 18 select patients with renal calculi. The study was performed in collaboration with the Muljibhai Patel Urological Hospital in India after obtaining IRB approval from both institutions and informed consent. Inclusion criteria included renal calculi 5-15 mm in size. All procedures were unilateral and patients with co-existing ureteral calculi or obstruction, uncontrolled infection, renal insufficiency, or solitary kidney status were excluded from the study. Mean stone size was 11.9 mm. All patients were pre-stented for approximately 2 weeks. The robotic catheter system was introduced into the renal collecting system manually under fluoroscopic control over a guidewire. All intra-renal maneuvers including stone relocation and fragmentation into 1-2 mm particles were performed exclusively using remote robotic control by the surgeon sitting at the console.

All procedures were technically successful without need for conversion to manual ureteroscopy. Mean operative time was 91 minutes, robot docking time was 7 minutes, and stone localization time was 9 minutes. Mean visual analog scale rating (1 worst, 10 best) of ease of stone localization was 8.3, ease of maneuvering was 8.5, and ease of fragmentation was 9.2. Complete stone clearance was achieved in 56% of patients at 2 months based on CT scan, and 89% at 3 months based in IVU. One patient required secondary ureteroscopy for residual stone. Complications included pyelonephritis (2), pyrexia (1), and temporary limb paresis (1). There was negligible fluid absorption based on calculation of inflow and egress and ethanol fluid absorption.

For references, please email the editor.

Key Point:
The novel flexible robotic platform can be used safely and effectively for retrograde intra-renal treatment of renal calculi in select cases. Ongoing technical refinements are likely to increase the incorporation of robotic technology in diagnostic and therapeutic flexible endoscopy.
Innovational Combination of 3-D Imaging, Articulating Laparoscopic Instruments and Novel Robotic Scope Holder: A New Concept of Laparoscopic Surgery

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

Surgical robots provide several advantages compared to the standard laparoscopic approach, such as 3-D vision that provides a sense of depth during surgery and articulating instruments that optimize surgical angles. Surgical robots, however, are expensive and require specific operating room space and a dedicated surgical team. We recently presented a combination of a new robotic endoscope holder, 3-D vision and articulated instruments to perform laparoscopic reconstructive urological surgery. This study received the best paper award during the Engineering in Urology Society 2008 meeting in Orlando, and the best movie award during the AUA 2008.

Ten dismembered pyeloplasties (LPP), 10 urethro-vesical anastomoses (UVA) and 10 partial nephrectomies (LPN) were performed in 10 farm pigs using this combination of the following three technologies: 1) Robotic endoscope holder (EndoControl), a novel small light robot fixed to the OR table; 2) 3-D vision (Viking System) displayed on a 3-D screen, and/or a personal head display, and/or 3-D special glasses developed for the study; 3) Articulated instrument (Radius Surgical System, Tuebingen Scientific) with deflectable and rotatable tips that provide 6 degrees of freedom. The stability and compatibility of the system were assessed. OR time, estimated blood loss (EBL), complication and quality of the sutures were recorded and evaluated.

All of the procedures were accomplished successfully. All three technologies were compatible and stable. No instrument failure was noted in any of the procedures. The mean OR time for LPP was 84 ± 19 minutes, and 55 minutes at the end of the learning curve (p<0.0001), EBL was 7 ± 4 cc. Tissue laceration and anastomotic leak on retrograde ureteropyelography occurred in the 3 first cases. The mean suturing time for the UVA was 32± 9 minutes in order to place 8 sutures and suturing time was 20 minutes at the end of the learning curve (p=0.0004); the mean OR time for LPN was 104 ± 30 minutes, warm ischemia time was 26 ± 6 minutes and 19 minutes at the end of the learning curve (p=0.019). EBL was 40±23 cc. Intraoperative complications included one renal vein injury that was suture-repaired.

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Key Point:

The combination of robotic-endoscope holder, 3-D vision and articulated instruments to perform reconstructive laparoscopic urological surgery represents an effective alternative to the main advantages of articulation and 3-D vision afforded by current robotic surgical systems. The combination of multiple compact robots with instrument tracking and tactile feedback is under investigation. This combination may provide the advantages of a robot in a more cost-effective way.

3-D visual display helmets.

A mini-robot is attached to an operating table and used as a scope holder.

Articulating laparoscopic instruments.
Halving Warm Ischemia Time During Laparoscopic Partial Nephrectomy

Inderbir S. Gill, MD, MCh, Mike Nguyen, MD, Monish Aron, MD

Preservation of renal function and oncologic cure are the 2 goals of partial nephrectomy (PN). The duration of warm ischemia is the single most important surgically modifiable factor affecting postoperative function. Although a threshold “safe” time below which renal damage is negligible or transient remains to be scientifically defined, generally speaking, 30 minutes has long been considered to be a “safe” limit. However, recent data indicate that this limit actually may be lower, especially in patients with pre-existing renal dysfunction. As such, every surgical attempt must be made to decrease ischemia time to a minimum.

Laparoscopic partial nephrectomy (LPN) traditionally has been associated with a mean ischemia time of approximately 31 minutes. Recently, we developed an early unclamping LPN technique, whereby ischemia time now has been decreased by more than 50% compared to previous reports. In this novel technique, during cold-scissor excision of the tumor, radiolucent Hem-o-lok® clips are employed selectively for pre-emptive control of the larger intra-renal blood vessels, if necessary. A precise initial, central, running suture is placed in a mattress fashion just underneath the clips (in order to exclude the clips) followed by immediate unclamping of the renal artery and vein. All subsequent renal repair is performed on the perfused, revascularized kidney. Specific figure-of-8 sutures are used to control any remaining active arterial and/or venous bleeding sites, and achieve water-tight collecting system closure. Biologic hemostatic and adhesive agents are applied topically to complete the renorrhaphy, with or without a bolster. This technique affords 2 advantages: (a) early hilar unclamping significantly reduces ischemia time (p<0.001), and (b) unclamping prior to completing the renorrhaphy unmasks bleeding from any unsecured intra-renal blood vessels, which are then specifically suture-controlled. The surgeon can thus secure the partial nephrectomy bed with assurance, minimizing postoperative hemorrhagic complications.

Our current mean warm ischemia time during LPN is 13.9 minutes. In 50 consecutive patients undergoing this early unclamping LPN technique, tumors were central in 88%, hilar in 38%, and completely intra-renal in 10%, requiring a deep resection with pelvi-calyceal entry in 98% of patients. Yet, ischemia was < 20 minutes in 94% of patients, 20-29 minutes in 6%, and 30 minutes or more in 0%. Further, post-operative hemorrhage rate was 2%. No patient had a positive margin, or required either dialysis or open conversion.

Our recent multi-institutional retrospective study comparing LPN with open partial nephrectomy in 1,800 patients with a clinical T1 tumor < 7cm confirmed equivalent 3-year oncologic and renal functional outcomes between the two techniques. Only 2 remaining issues were identified with LPN: a 10 minute longer ischemia time (30 vs. 20 min), and a somewhat higher postoperative hemorrhage rate (4.2% vs. 2%). Given our current data presented above, in our experience, LPN now equals open surgery in these 2 important aspects as well.

Key Point:

Recently, we developed an early unclamping technique for laparoscopic partial nephrectomy (LPN), whereby ischemia time now has been decreased by more than 50%. With an experience of more than 950 LPN surgeries, we are carefully expanding the indications of LPN to include patients with complex, anatomically challenging tumors, akin to open surgery.

5.5 cm, central, completely intraparenchymal renal mass in solitary right kidney treated with right LPN.

Hilar tumor in right kidney, treated with right LPN.
Building on our growing single-institutional experience with more than 950 LPN surgeries, we are carefully expanding the indications of LPN to include patients with complex, anatomically challenging tumors, akin to open surgery. As such, LPN is now being successfully employed for central, hilar, completely intra-renal, and multiple tumors, as well as tumor in a solitary kidney. At our center, elective LPN is now offered to select patients with a clinical T1 tumor (< 7 cm), with the final decision between LPN and open surgery based on individual patient and tumor characteristics, and surgeon preference.

For references, please email the editor.

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Improving Small Renal Cancer Diagnoses with Computer-Aided Analysis

Kazumi Kamoi, MD, Brian R. Herts, MD, Inderbir S. Gill, MD, MCh

Incidental detection of small renal masses has fueled the increase in incidence of renal cell carcinoma (RCC) in the United States from 7.1 to 10.8 cases per 100,000 in the last decade. That makes it all the more important to preoperatively differentiate benign from malignant tumors and histologic subtypes.

The major histologic subtypes include clear cell renal cell carcinoma (RCC), papillary RCC, and chromophobe RCC, as well as a small number of other unclassified tumors. Benign tumors including oncocytoma and angiomyolipoma account for approximately 20% of all renal cortical tumors. Conventional clear cell RCCs account for approximately 65% of renal cortical tumors and 90% of metastases. Papillary and chromophobe RCCs, which account for approximately 25% of renal cortical tumors and 10% of metastases, have less metastatic potential. The overall 5-year survival rate for patients with these tumors (80%–90%) is superior than that for patients with clear cell RCCs (50%–60%).

Preoperative imaging alone cannot classify histologic subtypes. However, certain characteristics seen on computed tomography (CT) have been associated with different subtypes. Recent research in other types of malignancies suggests that computer-aided diagnosis (CAD) can enhance the sensitivity of diagnostic imaging, so we tested the ability of three different types of computer-based analysis to predict the correct one of five histologic subtypes (clear cell RCC, papillary RCC, chromophobe RCC, oncocytoma, and angiomyolipoma) and to predict malignancy.

We compared data from thin-slice renal CT and demographic characteristics, such as age, gender and body mass index, with final histology from 158 patients undergoing laparoscopic partial nephrectomy. Computer-aided techniques employed included classification and regression tree (CART) analysis, neural networks, and logistic regression-based discriminant analysis.

Inspired by biological nervous systems, artificial neural networks are computer-based information processing systems that use a large number of highly interconnected processing elements that “learn” by example, so these systems are highly useful in pattern recognition. The CART approach is an alternative to artificial neural networks and more traditional logistic regression analysis. Unlike logistic regression, CART analysis does not assume a risk or probability and is not affected by outlying observations. Predictions are read directly from the tree diagram that does not even require a calculator to derive outcomes. We used a CART model with maximum parameters calculated by OncoCare® software from Siemens Medical Solutions. The software measures various volumetric, morphologic and enhancement characteristics of renal tumors.

The three analytic models had comparable diagnostic accuracy, correctly identifying the histologic subtype in approximately 80% of cases. The CART model best predicted final pathology on internal validation, identifying malignant tumor with a sensitivity of 93% and a specificity of 79%.

These initial data need external validation from other institutions to confirm the usefulness of CART analysis to improve diagnosis of small enhancing renal tumors. In the future, these techniques might supplement clinical judgment. But these types of analyses could prove to be a valuable “second opinion” for surgical decision-making in patients with a small enhancing renal mass.

For references, please email the editor.

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Auto-Transplantation for Intractable Nephrolithiasis

Alvin Wee, MD, Stuart Flechner, MD, Ho Y. Tiong, MD, Ray Littleton, MD, and Mark J. Noble, MD

Auto-transplantation historically has been used to treat a variety of disorders including bench surgical reconstruction of the renal artery for aneurism; bench excision of a malignant tumor; therapeutic intervention for Loin-Pain, Hematuria Syndrome; and preservation of a kidney when the ureter must be excised for a variety of reasons (e.g., long strictures or ureteral tumors). There are few reports of auto-transplantation to treat medically refractory stone disease, and even fewer reports of bilateral treatment. Yet, the literature suggests that the procedure is generally successful in both preserving the kidney(s) and also helping the patient to pass stones more easily (via pyelovesicostomy). We believe this procedure should be offered to more patients despite its complexity, as it has a high success rate in reducing the inevitable dependence on narcotics seen in many recurrent stone patients. It also seems to greatly reduce the tendency to form new stones. We present our results to date in a combined series with Henry Ford Hospital.

The basic surgical technique involves removal of a kidney (donor nephrectomy technique), flushing with preservation solution, bench removal of stones if needed, then transplantation into the ipsilateral iliac fossa with pyelovesicostomy (Fig. 1). There were 6 renal units in 4 patients in this series through a midline abdominal incision. Two females underwent bilateral staged auto-transplantation 2-3 months apart (Fig. 2). One renal unit (female patient) was transplanted for intractable uric acid nephrolithiasis; the other 5 kidneys were in 3 individuals with medically refractory cystinuria. Patients averaged more than 3 years of a variety of stone treatments including ESWL, ureteroscopy, percutaneous surgery, or combinations and all had completely failed medical management in spite of good compliance. Two patients averaged three UTIs per year, and all patients were on continuous narcotics preoperatively.

Mean pre-op creatinine was 1.08 and mean post-op creatinine was 0.90. All kidneys exhibited normal function postoperatively. There were no major complications. Patients were all off narcotics by the eighth postoperative week, and frequency of UTIs was reduced by 50%. Stone events per year were reduced by more than 100%.

Our series demonstrates the feasibility of auto-transplantation with direct pyelovesicostomy for treatment of medically refractory stone disease. The reflux (“washing machine effect”) helps remove small crystals before they grow into large stones, and any stones that do form can pass far more easily than if they needed to traverse a ureter.

Key Point:
We believe auto-transplantation for intractable nephrolithiasis should be offered to highly selected patients despite its complexity, as it has a high success rate in reducing the inevitable dependence on narcotics seen in many recurrent stone patients. It also seems to greatly reduce the tendency to form new stones.

There is no ureteral colic from gravel or stones < 8 mm. Larger stones that don’t pass can be lasered through a flexible cystoscope passed transurethrally, which is far less invasive than ureteroscopy or percutaneous stone removal.

Figure 1. Unilateral auto-transplant with (inset) anastamosis of a bladder flap (Boari) to the longitudinally-opened upper ureter and renal pelvis.

Figure 2. Bilateral auto-transplant with pyelovesicostomy, completed result.
Kidney failure is rapidly becoming an epidemic in the United States, fueled by epidemic diabetes, obesity and, paradoxically, improved cardiac care. Patients with hypertension and diabetes now live long enough to develop kidney failure.

Excellent outcomes from renal transplantation are limited by scarcity of donor organs so that fewer than 20% of patients with kidney failure ever receive a transplant, according to Organ Procurement and Transplantation Network data.

Most patients depend on hemodialysis and suffer extraordinary mortality and morbidity at great expense. Recent research has shown improved control of blood pressure, nutrition and cardiac disease with prolonged daily dialysis, but nationwide implementation of this strategy would overwhelm existing resources. Consequently, innovative efforts in tissue engineering and biomedical engineering strive to create alternatives to transplant and in-center dialysis.

The ideal alternative therapy should provide the following in a solution for end stage renal disease (ESRD) patients:

1. Relocation: The location of care must be relocated from the healthcare facility to the patient’s own home.
2. Reduction: There must be a significant reduction in disposables, which are expensive to purchase and expensive to discard.
3. Reliability: Monitoring and control of therapy must rely on integrated sensing and automated controls rather than on minute-to-minute monitoring by medical staff.

A wearable or implantable kidney integrated with the state-of-the-art electronics would certainly achieve the above characteristics.

Our group has focused on membrane technology as a limiting step in implantable or wearable therapy for ESRD because existing dialysis cartridges are physically large and require superphysiologic pressures for blood circulation. Tight control over pore size, geometry and chemistry can improve hydraulic permeability and molecular selectivity of dialysis membranes such that the entire dialysis machine can be implanted, facilitating home and portable therapy.

The requirement for large volumes of medical grade water presently limits patients to stationary, episodic treatments. A therapy that mimics the kidney’s own processes of filtering the blood and reabsorbing salt and water while excreting toxins would be enabling for a portable or implantable treatment. We describe our work on the design and testing of novel membranes prototyped using a unique technology toolkit, microelectromechanical systems (MEMS).

Thin flat-sheet membranes with highly uniform slit-shaped pores were produced using microfabrication techniques developed for the semiconductor industry. Tests with water, saline solutions and blood confirmed that existing theory for liquid flow and filtering are adequate to predict the properties of these novel nanoscale membranes.

Through a $3.2 million NIH grant, we are evaluating the feasibility of an implantable total artificial kidney to replace maintenance dialysis.
Development of an Implantable Total Artificial Kidney continued from page 33

To reproduce the metabolic activity of the kidney, human kidney cells were harvested from donated organs not suitable for transplant, and grown on these novel membranes. The cultured cells covered the membranes and appear to retain features of adult kidney cells.

These preliminary data formed the basis of a proposal to the NIH to fund development of an implantable artificial kidney at Cleveland Clinic. Shuvo Roy, PhD, adjunct staff, Biomedical Engineering, received a $3.2 million, three-year grant from the NIH to complete feasibility data for a total artificial kidney to replace maintenance dialysis.

Predicting Acute Kidney Injury

Sevag Demirjian, MD

Acute renal failure (ARF) has long been recognized as a major complication of surgery and invasive procedures. Cardiac surgery has been the example for studying the natural progression and outcome of acute renal failure. Mortality after cardiac surgery ranges between 2 and 8%; however, development of postoperative ARF increases the mortality rate to 50%. Previous attempts at therapeutic interventions have failed, and the survival rate associated with ARF remains dismal. Lately, it has become exceedingly evident that renal failure complicating major procedures has a modifying effect on overall outcome and is not a mere indicator of the extent of a patient’s illness.

Cleveland Clinic ARF score, developed and validated in our institution, has been a very powerful tool at bedside to instruct patients on their renal outcome and its subsequent impact on longevity. Across the country, the Cleveland Clinic ARF score has been used not only for patient counseling, but also for research purposes. It has the ability to predict the probability of suffering from severe kidney failure that will require dialysis. However, recent reports have shown that even mild to moderate impairment in renal function has far-reaching survival implications. As such we have turned our focus to study models that predict the slightest changes in renal function in the perioperative period, which would translate to a more precise and useful tool for counseling patients who will undergo major cardiac surgery.

By focusing on patients who are at high risk to sustain acute renal failure using the above-mentioned models (beyond the obvious risk factors such as chronic renal failure, diabetes mellitus, etc.), we are currently investigating the role of new promising biomarkers, such as NGAL, for earlier diagnosis and recognition of serious kidney injury. Traditional markers, namely serum creatinine, has been the Achilles heel for the diagnosis and secondary intervention of acute renal failure because of its inherent delay of at least 48 hours in estimating extent of injury. We are assessing the relationship of these biomarkers with the gold standard, iothalamic glomerular filtration rate.

Key Point:

We are currently investigating the role of new promising biomarkers, such as NGAL, for earlier diagnosis and recognition of serious kidney injury.

As new biomarkers are posed to deliver the promise of earlier and more accurate detection of acute kidney failure, we will be more efficient and timely in studying effective clinical therapies. Preclinical research has identified numerous promising therapeutic agents to prevent and treat kidney injury. In patients who are at high risk for kidney failure and who will undergo complex surgical procedures, we are currently studying promising medications that would prevent kidney failure and, subsequently, allow for the avoidance of dialysis while improving survival.

The following trials are ongoing for prevention and treatment of ARF:

Phase I/IIa trial examining the safety of small interfering RNA (siRNA) for prevention of ARF in patients undergoing major surgery.

Phase III randomized trial Evaluating Aranesp® (darbepoetin alfa) for the Prevention of Acute Kidney Injury (AKI) in High-Risk Patients Undergoing Cardiopulmonary Bypass (AVERT). Recently, there has been growing evidence that recombinant human erythropoietin (rHuEPO) and a novel analogue, darbepoetin alfa, which are indicated for the treatment of anemia associated with chronic kidney disease, are cellular survival factors. This cytoprotective effect has been shown in multiple animal models, including cerebral infarct reduction after middle cerebral artery occlusion, prevention of light-induced retinal degeneration, and enhancement of functional recovery of ARF.
Research Trials in the Prevention of Progression of Autosomal Dominant Polycystic Kidney Disease

William E. Braun, MD

There are several major studies, as well as pilot studies, investigating new treatments for autosomal dominant polycystic kidney disease (ADPKD), which affects approximately 12.5 million people worldwide.

HALT-PKD Study

The NIH is sponsoring the HALT-PKD study testing the effect of lisinopril plus telmisartan versus lisinopril plus placebo. Study A involves approximately 548 patients ages with an estimated GFR greater than 60 ml/min; Study B involves approximately 472 patients ages with an estimated GFR of 25 to 60 ml/min. In Study A, which is a two-by-two design, the patients are assigned to a standard blood pressure range (120-130/70-80 mmHg) or a low blood pressure range (95-110/60-75 mmHg). The primary endpoint for Study A is the percent change in total kidney volume as measured by MRI with testing at baseline, 24 and 48 months. No gadolinium is being used. In Study B, the patients will have their blood pressure controlled to a single range of 110-130/70-80 mmHg. The primary endpoint for Study B is the time it takes for a 50% reduction in estimated GFR (eGFR), occurrence of end-stage renal disease (ESRD), or patient death.

TEMPO-3/4 Trial

A second major study is the TEMPO-3/4 Trial, which involves the drug Tolvaptan that blocks the vasopressin V2 receptors in the kidneys. This is a Phase 3 study to assess the efficacy of Tolvaptan versus placebo in the treatment of ADPKD in the United States, Europe and Japan.

Experimental animal models have shown Tolvaptan’s effectiveness in ADPKD. Because this drug does block water reabsorption, patients will have very large urinary outputs and be required to ingest very large amounts of fluid.

Rapamycin Study

In a pilot study at Cleveland Clinic, the drug rapamycin (sirolimus) is being tested in 30 patients with ADPKD. Rapamycin blocks a pathway for cell proliferation and cyst formation (mTOR pathway) that is abnormally upregulated in ADPKD. In the rapamycin trial, 20 of the 30 patients will be treated with rapamycin at two different blood levels, and 10 patients will serve as controls. This study still has a few openings.

Because it will be several years before the results of these studies are known, the key and current approaches to treatment of ADPKD include:

- Control of hypertension and renal complications (e.g., urinary tract infections, kidney stones, bleeding, and pain)
- High water intake in the range of 3000 cc/day if the patient’s cardiopulmonary and renal status permit (This can at least partially mimic the effects of Tolvaptan by suppressing vasopressin that stimulates cyclic AMP with its propensity to provoke renal cyst development.)
- Avoidance of caffeine, which can allow phosphodiesterase to degrade cyclic AMP in its normal fashion
- Low-sodium diet

For complete inclusion and exclusion criteria for the HALT-PKD study and the rapamycin study in ADPKD, contact Rita Spirko at 216.444.4680.
Kidney (Chronic Kidney Disease)

Gene Expression in Anemia of Chronic Kidney Disease

**Saul Nurko, MD**

The progressive loss of kidney function results in multiple adaptive and maladaptive processes. This state is called chronic kidney disease (CKD), the hallmarks of which are biochemical and physiological abnormalities in almost every organ system.

Anemia and its consequences develop almost universally in patients with advanced kidney disease. Certain populations (e.g., Blacks and diabetics), are more prone to develop anemia at earlier stages of the disease. There is a general consensus that untreated anemia contributes to the large cardiovascular burden that this population of patients exhibit. In the late 1980s, the advent of recombinant human erythropoietin (Epo) for the treatment of anemia of kidney disease significantly changed the management of anemia, however, anemia management has come with a large economical cost — about $2 billion of Medicare expenditures in 2005.

A large body of epidemiological data suggests that treating anemia with erythropoiesis stimulating agents (ESAs) in CKD results in better clinical outcomes; however, randomized control trials have shown an improved quality of life for most patients but have failed to show unequivocally a better survival rate or morbidity. The response to ESAs is variable and some patients are completely hypo-responsive or respond only to very high doses. True hypo-responsiveness to ESAs is hard to define but has been associated with poor clinical outcomes and has been estimated to occur in 4 to 10% of the dialysis population.

The factors involved in ESAs hypo-responsiveness remain undefined, but iron homeostasis appears to be altered in patients with CKD. Some of the observed alterations implicate a diminished release of recycled iron from the reticuloendothelial system (RE), decreased enteral absorption and a diminished capacity to transport iron to the developing erythrocytes due to a lower serum transferrin. These decrease capacity to release and deliver iron to the bone marrow and force ESA-induced erythropoiesis to be dependent on external iron, usually delivered as parenteral iron. In other words, ESA-induced erythropoiesis in CKD is iron restrictive. This dependence in parenteral iron has resulted in a higher than normal percentage transferrin saturation (TSAT) and serum ferritin (SF). We have come to tolerate levels of 50% TSAT, and SF up to 500 ng/mL. The long-term clinical and molecular consequences of this practice are not well known and highly debated.

The recent discovery of hepcidin, a 25-amino acid peptide defensin-like peptide produced by the liver that profoundly influences iron metabolism in vivo by binding and internalizing ferroportin, the only known iron extruder transporter. This effect of hepcidin on ferroportin blocks iron release from enterocytes and macrophages of the RE, ultimately resulting in a lower serum iron. Therefore, it would be expected to find low hepcidin in states where iron is required, or high hepcidin if iron needs to be limited and/or is in excess as infection and hemochromatosis, respectively. Indeed hepcidin expression is downregulated by anemia/hypoxia where iron is required and upregulated by iron overload and inflammation where iron is not needed. It has been speculated that diminished iron absorption and blocked iron release from the RE seen in CKD could be mediated by an elevated hepcidin as a result of inflammation and/or a lower clearance. However, the hepcidin levels, role and/or function in CKD are not known.

**Key Point:**

The main goal of our laboratory is to better understand the molecular mechanisms involved in the response to erythropoiesis stimulating agents (ESA) in CKD by investigating the expression and function of hepcidin, ferroportin and other related iron regulatory proteins that would lead to identification of ESA hypo-responder patients and, eventually, to better outcomes.

We speculate that a diminished hepcidin expression in anemia of CKD is necessary for an erythropoietin response. The downregulation of hepcidin facilitates the release of reticuloendothelial system iron, necessary to support the augmented erythropoiesis; any alteration of this hepcidin response could have enormous clinical and economic implications in the management of anemia of CKD.
The main goal of our laboratory is to better understand the molecular mechanisms involved in the response to ESA in CKD by investigating the expression and function of hepcidin, ferroportin and other related iron regulatory proteins, that would lead to identification of ESA hypo-responder patients and eventually to better outcomes.

Our studies are based on a well characterized surgical mouse model of CKD. CKD is induced by electrocauterization of 85% of the right kidney surface, followed 2 weeks later by left nephrectomy. After 3 weeks mice become uremic and anemic and then exhibit a hemoglobin response after 3 weeks of intraperitoneal erythropoietin (Epo). Mice are sacrificed after 3 weeks of treatment and clinical hematological parameters are measured. Liver and spleen are snapped frozen for RNA isolation and non-heme iron quantification.

Our preliminary data have shown that anemia of CKD resulted in a lower hepcidin expression. Hepcidin expression decreased even further as iron requirements increased after reversal of the anemia by Epo. As expected, the further hepcidin downregulation seen in the Epo-treated mice facilitated the release of stored RE iron necessary to sustain Epo-stimulated erythropoiesis and manifested by a lower non-heme tissue iron. These findings suggest that anemia in this CKD model is characterized by a lower hepcidin expression, but that full hepcidin downregulation, which will result in RE iron release, is necessary for Epo response. We speculate that a diminished hepcidin expression in anemia of CKD is necessary for an Epo response. The downregulation of hepcidin facilitates the release of RE iron, necessary to support the augmented erythropoiesis; any alteration of this hepcidin response could have enormous clinical and economic implications in the management of anemia of CKD.

Chronic Renal Insufficiency Cohort Study

Cleveland Clinic Principal Investigator: Martin J. Schreiber, Jr., MD

The Department of Nephrology and Hypertension has been an active clinical site for the NIH multicenter CRIC study (chronic renal insufficiency cohort). Between 2002 and 2006, Cleveland Clinic enrolled 183 patients for this 5-year observational trial. The main goals of this study are to identify predictors of rapid progression of kidney disease while clarifying the relationship between kidney dysfunction and the risk of subclinical and clinical cardiovascular events, death and resource utilization through an initial 5-year follow-up.

Cleveland Clinic will be one of the study sites for CRIC-2, which will examine the longer term follow-up of patients with chronic kidney disease (CKD). We are increasingly engaged in focusing on determinants of progression in CKD patients and designing models of care that will result in extended survival and improved outcomes. To this end, we have designed those components of a CKD Clinic that we feel are critical to understanding how we can impact a change in the natural history of this disease.
Central Aortic Augmentation Pressure and the Gender Differences for Optimal Blood Pressure Targets

Mohammed Rafey, MD

Arterial pulse wave tracing and vascular mechanics are measured using a pencil-shaped tonometer that is placed on the radial, carotid or femoral artery. Sometimes a blood pressure cuff and/or EKG lead is placed for a comprehensive vascular profile. The data provided may offer valuable insight on arterial stiffness, vascular mechanics and health compared to office blood pressure measurements.

With each muscular contraction of the left ventricle during systole, an arterial pressure wave is generated and propagated forward in the arterial system. This is palpable as the peripheral pulse and represents not only the ventricular contraction, but also characteristics of the arterial tree. The pressure wave is then reflected back at multiple peripheral arteries that are the branch points of small muscular arteries and arterioles.

Thus the final pressure wave form that is seen as a tracing is a summation of the forward traveling wave generated by ventricular systolic contraction and the backward traveling wave that is reflected at peripheral branch points of the vascular tree.

In healthy individuals with normal arteries, the reflected wave merges with the forward traveling wave in early diastole and augments coronary blood flow. In patients with stiff arteries, the reflected wave returns faster and merges with the incident wave in systole. In the latter case, this results in an increase in left ventricular afterload and also a decrease in coronary perfusion.

Central aortic pressure (CAP), pulse wave velocity (PWV) and augmentation index (AIx) are the key parameters. Unlike brachial blood pressure, these indices are dependent not only on cardiac output and peripheral vascular resistance but also vary with changes in the stiffness of conduit arteries and the timing and magnitude of pressure wave reflections.

Several cross-sectional and longitudinal studies have indicated the independent predictive value of these indices, i.e., CAP, PWV, AIx, in predicting cardiovascular events. Because chronic kidney disease (CKD) patients are at increased risk, often several-fold higher, for cardiovascular disease and death, these indices acquire greater significance in risk assessment and management.

One interesting aspect of measuring central blood pressure indices has been to better understand gender differences in the cardiovascular risk profile. Women appear to have greater age-related left ventricular hypertrophy than men. And, morbidity and mortality secondary to heart failure is more common in women despite the fact that women appear to be better protected from ischemic heart disease in pre-menopausal years.

Preliminary studies demonstrate that women have stiffer arteries than men. As a result, women have a faster travel time of the reflected wave and thus a higher augmentation index.

We recently presented a study at the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Congress at Stockholm, showing similar results. The augmentation index was significantly higher in women than in men. It is plausible that as a result of a higher augmentation index, women have a higher vascular load, which may translate into an increased prevalence of cardiac hypertrophy as well as cardiomyopathy in women.

These findings on vascular mechanics raise questions about specific risk factors that could play a role in relatively severe arterial stiffness in women. Questions also exist regarding the need for more aggressive goals for blood pressure, lipids and diabetes control in treating women as compared to men, and whether women should be preferentially treated with antihypertensives that reduce arterial stiffness as a first-line therapy.

Key Point:
Several studies have indicated the independent predictive value of central aortic pressure, pulse wave velocity and augmentation index in predicting cardiovascular events. Because CKD patients are at higher risk for cardiovascular disease and death, these indices acquire greater significance in risk assessment and management.

Findings of our recent study on vascular mechanics utilizing these indices suggest women may have a higher vascular load than men, raising questions about their optimal targets for blood pressure, lipids and diabetes control.
Cell Surface Proteolytic Enzymes in Hypertension

Qingyu Wu, MD, PhD

Proteolytic enzymes, also called proteases, function to split other proteins in order to activate them, as in blood clotting, or to degrade them, as in food digestion. Most proteases are secreted soluble proteins. Recently, a new class of trypsin-like proteases has been identified that is anchored on the cell surface through an integral transmembrane domain. These membrane proteases participate in a variety of biological processes. We study two such proteases that are involved in hypertension and prostate cancer, corin and *hepsin*, respectively.

Corin is a protease we discovered from human hearts. It has a transmembrane domain near the amino terminus and an extracellular protease domain at the carboxyl terminus (Figure). In the heart, corin converts pro-atrial natriuretic peptide (pro-ANP) into active ANP, a cardiac hormone that regulates blood pressure and salt water balance. In mice, lack of corin causes salt-sensitive hypertension. Hypertension was exacerbated in pregnant corin knockout mice, reminiscent of preeclampsia in patients. In humans, corin gene polymorphisms have been found to be associated with hypertension and cardiac hypertrophy in Blacks, a population known for high prevalence of hypertension. In recent studies, we found that the gene variants alter corin protein structure and impair its biological activity. Our data indicate that corin is essential in maintaining normal blood pressure and that corin deficiency may contribute to hypertension and heart disease in patients.

*Corin shares a similar topological structure with hepsin. Recent studies have shown that hepsin plays an important role in prostate cancer. See page 22.*

Key Point:

Our data indicate that the corin protease is essential in maintaining normal blood pressure and that corin deficiency may contribute to hypertension and heart disease in patients.
Excision of Extruded Vaginal Mesh

Howard B. Goldman, MD

Transvaginal prolapse repairs utilizing mesh recently have become popular because of dissatisfaction with recurrence rates of traditional transvaginal repairs. Along with the increasing numbers of these repairs being performed we have seen an increase in referrals for complications related to mesh use. One of the common complications is extrusion of the mesh into the vagina. In women who are not sexually active this may be asymptomatic, but in some it may cause vaginal discharge. If a woman is sexually active, it may cause dyspareunia or pain to her sexual partner during intercourse. Published extrusion rates are about 10% but with more experience and better vaginal wall dissection techniques, the rate has dropped to the 2-4% range. Nevertheless, given the large number of these mesh procedures being performed, there are many women presenting with post-operative vaginal mesh extrusion.

We have found that the majority of these patients can be treated in a straightforward manner with excision of the extruded vaginal mesh.

The technique involves:
1. Identification of the limits of mesh extrusion; 2. Infiltration of the surrounding skin edges with a dilute lidocaine and epinephrine solution; 3. Dissection of the skin edges around the extrusion for just over 1 cm circumferentially with development of skin flaps; 4. Careful incision of the mesh; 5. Blunt and sharp dissection of the mesh from the underlying bladder or rectum making sure no mesh will be left at the skin closure site; 6. Closure of vaginal skin.

(A DVD detailing this procedure was presented at the 2008 AUA meeting in Orlando.)

We recently completed a study, together with our gynecologic colleagues, of our experience with 17 patients who underwent vaginal mesh excision. The indications for excision included mesh extrusion, chronic pain, dyspareunia and vesicovaginal fistula. Most patients had undergone a trial of conservative treatment - usually with local application of hormonal cream. There were no intra- or perioperative complications. At an average follow-up of 8 months, 93% were satisfied with the results of mesh excision. While some of the cases were felt to be technically difficult, most were accomplished without undue difficulty.

With the increase in the use of mesh for transvaginal prolapse repair the number of complications related to mesh placement has increased. In the majority of cases mesh excision will alleviate symptoms and lead to a high degree of patient satisfaction.

Key Point:
Many women are presenting with post-operative vaginal mesh extrusion. We have found that the majority of these patients can be treated in a straightforward manner with excision of the extruded vaginal mesh. After completing a study recently with gynecologic colleagues, we found that, of the 17 patients who underwent vaginal mesh excision, 93% were satisfied with the results at an average follow-up of 8 months.
Testing Stem Cell Homing for Stress Urinary Incontinence

Margot Damaser, PhD, Adonis Hijaz, MD, Lynn Woo, MD, Hadley Wood, MD, Raymond R. Rackley, MD, and Marc Penn, MD, PhD

Prevalence data suggest that during their lifetimes, up to half of U.S. women experience some level of female pelvic floor disorders (FPFD): urinary incontinence, including stress urinary incontinence (SUI); pelvic organ prolapse, including uterine and rectal prolapse; and fecal incontinence. FPFD entail substantial and cumulative costs and can dramatically impact quality of life. Because a large portion of the U.S. population is aging, there will be a dramatic increase in FPFD in the coming decades. However, despite the prevalence of FPFD, little is known about their pathophysiology.

Development of FPFD later in life are strongly linked to vaginal delivery of children. Increased time in second stage of labor, increased fetal weight, and increased age of the mother, all increase the risk of developing FPFD, particularly SUI. We have been working with several animal models of FPFD and have developed a method of simulating childbirth injuries in rodents via a vaginal distension procedure. We also have developed a method of determining the competence of the continence mechanism in these animals, using a version of leak point pressure (LPP) measurement adapted for animals. In the animals, recovery depends on duration of distension: the longer the duration of distension, the longer the time to recovery. There is therefore a healing and recovery mechanism that occurs endogenously in the animals. If this molecular mechanism could be exploited and applied clinically, it could be used to accelerate recovery from childbirth injuries and potentially treat or prevent SUI and FPFD.

Findings after cardiac infarction suggest that the injury triggers the transient over-expression of homing cytokines which mobilize the animal’s own bone marrow stem cells to migrate or home to the area of injury for repair, resulting in improved cardiac function. We hypothesized that the recovery of continence after vaginal distension may be a result of expression of these homing molecules and subsequent migration of stem cells to the injured area. In our laboratories, we have determined that one of these homing molecules (MCP-3) is strongly overexpressed in the urethra and vagina after vaginal distension but the other one (SDF-1) is not. Likewise, one of the receptors for MCP-3 (CCR1) is overexpressed but the receptor for SDF-1 (CXCR4) is not, further confirming that MCP-3 is likely the active homing agent involved in recovery from this simulated childbirth injury.

We recently have infused bone marrow stem cells intravenously after vaginal distension to test the hypothesis that they will home to injured tissues and enhance recovery of urethral function. We demonstrated stem cell homing to the urethra that increased with time after injury suggesting that the cells not only home to the injured tissues but also engraft or lodge there permanently. We have also demonstrated that animals who received stem cells recovered normal urethral function, as measured by LPP, more quickly than animals who received only saline. Thus, IV infusion of stem cells after an injury may provide a mechanism to facilitate healing after an injury such as during vaginal delivery. Alternatively, injection of homing molecules could be used to attract a patient’s own bone marrow stem cells to the site of injury and facilitate the natural healing response to injury.

Key Point: 
If the molecular healing and recovery mechanism that occurs endogenously in animals could be exploited and applied clinically, it could be used to accelerate recovery from childbirth injuries and potentially treat or prevent some female pelvic floor disorders. IV infusion of stem cells may provide a mechanism to facilitate healing after an injury such as during vaginal delivery. Alternatively, injection of homing molecules could be used to attract a patient’s own bone marrow stem cells to the site of injury and facilitate the natural healing response to injury.

Work in the near future will focus on preclinical testing of these two possible clinical therapies. The results of this study will help us better understand the mechanism of injury and recovery in the lower urinary tract after vaginal delivery. It will also provide us with a potentially new therapy for medical intervention using recruitment of stem cells as a treatment modality for SUI and other FPFD.

Cross-section of the rat urethra showing bone marrow stem cells that were injected intravenously and have migrated to the urethra after simulated childbirth or vaginal distension. Magnification = 40 times.
Female Stress Urinary Incontinence: Women’s Choices and Guidelines for Evaluation

Gamal M. Ghoniem, MD, FACS

Current treatments for female stress urinary incontinence (SUI) are effective as measured objectively with pad tests and urodynamics, but these measures do not take into account women’s expectations or what they consider to be acceptable outcomes for treatment.

Treatment of SUI is based on improving a patient’s quality of life, the definition of which varies from woman to woman. For a woman with gross incontinence, wearing a panty-liner “just in case” may be acceptable, but a woman with mild SUI may find only a complete cure acceptable.

Women’s Expectations for Treatment and Symptoms

In a prospective, cross-sectional study of 100 women (clinical paper 1st prize winner, presented at the Society for Urodynamics and Female Urology winter meeting, San Diego, 2007), we attempted to address the women’s actual expectations of treatment for SUI and to correlate this to other factors that may influence their satisfaction with treatment. We also examined the symptoms a woman would be willing to accept after treatment and correlated these to the same factors. All women were initially interviewed by our nursing staff and assessed to have a chief complaint of SUI. The women were then given the short form Urogenital Distress Inventory-6 (UDI-6), American Urological Association quality-of-life questionnaire, and validated structured questionnaires addressing expectations and acceptable post-operative symptoms. Of the 100 women, 22% overall expected a complete cure, 57% a good improvement, 12% to be able to cope better, and only 9% expected any improvement at all. We found this to be a realistic expectation of possible outcomes of treatment, with 79% expecting a good improvement or cure for their SUI.

The women also were asked what type of treatment they found acceptable for their SUI: 22% found a major surgery acceptable, 39% found a minor surgery acceptable, 32% found a clinical procedure acceptable and 7% found medication acceptable. The majority of women (71%) found a minor surgery, like a transobturator tape, or a clinical procedure, like bulking agent injection, most desirable.

Overall, the women in this study were realistic in their expectations of treatment for SUI and hoped for a good improvement in symptoms or cure.

Age, quality of life and current level of distress over SUI had a significant impact on treatment choices. As SUI is a significant quality-of-life issue and treatment is usually elective, it is imperative to determine the woman’s expectation of outcome and acceptability of treatment. It may be beneficial to consider the UDI-6, age and QOL score as a part of the evaluation and treatment for women for SUI to better meet the patient’s expectations.

Key Points:

As SUI is a significant quality-of-life issue and treatment is usually elective, it is imperative to determine the woman’s expectation of outcome and acceptability of treatment. It may be beneficial to consider the UDI-6, age and QOL score as a part of the evaluation and treatment for women for SUI to better meet the patient’s expectations.

An international committee has created guidelines for SUI outcome measures used for clinical practice and for clinical research.

Acceptable outcome according to UDI-6. The group with severe symptoms and bother (>70%) accept small leak or panty-liners, p = 0.042.
Guidelines for Clinical Practice and Research

I chaired an international committee from the International Urogynecological Association (IUGA) to form guidelines for SUI outcome measures used for clinical practice and for clinical research. Millions of women are afflicted with SUI and Pelvic Organ Prolapse (POP), and the literature is abundant with different types of surgery to correct these problems. Only recently have outcome measures been applied to research in these areas. As the population of aging women increases worldwide, it is inevitable that these women’s disorders will become more prevalent. This will pose a major challenge to the healthcare systems. A combination of a systematic review of literature (MEDLINE®), Cochrane database, International Consultation on Incontinence recommendations, and expert opinion, including history, physical examination, questionnaires, tests, surgical treatment, outcome measures, and follow-up were evaluated and categorized into:

• Recommended (R)
• Optional (O)
• Not recommended (N)

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<th>PARAMETER</th>
<th>CLINICAL PRACTICE</th>
<th>RESEARCH</th>
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<td>1. Clinical Evaluation</td>
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<td>2. Voiding Diary</td>
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<td>3. a. Cough Stress Test</td>
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<td>b. Empty Supine Stress Test</td>
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<td>d. Pad test (one and 24 hours)</td>
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Laparoscopic-Assisted Vaginal Tape Procedures: A Simplification of Vaginal and Abdominal Approaches to Pelvic Organ Prolapse and Uterine Preservation for the Urologist Moving to an Extracorporeal Approach

Raymond R. Rackley, MD, Sandip Vasavada, MD, Howard B. Goldman MD, and Courtenay K. Moore, MD

With the expanding use of laparoscopic techniques in female urology, there has been a surge in interest for incorporating minimally invasive approaches to pelvic organ prolapse (POP) repair and uterine preservation procedures. These approaches have the potential to combine the success, versatility, and durability of traditional open abdominal repairs with the minimally invasiveness and recovery afforded by vaginal approaches. The current experience with minimally invasive technology is obviating the complex traditional, as well as, newer large mesh-dependent transvaginal approaches with the recent return to intracorporeal abdominal approaches of single port and natural orifice laparoscopy. We are keeping an eye toward the future for developing a completely innovative extracorporeal approach.

We have recently introduced an innovative technique for laparoscopic-assisted vaginal tape vault suspension that is also applicable to uterine support restoration for women desiring uterine preservation as part of their reconstructive repairs. Aside from the obvious benefits in recovery time and incision size, one of the benefits of laparoscopy in pelvic surgery is the ability to visualize internal anatomy while working on an external structure. This principle was utilized in creating the laparoscopic-assisted vaginal tape vault suspension (Figure 1), and subsequently, the uterine suspension procedure (Figure 2). In these novel procedures, the surgeon, operating vaginally, passes a strip of synthetic mesh percutaneously under the lateral walls of the vagina using angled trocar needles while monitoring the needle’s passage both with vaginal inspection and laparoscopic visualization. In order to avoid bladder and bowel injury and spare the uterus, the mesh strips are passed along the lateral walls of the vagina. As shown in Figure 1, this allows the mesh to provide paravaginal support along the full length of the vagina, rather than just supporting the apex as in other sacrocolpopexy procedures; consequently, fewer concomitant transvaginal procedures (perineal body repairs, rectocele repairs) are required. This novel technique removes the technical barriers to considering the adoption of a laparoscopic approach to pelvic organ reconstructive support procedures and obviates the need for using current laparoscopic robotic multiport assistance in performing a traditional laparoscopic sacrocolpopexy procedure. Furthermore, we have adopted this approach in successfully achieving translation of this technology into a

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**Key Point:**

Minimally invasive technology is leading to advances that are obviating the traditional transvaginal approaches to pelvic organ prolapse and uterine preservation. The momentum of this movement continues to drive combinations of intra- and extracorporeal techniques as we progress to total extracorporeal approaches. Novel techniques such as the laparoscopic vaginal tape procedures represent the latest effort to meet innovative challenges in laparoscopic surgery.

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**Figure 1:** Laparoscopic-assisted vaginal tape placement for vault and pelvic organ prolapse repair.

**Figure 2:** Laparoscopic-assisted vaginal tape placement for uterine and pelvic organ prolapse repair.
single port approach as we move forward to a natural orifice and subsequently a totally extracorporeal approach to complex pelvic organ prolapse reconstructions.

For many years uterine prolapse has traditionally been an indication for hysterectomy, apart from the presence or absence of any uterine disease, and remarkably, independent of the patient’s wishes. While hysterectomy was considered standard practice for correction of uterovaginal prolapse, recent changes have been driven by the knowledge that the descent of the uterus is a consequence, and not the cause, of prolapse. Contemporary lifestyles, beliefs and perspectives of women with regards to sexual function and pregnancy have undergone profound changes and many patients who undergo surgery for genital prolapse want to preserve the uterus. Uterine preservation during prolapse surgery is not new, but few studies on uterus preservation have been reported and there are no clear indications for uterus sparing or removal in open or vaginal surgery for advanced prolapse. We have performed more than 100 laparoscopic sacrocolpopexies in women with and without hysterectomy for uterovaginal prolapse for many years with satisfactory results. However, in the treatment of uterovaginal prolapse, sacropexy with uterus conservation may be associated with less operative and post-operative morbidity and similar long-term outcomes as hysterectomy with sacropexy. Thus, we are prospectively identifying eligible patients and offering them the chance to avoid hysterectomy and its associated morbidities in an attempt to study the benefits of laparoscopic-assisted uterine preservation when addressing uterovaginal prolapse. The findings of others in similar studies are revealing that uterine preservation may become the new standard in repairing uterovaginal prolapse and that the indications for concomitant hysterectomy will need to be better justified.

A variety of laparoscopic techniques with a growing armamentarium of accessory technology such as robotics for facilitating the repair of pelvic organ prolapse and uterine preservation are available to the urologist. The current experience with minimally invasive technology is leading to advances that are obviating the traditional transvaginal approaches with the recent return to the current intracorporeal abdominal approaches of laparoscopy. The momentum of this movement continues to drive combinations of intra- and extracorporeal techniques as we progress to total extracorporeal approaches to the restoration of pelvic organ support (Figure 3). Novel techniques like the laparoscopic vaginal tape procedures represent the latest effort to meet innovative challenges in laparoscopic surgery, which is not to simply recreate the open procedure as seen in ancillary robotic applications, but to use the unique advantages of laparoscopy to create improved procedures for our patient.

Figure 3: March of innovative approaches to pelvic organ prolapse reconstruction from open to extracorporeal.
Female Urology

Courtenay K. Moore, MD

Genital sensory function is known to play a role in normal sexual function. Given this fact, several studies have suggested that alterations in tactile sensitivity of the female genitalia are linked with female sexual dysfunction (FSD), particularly arousal, orgasmic and pain disorders. Interestingly, little is known about normal sensory nerve thresholds in female genitalia.

Several studies have shown difference in tactile sensation between women with and women without sexual dysfunction using von Frey and Semmes-Weinstein monofilaments. However, these tests do not differentiate between the different types of afferent fibers being tested. The Neurometer® CPT, a sine-wave electrical stimulator, can. Different afferent fibers can be selectively stimulated using certain voltages. C fibers are stimulated by using 5-Hz, while A-δ and A-β fibers are stimulated using 250-Hz-2000-Hz respectively.

The Neurometer® CPT (current perception threshold) is an electrical stimulator that delivers sinusoidal electrical stimuli via surface electrodes at frequencies of 5, 250, and 2,000 Hz and at a current intensity range of .01 to 9.99 milliamperes (mA). It is the only commercially available instrument applying this technology to evaluation of sensory nerve function. The Neurometer® CPT uses painless automated, sensory nerve conduction threshold (sNCT®) evaluation through application of constant current neuroselective electrical stimuli. This electro diagnostic procedure has been used in various clinical settings to establish normative painless CPT values for various cutaneous sites. The Neurometer® CPT also has been used to detect axonal and demyelinating peripheral neuropathies in patients with diabetes mellitus. Studies have demonstrated the neuroselectivity of the Neurometer® CPT in evaluating large unmyelinated, and small myelinated fiber function. This device also can detect small fiber pathology with associated symptomatology including autonomic dysfunction. The Neurometer® CPT has been used to assess afferent autonomic sensation of the bladder. Studies using the Neurometer® CPT in the human bladder suggest that CPT may be a useful method in identifying the subselective disturbances of the autonomic neuropathy in lower genitourinary tract. Given its previous uses we conducted a study to establish normative female genital sensory thresholds in sexually active women. By establishing normative values we hope to be able to further expand this test to evaluate with various forms of female sexual dysfunction.

Twenty healthy, sexually active pre-menopausal volunteers were recruited to participate in this study. Volunteers completed the FSFI validated questionnaire. CPT measurements were obtained at 3 sites: clitoris (innervated by dorsal nerve of clitoris S2-4), posterior labia majora (innervated by posterior labial nerve S2-4) and the index finger on distal phalans of non-dominant hand (median nerve C7) as a control/reference value. CPT values will be obtained at three different neuroselective sine-wave currents: 5-Hz for C fibers, 250-Hz for A-δ fibers and 2000-Hz for A-β fibers. Each site was tested twice in random sequence.

Twenty women with a mean age of 36.4 years underwent CPT testing. Four of the 20 women were post-menopausal, 2 of whom were on hormonal replacement therapy. The table lists the results of labial and clitoral CPT testing at the 3 frequencies.

This study reports the CPT values of 20 normal sexually active females. By establishing normal reference value we hope to be able to use CPT measurements to assess changes in sensory afferent function in women with female sexual dysfunction.

Mean labial and clitoral CPT values

<table>
<thead>
<tr>
<th>CPT (HZ)</th>
<th>Labia (mA)</th>
<th>Clitoris (mA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>236.8</td>
<td>211.0</td>
</tr>
<tr>
<td>250</td>
<td>99.5</td>
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</tr>
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<td>5</td>
<td>50.23</td>
<td>48.72</td>
</tr>
</tbody>
</table>

For references, please email the editor.

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Laparoscopic Varicocelectomy: Modified Technique and New Technology

Jeffrey S. Palmer, MD, FACS, FAAP

Varicoceles, tortuous veins of the pampiniform plexus of the spermatic cord, principally occur on the left side due to the anatomy of venous flow. This condition is usually asymptomatic and first becomes apparent after age 9. The varicocele has been associated with testicular injury and infertility with several indications for surgical intervention, including loss of testicular volume. Several techniques have been described to treat varicoceles, including open (inguinal and retroperitoneal approaches), transvenous and laparoscopic modalities. The complications associated with these surgical techniques include hydrocele formation and varicocele recurrence.

We have successfully modified the laparoscopic technique in order to reduce the incidence of postoperative complications. A Hassan technique is used to safely obtain initial port access to the abdominal cavity. Two additional ports are then inserted under direct vision. The testicular vessels are identified and two small incisions are made in the posterior peritoneum, one medial and the other lateral to the vessels (Figure 1). Minimal dissection is then performed to isolate the vessels from the lymphatics and the other surrounding structures (Figure 2). The vessels are mass ligated and transected leaving clips both proximally and distally (Figure 3). This minimal dissection technique has not resulted in a single hydrocele, recurrence of the varicocele, or any other complications.

Recently, we also have applied a new laparoscopic technology to perform varicocelectomy. Single-access, multicannula laparoscopic ports allow for surgery to be performed through a single port without the need for additional ports (See article, page 24). This allows for a single incision, thereby improving cosmesis. We have used a novel 20-mm laparoscopic port with three working channels and gas insufflation access to successfully perform the first reported laparoscopic varicocelectomy and the first use of this technology in children. A Hassan technique is performed through an infraumbilical incision to insert the port and then curved instruments are used to perform the operation. The insertion of additional ports has not been necessary and the operative time has been less than 1 hour for each procedure. All patients have been discharged on the same day as their surgery without an incidence of hospitalization. No complications have occurred including hydrocele formation, varicocele recurrent, or intrabdominal injury.

These modifications in laparoscopic varicocelectomy with minimal dissection and the use of the multicannula single laparoscopic port maximize results, minimize complications and improve cosmesis. This new technology may have additional applications in pediatric urological surgery in the future.

Key Point:

We have successfully modified the laparoscopic technique to treat varicoceles. By using the Hassan technique and the single-access, multicannula laparoscopic ports we have performed surgical techniques to treat varicoceles in children without complications.

Figure 1: The testicular vessels are identified and two incisions are made in the posterior peritoneum, one medial and the other lateral to the vessels.

Figure 2: Minimal dissection is performed to isolate the vessels from the lymphatics and the other surrounding structures.

Figure 3: Vessels are mass ligated and transected leaving clips both proximally and distally.
Pediatric Urology

Urology & Kidney Disease News

Jeffrey S. Palmer, MD, FACS, FAAP

A significant way to reduce cost for surgical procedures would be to make modifications to convert to an outpatient procedure a common operation that traditionally requires one- to two-day hospitalization.

Ureteral reimplantation is the gold standard for the surgical treatment of vesicoureteral reflux (VUR) in the pediatric population. There are two surgical approaches – intravesical and extravesical – which typically have a 98-100% success rate. The intravesical approach (e.g., Cohen cross-trigonal), the preferred technique by most urologists, involves opening the bladder and then mobilizing and reimplanting the ureter. The extravesical approach involves splitting the detrusor muscle (i.e., detrusorrhaphy), creating detrusor flaps, advancing the ureter, and then closing the flaps over the ureter.

The extravesical approach has several advantages compared to the intravesical techniques, including less morbidity (e.g., no postoperative hematuria or bladder spasms), and places the ureter in a normal anatomic course for simplified future retrograde access (e.g., stent insertion).

More recently, endoscopic treatment has been promoted as an outpatient, noninvasive technique with low morbidity. The proponents of the technique claim that although the material injected is relatively expensive, the cost of the procedure is less than the open surgical repair mainly due to reduced operative time and the fact that it is an outpatient procedure. However, the pitfalls of this technique are that the success rate is significantly lower than ureteral reimplantation, it is contraindicated for several associated ureteral/bladder anomalies, and it requires a postoperative voiding cystourethrogram (VCUG) due to the lower success rate.

Therefore, an ideal operation would be an outpatient ureteral reimplantation even for associated ureteral/bladder anomalies, without postoperative urinary retention even after bilateral surgery, that has high parental and patient satisfaction, and is cost-effective.

We have accomplished these goals. We modified the extravesical ureteral reimplantation technique and developed a critical pathway in order to consistently have same-day discharge of unilateral, bilateral and complicated reimplantations without urinary retention or increased morbidity while having high parental and patient satisfaction. The modified surgical technique limits ureteral dissection and mobilization, and detrusor dissection to as distally as possible. No surgical dissection occurs in proximity to the obliterated umbilical artery, nor is the artery ligated. Children follow a strict postoperative critical pathway, and parents receive extensive preoperative and postoperative education. A child is required to fulfill strict criteria in order to be discharged. Parents must feel comfortable taking the child home.

We have implemented this technique and protocol in more than 50 outpatient unilateral and bilateral extravesical reimplantations with and without ureteral tapering and for single systems, duplex systems, and associated Hutch diverticulum. None of the children has had any significant complications, hospitalization or urinary retention. Parents and patients have expressed high satisfaction with their experience, especially with the ability of the child to return home the same day as surgery. Although this technique does not reduce operative time, it significantly reduces cost by converting this operation into a routinely outpatient procedure.

Dissection of the ureter to the bladder hiatus keeping the bladder mucose intact.

Two ureteral advancing/fixation sutures are placed in a horizontal mattress fashion between the distal detrusor muscle tunnel then to the corresponding position of the distal ureter extra-mucosally, and then back to detrusor muscle. Traction on these two sutures brings the distal edge of the ureter under the lip of the detrusor muscle.

The ureter is placed within the detrusor trough and the detrusor muscle flaps are then closed over the ureter in an interrupted fashion.

The completed procedure with the final ureteral tunnel length being five times the width of the ureter.

Key Point:

Outpatient ureteral reimplantation, preoperative and postoperative education, and implementation of the critical pathway has markedly changed the way VUR is surgically treated, has enhanced parental and patient satisfaction, and has dramatically reduced the cost for this common procedure. These cost-reduction modalities not only allow parents whose insurance companies will not pay for out-of-network services to be able to more easily afford the cost of the operation, but have their child sleeping in his or her own bed that same evening.

Outpatient Ureteral Reimplantation: Cost Efficient While Improving Quality of Care
Neuromodulation for Male Overactive Bladder

Khaled Fareed, MD

Approximately 30% of men over 50 report lower urinary tract symptoms (LUTS), while 8% fail medical treatment and require surgery to relieve bladder outlet obstruction (BOO). In many cases, the cause of such symptoms remains unknown. In the past LUTS were largely attributed to benign prostatic hyperplasia (BPH) and treatment (often surgical) was directed at this entity. Recent data have demonstrated that many men with irritative voiding symptoms actually have overactive bladder (OAB) instead of symptoms of prostatic origin.

With time, BPH may cause benign prostatic enlargement (BPE), which, in turn, can lead to BOO. Voiding symptoms (slow stream, hesitancy and intermittency) associated with BOO may be logically explained by the dynamic compression of the urethral luminal capacity associated with the enlarging adenoma of BPE. However, storage symptoms (frequency, urgency, and urge incontinence) seen with advancing age and often associated with outlet obstruction, are not as easily explained by obstruction alone.

Nonetheless, several pieces of evidence do firmly suggest that relieving BOO, can improve both domains of LUTS. Moreover, animal models of infravesical obstruction resulted in bladder dysfunction. The facts that women (in whom BOO is uncommon) often have storage symptom complexes similar to men, and that urodynamic obstruction does not correlate with symptom severity suggest that obstruction alone is not the sole cause of LUTS in men.

Symptoms of OAB, which include urgency, with or without urge incontinence (usually associated with frequency and nocturia) overlap with those attributed to BOO secondary to BPE. Like BOO, the prevalence of OAB increases with age, with one study estimating that 16% of all adults suffer from symptoms of OAB. While many of these patients are women, the prevalence of OAB symptoms in men exceeds that of women, particularly beyond the age of 60. Since many men will not respond to either pharmacologic or surgical treatment of BOO, and that women with very similar symptoms respond in a majority of cases to treatments aimed at the bladder, there is reason to suspect that in some men, outlet obstruction is not solely responsible for the development of LUTS. BOO and detrusor overactivity (DO) frequently coexist, however, it is not always clear that DO is outlet-induced, or an independent attribute of the bladder that may be a response to aging, ischemia, or an unknown event.

Key Point:

We now offer neuromodulation for both men and women with refractory overactive bladder. Our experience has demonstrated its efficacy as matching that of women with the same condition. The procedure is offered on an outpatient basis and we anticipate performing it soon as an office-based procedure.

Although voiding symptoms are more prevalent, storage symptoms are more bothersome and have greater impact on quality of life. It is estimated that up to 33% of men will have persistent storage symptoms after relief of BOO.

Patients who fail conservative management (antimuscarinics, behavioral modification, biofeedback and intravesical therapy) are therefore considered refractory and are candidates for sacral nerve stimulation.

We offer neuromodulation to the challenging subset of men with refractory storage symptoms without evidence of outlet obstruction. Our experience has demonstrated efficacy for refractory overactive bladder in men that matches its efficacy in women with the same condition.

It has long been recognized that selected men with nonobstructive urinary retention may respond to neuromodulation, but its use for refractory OAB has been traditionally relegated to female patients. We now offer this option for both men and women with refractory OAB.

Currently, the staged implant is offered as an outpatient procedure under conscious sedation. Patients responding to the test stimulation undergo permanent implantation. Both procedures are performed on an outpatient basis.

Percutaneous Nerve Evaluation will be offered under fluoroscopic guidance. We anticipate offering this option to men with refractory nonobstructive LUTS in an office-based setting in the near future.
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.

We have identified several specific aims for this research. The first is to scientifically determine if animals that are exposed to smoke get more bladder tumors than animals that are not. 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.

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, a urology resident in his research year; and Thomas Powell, PhD, the primary grant writer. 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.
Utility of Antiangiogenic Agents in Bladder Cancer

Jorge A. Garcia, MD, and Andrew J. Stephenson, MD

Urothelial carcinoma of the bladder remains one of the most challenging and lethal urologic cancers. Despite improvements in surgical techniques and multimodal therapy, 5-year survival rates for patients with muscle-invasive bladder cancer remain suboptimal. Almost 50% of patients will eventually progress and develop systemic disease. Although various single chemotherapeutic agents have shown activity in patients with advanced or metastatic disease, randomized trials have demonstrated the utility of cisplatin-based combinations regimens. Despite relatively high objective response rates, the impact on survival in patients with advanced disease has been quite limited. Significant progress in understanding the biology of bladder cancer has led to the identification of the vascular endothelial growth factor (VEGF) and platelet derivative growth factor (PDGF) as key mediators of angiogenesis, tumor growth and proliferation. Several authors have reported a positive correlation between tumor stage, cancer progression and tumor vascularity. Significant differences in VEGF serum level and angiogenic activity between healthy controls and patients with bladder cancer also have been identified. High VEGF and PDGF expression are closely associated with muscle-invasive disease as compared to non-muscle-invasive papillary tumors. As a result, inhibition of VEGF and PDGF signaling pathways in bladder cancer patients may lead to enhanced anti-tumor activity, alone or in combination with established chemotherapy regimens. Early animal studies utilizing different anti-VEGFR strategies have shown to inhibit tumorigenesis, angiogenesis, and metastasis of bladder cancer. These initial studies, coupled with the availability of known active anti-angiogenic agents, support the rationale for targeting the VEGF and PDGF pathways in bladder cancer.

To date, three agents capable of blocking VEGF and/or PDGF at different levels are undergoing clinical testing in bladder cancer. Bevacizumab, a recombinant human monoclonal antibody against VEGF (Avastin®) that binds and neutralizes all biologically active isoforms of VEGF is undergoing phase II testing in patients with advanced disease in combination with gemcitabine and cisplatin. An alternative approach to VEGF inhibition involves small-molecule tyrosine kinase inhibitors. These agents inhibit not only the VEGFR, but also other receptors in the tyrosine kinase superfamily, such as PDGFR.

Sorafenib (Nexavar®) is an oral Raf kinase inhibitor. Activated Ras promotes cell proliferation through the Raf/MEK/ERK pathway by binding to and activating Raf kinase. Sorafenib also has demonstrated direct inhibition of VEGFR and PDGFR. Unfortunately, minimal clinical activity has been observed when sorafenib is administered as a single agent in chemotherapy-refractory advanced bladder cancer. Sunitinib (Sutent®) is an oral multi-tyrosine kinase inhibitor of VEGFR and PDGFR. In vitro assays have demonstrated inhibition of VEGF-induced proliferation of endothelial cells and PDGF-induced proliferation of mouse fibroblast cells. Investigation in mouse xenograft models demonstrated growth inhibition of various implanted solid tumors and eradication of larger, established tumors. Contrary to sorafenib, clinical activity has been observed when single agent sunitinib is administered in chemotherapy-refractory as well as in untreated advanced bladder cancer patients unable to receive cisplatin-based chemotherapy.

Currently there are minimal data concerning potential tumor tissue effects of antiangiogenic agents and the impact these novel agents might have in patients with non-invasive and locally advanced bladder cancer. Thus, 2 phase II studies evaluating sunitinib in these two cohorts of patients are under way at Cleveland Clinic. The first study evaluates the activity and safety of one cycle of sunitinib administered at 50 mg orally given daily for four weeks followed by two weeks off (1 cycle) in patients with muscle-invasive locally advanced disease who are scheduled to undergo radical cystectomy. The second trial has been directed to patients with superficial BCG-refractory bladder cancer in the hope that sunitinib can delay progression and avoid radical cystectomy. In this study patients receive 3 cycles of continuous sunitinib at 37.5 mg orally for 12 weeks. Immediately after treatment, patients achieving clinical complete responses will continue standard surveillance as per American Urological Association guidelines. Clinical trials of targeted agents have come late to bladder cancer, but are finally under way. The recent paradigm shift in the therapeutics of renal carcinoma provides a window of hope that the next decade will see the integration of novel and effective “targeted” agents into our armamentarium, allowing for real progress in the management of this aggressive cancer.

For references, please email the editor.
Novel Approaches to Locally Advanced Bladder Cancer: Neoadjuvant Targeted Therapy

Steven Campbell, MD, PhD, Christopher Weight, MD, Andrew J. Stephenson, MD, Michael Gong MD, PhD, Amr Fergany, MD, Eric A. Klein, MD, Robert Dreicer, MD, and Jorge A. Garcia, MD

Locally advanced urothelial cancer (UC), variably defined as muscle invasive UC with a large or palpable mass, local extension or fixation, or lymph node enlargement, represents a challenging clinical dilemma. These patients are at high risk for systemic progression and occult micrometastasis and mandate a careful metastatic evaluation. Many are symptomatic with disabling voiding symptoms, incontinence, or refractory hematuria. Hydronephrosis is common and represents yet another poor prognostic parameter, particularly if bilateral. Clinical understaging is common, with the majority having extravesical extension, substantial lymph node involvement, or other adverse pathologic findings. Aggressive histologic subtypes tend to congregate in this patient population, requiring careful pathologic review and, occasionally, alternative management strategies.

Given all of these considerations, the prognosis for patients with locally advanced UC is compromised; systemic recurrences are relatively common if managed with definitive local therapies alone, and most patients must consider a multimodal approach using either neoadjuvant or adjuvant strategies. The relative merits of these two strategies for invasive UC patients taken as a whole remain controversial; however, for locally advanced disease, in which systemic therapy is almost universally required, it is best administered prior to surgery. The neoadjuvant approach optimizes the likelihood that the patient will be able to receive all of the required treatments, and recent studies have shown that radical cystectomy is well tolerated after neoadjuvant chemotherapy with no substantial increase in perioperative complications. In addition, at cystectomy about 30-40% of patients will have no evidence of disease (pT0), which can facilitate surgery. Clearly, some highly symptomatic patients with locally advanced UC will require surgery up front to address disabling symptoms, but most are best managed with a neoadjuvant approach.

Existing randomized studies suggest that MVAC chemotherapy should be the standard neoadjuvant regimen for high-risk UC patients. However, cisplatin plus gemcitabine (GC) is a reasonable alternative based on similar efficacy in the setting of metastatic disease and is associated with far less toxicity. Meta-analysis of neoadjuvant studies evaluating cisplatin-based regimens demonstrates a 6.5% absolute improvement in 5-year overall survival. Similar robust data for the subpopulation of patients with locally advanced UC are not available, but clinical experience indicates a compelling need for novel therapeutic strategies.

Recognizing this, we have recently initiated a neoadjuvant protocol for this patient population that utilizes sunitinib, a novel oral multityrosine kinase inhibitor of VEGF-R, PDGF-R, cKIT and FLT3. The conceptual and experimental rationale for the use of this drug for patients with UC is arguably as strong as that for kidney cancer, where this drug has recently demonstrated promising results. In this protocol patients receive sunitinib 50mg PO daily for 4 weeks followed by 2 weeks off (1 cycle). Patients will undergo standard radical cystectomy and bilateral lymph node dissection at the completion of the entire cycle of sunitinib. The primary endpoint of this study is to determine the efficacy and safety of sunitinib in the neoadjuvant setting.

Key Point:
We have recently initiated a neoadjuvant protocol for this patient population that utilizes sunitinib, a novel oral multityrosine kinase inhibitor of VEGF-R, PDGF-R, cKIT and FLT3. The conceptual and experimental rationale for the use of this drug for patients with UC is arguably as strong as that for kidney cancer, where this drug has recently demonstrated promising results. In this protocol patients receive sunitinib 50mg PO daily for 4 weeks followed by 2 weeks off (1 cycle). Patients will undergo standard radical cystectomy and bilateral lymph node dissection at the completion of the entire cycle of sunitinib. The primary endpoint of this study is to determine the efficacy and safety of sunitinib in the neoadjuvant setting.

Current Algorithm for the Management of Locally Advanced Bladder Cancer

Locally advanced Bladder Cancer
(large or palpable mass, local extension or fixation, or lymph node enlargement)

→ If highly symptomatic (severe incontinence, refractory hematuria, etc)
   → Radical Cx, extended BPLND, urinary diversion followed by adjuvant systemic chemotherapy

→ Most other patients with manageable local symptoms
   → Consider neoadjuvant systemic chemotherapy followed by definitive local therapy, including
     Radical Cx, extended BPLND, and urinary diversion if reasonable surgical candidate, or pelvic XRT otherwise

Or

→ Consider neoadjuvant Sunitinib protocol followed by Radical Cx, extended BPLND, and urinary diversion

For references, please email the editor.
Bladder Cancer Subtypes and Treatment Options

Donna E. Hansel, MD, PhD, and Andrew J. Stephenson, MD

Bladder cancer can be subdivided into different types on the basis of morphology, and knowledge of cancer subtype is useful in both directing patient care and predicting subsequent patient outcomes. Although bladder cancer is an aggressive disease, some patients respond well to treatment regimens that can include surgical intervention, immune-modulatory agents such as bacillus Calmette-Guerin (BCG), chemotherapy or a combination of these.

Urothelial carcinoma comprises greater than 90% of all bladder cancers in the United States, and most treatment paradigms have been developed and studied in this cancer type. Smoking represents perhaps the greatest risk factor for this form of bladder cancer. Although urothelial carcinoma itself can be even further subdivided into 14 other categories, each with distinct histopathologic features and biologic behavior, most treatment regimens consider these carcinomas as a single entity. Non-invasive high-grade disease, either in the form of flat urothelial carcinoma in situ or high-grade papillary urothelial carcinoma (Ta), and early invasive disease into the lamina propria (T1) are commonly treated by instillation of induction and/or maintenance BCG into the bladder followed by close monitoring, or immediate radical cystectomy at diagnosis in select cases. Of the former group, approximately 50% of patients will experience recurrent bladder cancer despite BCG and require radical cystectomy. It is imperative to identify these patients before the cancer has progressed to muscle-invasive disease (T2), as the ability to “salvage” these patients with cystectomy is reduced substantially. For T2 disease, radical cystectomy with regional lymph node dissection is the standard of care. Although the number and location of dissected lymph node packets varies significantly in many cases, recent work suggests that a more standardized approach using extended lymph node dissection, with re-evaluation of current nodal staging systems, may more accurately predict patient outcomes. Patients with lymph node metastases or extravesical disease identified at cystectomy subsequently receive adjuvant chemotherapy with either MVAC or gemcitabine-cisplatin. Despite the current treatment paradigms for patients with urothelial carcinoma, long-term outcomes in this population are still poor, with many patients developing metastatic disease following cystectomy and limited responses to chemotherapeutic intervention.

Additional types of bladder cancer that occur in a more limited patient population include squamous cell carcinoma, adenocarcinoma and small cell carcinoma, which combined affect less than 10% of all patients with bladder cancer. Our understanding of the molecular changes that occur in these cancer subtypes is significantly more limited than for urothelial carcinoma, and treatment options are limited.

Squamous cell carcinoma represents approximately 5% of bladder cancers in the United States, but is significantly more common in areas of the Middle East and Africa, where infection with Schistosomal species is a major risk factor for disease development. In the remainder of cases, additional risk factors include smoking and processes that lead to ongoing injury of the bladder mucosa, such as chronic catheterization and long-term infection. Based on recent work, patients with squamous cell carcinoma of the bladder appear to develop distinctive pathological features early in the course of disease that may be useful in identifying patients at risk for progression. Once invasive disease occurs, however, the only current treatment option involves radical cystectomy with lymph node dissection. Administration of chemotherapy or radiation therapy appears to offer no benefit to patients with this disease, and surgical debulking of disease may provide the best survival benefit currently.

Adenocarcinoma of the bladder occurs in only 2% of the population and is often associated with abnormal glandular changes of the surface urothelium or in association with urachal remnants. The most important distinction for this entity is the exclusion of metastatic adenocarcinoma that secondarily involves the bladder. Although many studies have examined ancillary techniques that may allow this distinction, no marker to date has proven effective in all cases. Radical cystectomy is the primary treatment option for these patients, with follow-up monitoring for metastatic disease over subsequent years.

Finally, small cell carcinoma of the bladder is an aggressive form of bladder cancer that affects less than 1% of patients and may occur in association with urothelial carcinoma, adenocarcinoma or squamous cell carcinoma, most likely representing an evolution of pre-existent cancer into this morphologic subtype based on reported molecular findings. If localized to the bladder, radical cystectomy with lymph node dissection is the primary treatment option.
A urethral sling placed via a transobturator approach has recently emerged as a treatment option for men with mild to moderate post-prostatectomy incontinence. The primary difference between this device (Advance™ Male Sling) and previous slings for male incontinence is the location of the sling at the level of the most proximal portion of the bulb of the corpus spongiosum.

Sling placement proceeds through a midline perineal incision. The bulbospongiosus muscle is opened in the midline and the attachment of the central tendon to the bulb of the corpus spongiosum is taken down sharply to allow tension-free proximal relocation of the bulb (Fig. 1). The needles are passed through the upper medial aspect of the obturator foramen just below the adductor longus tendon, and exit in the angle between the bulb and the corpus cavernosum under index finger guidance (Fig. 2). The sling is then attached and pulled through on each side (Fig. 3). The wide part of the sling is sutured securely to the corpus spongiosum at the most proximal part of the bulb (Fig. 4) and the sling is maximally tensioned and then cut at skin level. With the craniocaudal direction of force provided by transobturator placement, the sling relocates the bulb approximately 3 cm superiorly and thereby provides support to the posterior urethra and bladder neck. This results in more effective closure of the bladder neck at rest, increased length of the membranous urethra and increased mean urethral closure pressure. The outcome is improved continence in the majority of patients without compromise of urinary flow rates as there is minimal direct compression of the urethra.

These findings correlate with the clinical observation that it is important for the patient to have a visually intact urethral sphincter mechanism at the time of cystoscopy with the ability to contract the sphincter voluntarily for the procedure to be effective. Transobturator sling placement also allows for adequate posterior urethral support without the need for bone anchors or other types of fixation, which are necessary when using a compressive mid bulbous urethral sling. The procedure is, therefore, very well tolerated with minimal postoperative discomfort, and urinary retention is uncommon. An initial study of 20 patients with a wide range of severity of urinary incontinence demonstrated a cure rate at 6 weeks postoperatively of 40%, with an additional 30% of patients being improved.

Additional experience has resulted in significant improvement in these results when the procedure is limited to men with mild to moderate post-prostatectomy incontinence. We have treated more than 30 such patients with approximately 85% becoming virtually pad-free after the procedure. It is important to emphasize that the patients must limit strenuous activity for 6 weeks following surgery to avoid loosening of the sling and recurrent incontinence. It is clear that the transobturator sling will continue to have a prominent role in this setting in the near future. Assessment of efficacy for patients with moderate to severe incontinence and intermediate-term results are anxiously awaited. ■

For references, please email the editor.

This article is written for educational purposes only and as a convenience. Cleveland Clinic has no financial interest in nor is it endorsing any product or device described in this article.
Evidence from our latest study has demonstrated a cause and effect relationship between cell phone usage and poor semen quality, recognized as a common cause for male factor infertility.

This study was the next step in our quest to define the relationship between cell phones and fertility that we first demonstrated in 2007. Our observational research demonstrating a strong negative correlation between cell phone usage and semen quality made national headlines. In general, semen quality tended to decline as daily cell phone use increased. Men who said they used their phones for more than four hours each day had the lowest average sperm count and motility and the lowest numbers of normal, viable sperm.

Our research over the past decade has demonstrated that oxidative stress impacts sperm health and semen quality. Reactive oxygen species (ROS) are produced continuously by spermatozoa, and they are neutralized by antioxidants present in the semen. A state of oxidative stress is created when ROS production exceeds the antioxidant capacity. We hypothesize that radiation emitted by cell phones in talk mode causes oxidative stress in the spermatozoa, which leads to the observed decline in semen quality.

We recently undertook a pilot study to test our hypothesis in a controlled, in vitro setting. In this study, semen samples from 23 healthy donors and nine patients presenting to the infertility clinic were divided into a control group (unexposed) and exposed group. Samples in the experimental group were exposed to radiofrequency electromagnetic waves (RF-EMW) emitted from a cell phone in talk mode for one hour. The control samples were kept under identical conditions but without RF-EMW exposure.

We then measured the level of oxidative stress by measuring the level of ROS and the total antioxidant capacity in a combined parameter known as the ROS-TAC score, which we have demonstrated to be a more accurate measure of oxidative stress than either ROS or TAC alone.

The most remarkable finding was an increase in ROS levels in RF-EMW-exposed semen samples. This increased ROS production possibly could be due to stimulation of the spermatozoa’s plasma membrane redox system by RF-EMW or the effect of EMW on leukocytes present in the semen.

We also found a decrease in sperm motility, viability and ROS-TAC score in exposed samples. Short-term in vitro exposure to RF-EMW should not cause a decline in sperm concentration, and our data bore out this expectation. However, chronic oxidative stress may have deleterious effects on sperm concentration. Smoking and varicocele are two common real-life examples of oxidative stress-provoking situations that we believe are worth considering in an evaluation for male factor infertility.

We found no change in sperm DNA integrity in the EMW-exposed group compared with the unexposed controls. This lack of DNA damage may be explained by the brevity of exposure to cell phone radiation or by the scavenging of free radicals by antioxidants in seminal plasma.

Nonetheless, the results of our study were significant and striking. The data lead us to speculate that carrying a cell phone in a pocket in talk mode leads to deterioration of sperm quality through oxidative stress. Immature and abnormal spermatozoa may be more susceptible to these effects than are mature spermatozoa.

One of the main differences between our experimental conditions and real-life is the multiple tissue layers that separate the cell phone and the reproductive organs in vivo. Further studies are needed to allow valid extrapolation of the effects seen under in vitro conditions to real-life conditions, and these are already under way in our laboratory.
Ashok Agarwal, PhD, Rakesh Sharma, PhD, Edmund Sabanegh, MD

Failure to conceive naturally or with assisted reproduction despite the presence of morphologically normal motile sperm may be caused by poor sperm quality. Poor quality sperm includes DNA-damaged and apoptotic sperm.

Poly (ADP-ribose) polymerases (PARP) constitute a large family of 18 proteins. Poly (ADP-ribose) metabolism is critical in a wide range of biologic processes, including DNA repair and maintenance of genomic stability, transcriptional regulation, centromere function and mitotic spindle formation, centrosomal function, structure and function of vault particles, telomere dynamics, trafficking of endosomal vesicles, apoptosis, and necrosis.

PARP cleavage has been reported as an apoptosis or necrosis marker in other cell types, depending on the type of cleavage. This molecule also has been reported in testicular germ line maintenance and its development; however, reports of PARP’s presence on ejaculated sperm have not been established.

Our recent study conclusively establishes the presence of PARP-1 (~75 kDa) and its homologues PARP-9 (~63 kDa) and PARP-2 (~60 kDa) in both mature and immature human sperm and demonstrates that sperm from infertile men has lower PARP levels.

Using peptide mass fingerprinting analysis, we confirmed the presence of PARP immunopositive proteins PARP-1, PARP-9, and PARP-2.

Among PARP homologues’ many cellular functions, DNA damage detection and repair by PARP-1 and PARP-2 are the most important. DNA fragmentation is higher in infertility patients and in immature sperm, corresponding with the low PARP levels we observed in mature sperm of infertile patients compared with levels observed in the mature sperm of donors. These findings lead to speculation that the reduced levels of PARP homologues in mature sperm might be responsible for the ineffective protection against and repair of post-testicular sperm lesions.

PARP-2 may have a role in prevention of oxygen species/oxidative stress and chemical (staurosporine)-induced sperm cell apoptosis. The presence of the PARP homologue PARP-1 (~75 kDa) suggests its role in preventing damage of mature sperm.

Additionally, we documented low levels of PARP-1, -2, and -9 in the immature sperm fractions of both donors and infertile males, suggesting a potential role for these homologues during sperm maturation.

PARPs appear to have an active role in sperm cell physiology in preventing apoptosis and cellular DNA damage. Additionally, low PARP levels negatively affect sperm maturity, and potentially male fertility. PARP-1 and PARP-2 may have a role in conferring protection to the ejaculated sperm, particularly following exposure to oxidative stress and apoptosis inductors. The role of PARP-9 remains undefined.

Additional research is needed to describe the exact role of PARP homologues in sperm physiology and to confirm a causative relationship between low PARP levels and male fertility. We will continue to explore PARP’s precise role in the pathophysiology of male infertility with the ultimate goal of improving the medical management of male factor infertility and success rates for assisted reproduction technologies.

Possible mechanism of poly (ADP-ribose) polymerase (PARP) in cell survival or cell death. PARP together with other DNA repair enzymes can repair the DNA damage in the presence of low DNA damage and high available energy. In the case of high DNA damage (due to reactive oxygen species and lack of adequate energy) PARP can be cleaved and result in apoptosis or necrosis and eventually cell death.

PARPs appear to have an active role in sperm cell physiology in preventing apoptosis and cellular DNA damage. Additionally, low PARP levels negatively affect sperm maturity, and potentially male fertility.

Key Points:
The results from our study indicate an active role for PARPs in sperm cell physiology in preventing apoptosis and cellular DNA damage. We also demonstrated that low PARP levels negatively affect sperm maturity, and consequently, may affect male fertility.

PARP-1 and PARP-2 may have a role in conferring protection to the ejaculated sperm, particularly following exposure to oxidative stress and apoptosis inductors. The role of PARP-9 remains undefined.

Additional research is needed to describe the exact role of PARP homologues in sperm physiology and to confirm a causative relationship between low PARP levels and male fertility. We will continue to explore PARP’s precise role in the pathophysiology of male infertility with the ultimate goal of improving the medical management of male factor infertility and success rates for assisted reproduction technologies.
Seminal Total Antioxidant Capacity Identifies Infertile Men
Cleveland Clinic establishes TAC reference value

Ashok Agarwal, PhD, Rakesh Sharma, PhD, Edmund Sabanegh, MD

Development of a simple colorimetric assay that discriminates proven fertile from infertile men based on total antioxidant capacity (TAC) holds promise as a diagnostic and prognostic tool in the management of male infertility. Our research has established the normal range for seminal plasma TAC to differentiate infertile from fertile men.

Male factor infertility accounts for 30 to 50 percent of all infertility. Defective spermatozoal function is the most common cause of male infertility, resulting from testicular pathologies; genetic disorders; exposure to drugs, toxins or irradiations; or oxidative stress.

Oxidative stress results when levels of reactive oxygen species (ROS) exceed the available total antioxidant capacity. An increase in seminal ROS levels without a concomitant rise in antioxidant defenses leads to oxidative stress, which can cause damage to the spermatozoa, oocyte and embryo. Through the work of our laboratory and other leading infertility centers worldwide, the role of oxidative stress in the pathogenesis of male and female infertility and the failure of assisted reproductive techniques is now widely recognized.

Under normal conditions, seminal plasma has a very effective antioxidant system that provides the spermatozoa with a protective environment against oxidative stress. This system involves a combination of enzymatic (e.g., superoxide dismutase, catalase and glutathione peroxidase) and nonenzymatic (e.g., ascorbate, urate, vitamin E, pyruvate, glutathione, taurine, and hypotaurine) antioxidants that are very efficient under normal conditions in scavenging reactive oxygen species to maintain homeostasis in the cellular environment. This system breaks down under conditions that cause an excess of ROS or depletion of antioxidant levels.

Seminal total antioxidant capacity (TAC) is a measure of the seminal plasma’s ability to scavenge ROS and prevent oxidative stress. Several reports relate low seminal plasma TAC levels to male infertility, as well as in embryo culture media from the oocytes, cumulus cell mass, and spermatozoa used for insemination in conventional in vitro fertilization. The potential cellular sources of TAC in an intracytoplasmic sperm injection setting are the spermatozoa and the injected oocytes.

From the clinical perspective, an accurate assessment of the patient’s TAC is an important factor in the diagnosis and management of male infertility. Seminal TAC can be measured as the total available antioxidant protection in the seminal plasma by a variety of colorimetric assays. TAC measurement by colorimetric assay is simple, rapid and economical.

Despite the availability of an assay for TAC, studies have established a normal reference range. We recently published a study that identifies a cutoff value for seminal plasma TAC level that can differentiate infertile from fertile men with high sensitivity (76%) and specificity (64%) of the test and low operator variability.

The seminal plasma TAC assay is cost-effective, rapid and easy to perform. The establishment of a reference value now gives it clinical relevance as a quick in-office test for the evaluation of patients with male infertility.

Key Points:

- We recently published a study that identifies a cutoff value for seminal plasma TAC level that can differentiate infertile from fertile men with high sensitivity (76%) and specificity (64%) of the test and low operator variability.
- The seminal plasma TAC assay is cost-effective, rapid and easy to perform. The establishment of a reference value now gives it clinical relevance as a quick in-office test for the evaluation of patients with male infertility.

Despite the availability of an assay for TAC, studies have established a normal reference range. We recently published a study that identifies a cutoff value for seminal plasma TAC level that can differentiate infertile from fertile men with high sensitivity (76%) and specificity (64%) of the test and low operator variability.

In our study, the infertile patient group showed lower seminal plasma TAC levels compared to both the proven fertile and the sperm donor groups. We established the cutoff value of 1,420 micromoles of Trolox for seminal plasma TAC.

The seminal plasma TAC assay is cost-effective, rapid and easy to perform. The establishment of a reference value now gives it clinical relevance as a quick in-office test for the evaluation of patients with male infertility.

We recommend further studies to establish reference values for different clinical diagnoses of male infertility such as varicocele and infection as well as conditions related to poor semen parameters such as hyperviscosity and varying abstinence periods. Ongoing research using this assay may allow targeted antioxidant and other therapies to restore fertility.

Delicate balance between the formation of reactive oxygen species and the scavenging mechanism of the various enzymatic and nonenzymatic antioxidants. An imbalance between the two results in oxidative stress.
Penile prosthesis implantation is the oldest effective treatment for erectile dysfunction and it remains the only treatment that is potentially effective for all men with this disorder. Inflatable penile prostheses were introduced in the mid 1970s, and some three decades later these devices continue to undergo design improvements.

In 2001, American Medical Systems introduced two new surface coatings to their three-piece inflatable penile prosthesis product line. Parlyene, a substance with a low coefficient of friction, was added to the inner and outer silicone surfaces of the cylinders, while InhibiZone®, a minocycline-rifampin antibiotic coating, was added to all surfaces of the device except for tubing connectors and rear tip extenders. Based on bench testing, parlyene is expected to extend cylinder life, while InhibiZone® has already been shown to reduce the device associated infection rate by about one half.

The AMS 700 MS™ Series was introduced in 2006 (Figure 1). This device has a new pump with a built in lock-out valve to prevent auto inflation. The rear portions of the cylinders and the rear tip extenders are redesigned to facilitate implantation. Parlyene is still present on the silicone surfaces of the cylinders, and with the MS series it also has been added to the reservoir. Ultrex cylinders, introduced in 1990, have been renamed LGX. These remain the only penile prosthesis cylinders that produce like a normal erection regarding both penile girth and length expansion. In Figure 2, one LGX cylinder is shown deflated while its companion is shown inflated. Our work has shown that Ultrex (LGX) cylinders produce an average of 2 cm of length expansion. In our experience, 10-year survival free of mechanical failure for the AMS three-piece inflatable prosthesis is 81 percent. This was before the introduction of parlyene coatings, which are expected to result in even better future device durability.

What can we expect in the future? We have been working on novel penile prosthesis development. Technology being considered includes a motorized pump controlled either by a single click of an intrascrotal switch, or extracorporeally by a radiofrequency transmitter not unlike an automotive keychain device. Other technologies would involve replacement of saline, which currently fills these devices, with peptide hydrogels that reversibly solidify and liquefy within a physiologic temperature range. Clearly, penile prostheses will continue to supply an important need, and future technological improvements will allow this need to be fulfilled more effectively.

Key Point:
In our experience, 10-year survival free of mechanical failure for the American Medical Systems’ three-piece inflatable prosthesis is 81 percent. This was before the introduction of parlyene coatings, which are expected to result in even better future device durability.
Identifying Risk for Rejection of Transplanted Kidneys

Emilio Poggio, MD

Kidney transplantation continues to be the best therapeutic alternative for patients suffering end-stage renal disease, providing better quantity and quality of life than other forms of renal replacement therapy. However, organ shortage continues to be a major limitation and, therefore, prolonging the half-life of currently available transplanted kidneys is important.

Even when organs become available for a particular patient, current approaches to the medical management including the immunosuppression protocols are not individualized, and thus prospective recipients are treated equally regardless of their risk for poor or good outcomes. Patients at low risk for organ rejection, receive the same therapies as those at high risk, unnecessarily exposing them to the side effects related of these drugs. Despite significant advances in the development of newer immunosuppressive medications, the long-term success of kidney transplantation remains curtailed by graft failure due to immune-mediated injury to the transplanted organ.

This immune risk against transplant antigens cannot be fully predicted by routine laboratory testing, and personalization of care is difficult to provide. There is some evidence that the strength of the immunity against human organ transplants in general begins even before the actual time of transplantation, especially when patients are awaiting kidney transplantation during the dialysis treatment. For example, antibodies against common transplant antigens can be generated in patients with previous transplants, blood transfusions or pregnancy. Similarly, the immune system could build up immunity to transplant antigens through infections or other medical events (by cross-reactivity) common to patients on dialysis treatment. As a result, all patients on the waiting list for a kidney transplant are routinely tested for such alloantibodies (humoral arm of the immune system) by the Panel of Reactive Alloantibodies (PRA) test. The higher the number of pre-formed antibodies, the more difficult to find a matched organ with no antigens for the present antibodies.

Analogously, T cells reactive to transplant antigens (cellular arm of the immune system) also can be present or developed while awaiting transplantation and could have a negative impact in the post-transplant period. Thus, early identification of patients with such allo-reactive T cells (lymphocytes reactive to transplant antigens) could be important for risk-stratification of patients. Knowing who is at high or low risk for cellular immune mediated transplant injury may allow for individualization of immunosuppressive therapy, thereby allowing more immunosuppression to those at high risk and less to those at low risk.

In collaboration with Peter Heeger, MD, from Mount Sinai Medical Center, we developed a test to detect these T cells reactive (the Panel of Reactive T cells [PRT] assay); to transplant antigens analogous to the PRA test that detects antibodies to the same antigens. This test complements the already clinically available PRA test. We showed that the PRT assay provides complementary information to the PRA test and helps to identify high-risk kidney transplant candidates and thus predict post-transplant outcome.

We are currently improving this immune monitoring tool with the support of funding from the NIH and other organizations to further expand on these preliminary results and overcome the barriers to bring this promising biomarker tool to the bedside.

For references, please email the editor.

Key Point:

Through NIH funding, we are working with other organizations to improve the PRT assay to detect T cells reactive to transplant antigens. This tool complements the PRA test in identifying kidney transplant candidates at high risk for rejection.
Acute Humoral Rejection of Renal Allografts

Robert L. Fairchild, PhD

The detected incidence of antibody-mediated rejection of renal grafts is increasing, occurring in 6-9% of renal transplant patients. The presence of graft-reactive antibodies is associated with poorer renal graft function and survival. Acute rejection of renal allografts is also more severe in recipients with serum anti-donor class I HLA antibodies, and the presence of anti-HLA antibodies is implicated in late loss of kidney grafts. Importantly, acute humoral rejection (AHR) is resistant to the immunosuppressive strategies that inhibit T cell mediated rejection.

The increased detection of AHR is linked to newly developed approaches to monitor deposition of the complement split product C4d in the renal allograft as an indication of antibody binding to peritubular capillaries, and correlates with the presence of circulating donor-specific antibodies and with a poor graft outcome. The use of C4d as an indicator of antibody binding to renal allografts has led to the establishment of four diagnostic criteria for AHR of renal allografts: 1) clinical evidence of graft dysfunction (e.g., elevated serum creatinine levels); 2) histologic evidence of tissue injury (e.g., margination of neutrophils and macrophages in the peritubular capillaries); 3) demonstration of complement activation in peritubular capillaries (e.g., deposition of complement activation split products such as C3d or C4d); and, 4) serologic evidence of anti-donor antibody at the time of the biopsy.

Recognition of the high incidence of AHR has generated considerable interest in developing appropriate animal models to define mechanisms by which donor-specific antibody mediates graft tissue injury. To date, approaches in animal models that have been used to study the graft pathology induced during antibody-mediated rejection of allografts have been restricted to the passive transfer of antibody to graft recipients and to organ transplantation into donor-sensitized recipients. Both approaches have severe limitations in the study of AHR. A recent study from this lab reports that the rejection of orthotopically transplanted MHC-mismatched renal allografts by CCR5-deficient recipients is mediated by donor-reactive antibody with elevated serum creatinine. The rejected allografts had neutrophil and macrophage margination and diffuse C3d deposition in peritubular capillaries, interstitial hemorrhage and edema, and glomerular fibrin deposition. Circulating donor-reactive antibody titers were 40-fold higher in CCR5-/- vs. wild-type recipients.

Unlike other models, the donor-reactive antibody response is initiated about 4-5 days after transplantation and increases to high titers within a few days thereafter so that the pathology of rejection can be studied as the antibody response is induced and increases. These results indicate the rapid rejection of renal allografts in CCR5-/- recipients and that the histopathology of this rejection shares features of those observed during antibody-mediated rejection in human renal allografts. All of the BANFF criteria for determination of AHR are present in the CCR5-deficient renal allograft recipients supporting the use of CCR5-/- recipients as a novel model to study the development of donor-reactive antibody responses and AHR of renal allografts.

Key Point:

We have developed a novel model of antibody mediated rejection of kidney grafts in a mouse model that recapitulates the pathology observed in clinical grafts experiencing this rejection. This model will allow us to investigate mechanisms of antibody-mediated rejection and strategies to prevent it.

For references, please email the editor.
Do Patients Pay the Price When Residents Perform Their Urological Procedures?

Carvell T. Nguyen, MD, and J. Stephen Jones, MD, FACS

Adequate training in surgical procedures is a critical aspect of urological residency training. Despite the importance of textbook learning, observation, and the increasing use of simulated training environments (e.g., virtual or animal dry labs), resident performance of various procedures on actual patients still is required to develop proper skill and technique. A key question is whether patients experience greater pain or morbidity when residents rather than staff perform their procedures. The answer could have a significant impact on the way residency training is accomplished. Surprisingly, a search of the literature reveals a profound lack of data regarding the impact of urological resident training on patient care.

In order to answer this critical question, we have conducted and recently published several studies to determine whether pain experienced during office-based urological procedures was influenced by whether a staff urologist or resident performed the procedure. Cystoscopy, vasectomy, and prostate biopsy are all common and relatively low-risk procedures that can be performed in the office under local anesthetic. There is potential for significant pain and morbidity for patients if these procedures are performed by unskilled hands. This can lead to decreased patient confidence and tolerance, and limit the ability for young urologists to develop skills necessary for the care of their own future patients.

Patients scheduled to undergo cystoscopy, vasectomy or prostate biopsy were assigned to either the staff or resident based primarily on whether the resident was in the clinic at the time (the default is for the resident to perform the procedure if present in the clinic). The staff surgeon demonstrated the first procedure each month when a new resident rotated on service, and all resident procedures were directly supervised and physically assisted by the staff surgeon.

We found that when resident urologists performed cystoscopy, vasectomy, and prostate biopsy, the resulting pain scores were comparable to that of the staff surgeon (Table). As might be expected, pain scores for each procedure were generally slightly lower when the staff surgeon was the primary surgeon, but the differences with resident pain scores were not statistically significant for cystoscopy, vasectomy, or injection of the periprostatic block for prostate biopsy. The difference between staff and resident did reach statistical significance for ultrasound probe placement and biopsy, but the magnitude of the differences was minimal and therefore not likely to represent a major detriment to patients.

Furthermore, we found no significant differences in pain scores for any of the procedures when the data were stratified by year of resident training, suggesting that the technical maneuvers of cystoscopy, vasectomy, and prostate biopsy can be performed early in the training experience with proper instruction and oversight.

These data are the first in the literature to indicate that the training of residents in ambulatory urological procedures can be accomplished without compromising patient experience. However, it must be emphasized that proper instruction and supervision by an experienced staff urologist are critical to the process. Our findings suggest that prostate biopsy is technically more challenging than the other procedures and perhaps more difficult to teach. The implications of poor technique in this important cancer screening tool could extend beyond pain to a difference in diagnostic accuracy. As such, direct staff involvement is requisite for both resident education and maintenance of patient comfort.

**Key Point:**

Pain scores reported by patients undergoing cystoscopy, vasectomy and prostate biopsy were not significantly different when the procedures were performed by a staff surgeon versus a resident. Some statistical significance in pain scores was noted when ultrasound probe placement and biopsy were performed by a staff surgeon versus a resident. The difference, however, is not likely to represent a clinical impact to patients.

**Table: Summary of pain scores for urological procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Staff N</th>
<th>Resident N</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystoscopy</td>
<td>18.7</td>
<td>22.7</td>
<td>0.89</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>19.5</td>
<td>21.8</td>
<td>0.25</td>
</tr>
<tr>
<td>Prostate biopsy</td>
<td>403</td>
<td>249</td>
<td></td>
</tr>
<tr>
<td>Probe insertion</td>
<td>30.5</td>
<td>37.1</td>
<td>0.0004</td>
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<tr>
<td>Anesthetic injection</td>
<td>29.3</td>
<td>28.8</td>
<td>0.79</td>
</tr>
<tr>
<td>Biopsy</td>
<td>30</td>
<td>33.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Providing Screenings, Education and Treatment to Underserved Populations: The Minority Men’s Health Center and Health Fair

Charles S. Modlin, Jr., MD, FACS

Cleveland Clinic Minority Men’s Health Center (MMHC) is a nationally acclaimed, specialized center within the Glickman Urological & Kidney Institute. The MMHC is dedicated to reducing and eliminating health disparities in minority men – men who are more likely to suffer from higher incidence of and death rates from a variety of medical conditions. The MMHC is a unique community resource that serves as one of the first programs of its kind in the nation committed to providing comprehensive health access, treatment and education to historically underserved populations of both minority and non-minority men.

Through an integrated program of clinical patient-centered care, facilitated patient access, interdisciplinary research, patient and health provider education, mentorship, advocacy and extensive community outreach, the mission of the center is to eliminate health disparities in minority men. We strive to do this by not only treating preexisting medical conditions, diseases and disorders, but also by providing minority and underserved men with health education designed to prevent the onset of many conditions that may be preventable or controllable if recognized in early stages. This helps reduce morbidity and mortality associated with presentation of diseases/conditions in advanced stages.

The center’s annual Minority Men’s Health Fair provides both health education and the delivery of culturally sensitive free health screenings yearly to thousands of predominantly minority males. In April of this year, more than 2,000 minority men received a variety of free health screenings and health education at the 6th annual Minority Men’s Health Fair. More than 300 Cleveland Clinic and community volunteers, along with 150 Cleveland Clinic Departments/Institutes and community agencies/organizations rallied together to make the health fair a great success. The health fair benefits hundreds of minority and underserved men through the diagnosis of and then subsequent treatment of (in the twice weekly MMHC clinic) serious and previously undiagnosed medical conditions (e.g., prostate disease, prostate, colorectal and bladder cancer, hypertension, diabetes, kidney disease, hyperlipidemia, and other conditions).
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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 bisectedal 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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