Advances in multiparametric magnetic resonance imaging and the fusion of that information with real-time transrectal ultrasound imaging (termed MP-MRI-US fusion biopsy; see article on p. 30) have improved diagnostic accuracy for prostate cancer. This image shows a prostate cancer lesion identified using diffusion-weighted imaging. Reprinted from Natarajan S, Mark S, Margolis D, et al. Clinical application of a 3D ultrasound-guided prostate biopsy system. *Urol Oncol* 2011; 29(3):334-342. © 2011, used with permission from Elsevier.
Center for Chronic Kidney Disease
Pulmonary Hypertension and Kidney Disease: A Deadly Duo

Center for Genitourinary Reconstruction
Erectile Dysfunction Is a Major Cause of Peyronie Disease: A Personal View
Staged Buccal Graft Urethroplasty for Difficult Strictures

Center for Reproductive Medicine
Proteomics and the Future of Sperm Testing

Center for Endourology and Stone Disease
Renal Access for Percutaneous Nephrolithotomy: Where Are We Today?

Center for Female Pelvic Medicine and Reconstructive Surgery
Predictors of Pelvic Organ Prolapse Progression
Distribution and Homing of Bone Marrow-Derived Mesenchymal Stem Cells Following Postpartum Intraperitoneal Injection into LOXL1 Knockout Mice

Center for Renal and Pancreas Transplantation
Kidney Transplantation at Cleveland Clinic: A Global Resource
Impact of Low Testosterone in Renal Disease and Kidney Transplantation
A Surgical Approach to Patients with Intractable Nephrolithiasis

Center for Dialysis
Dialysis Therapies and Cleveland Clinic: Bringing Patients Back Home
Urgent-Start Peritoneal Dialysis at Cleveland Clinic: A Multidisciplinary Approach

Center for Pediatric Urology
The Changing Paradigm of Management of Children with Vesicoureteral Reflux
Transitional Urology Prepares Patients with Congenital Genitourinary Problems for Adult Care

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Dear Colleagues,

Welcome to the Winter 2015 issue of Glickman Urological & Kidney Institute's Urology & Kidney Disease News. As these pages demonstrate, 2014 was a banner year for our institute and its talented clinicians and researchers.

I am proud to report that our urology program was named the nation's best and our nephrology program was No. 2 in U.S. News & World Report's annual rankings of America's top hospitals. Our Urology Residency Program also was judged to be the country's finest in an assessment by the online physician network Doximity in collaboration with U.S. News & World Report. And the American Society of Hypertension accredited our Department of Nephrology and Hypertension as the first Comprehensive Hypertension Center in Northeast Ohio, and one of only 12 nationally.

These achievements are the result of a relentless drive for excellence by the programs' directors and the Urological & Kidney Institute's staff. I am pleased that their efforts have brought us recognition. Please be assured that we don't take the honors for granted, and we don't intend to rest on past accomplishments. Continuously improving our patients' medical and surgical care, conducting research that alters disease outcomes, and providing superlative training for the next generation of urologists and nephrologists will remain our top priorities.

Urology & Kidney Disease News offers a rich digest of what we've done and learned in the past year, and where we're headed. You’ll find comprehensive reports on:

• Surgical innovation, including intracorporeal hypothermia during robotic partial nephrectomy to preserve long-term renal parenchymal function; renal autotransplantation and pyelovesicostomy to resolve chronic pain in patients with intractable nephrolithiasis; and robotic radical perineal prostatectomy for localized prostate cancer.

• High-impact research that may lead to new treatment options, including tracking mesenchymal stem cells’ preferential homing to pelvic organs in a mouse model of pelvic organ prolapse; using proteomic studies to identify novel biomarkers for sperm dysfunction; and examining the effect of low testosterone in renal disease and kidney transplantation, as a disease severity indicator and a therapeutic target.

• Clinical best practices, such as our efforts to educate patients about peritoneal dialysis and home hemodialysis, and advice on how to transition adolescent patients with congenital genitourinary problems to adult care.

• Strategies to improve outcomes prediction in pelvic organ prolapse, after primary whole gland prostate cryoablation, and in salvage therapies for radioresistant prostate cancer.

This issue also brings you two thought-provoking prostate cancer articles — on our increasing use of brachytherapy (while other institutions are turning away), and on research that’s overcoming the negative perceptions of systemic chemotherapy for castration-resistant cases. And we offer progress reports on our kidney transplant program and our expansion of urology services in Las Vegas.

I hope you find UKD News informative and helpful in your practice. If we can assist in any way, please let us know.

Eric A. Klein, MD
Chairman
Glickman Urological & Kidney Institute
New Glickman Urological & Kidney Institute Staff

Jay Krishnan, DO, MBA, joined Cleveland Clinic Urology, Las Vegas, in 2014. Dr. Krishnan received his medical degree from the New York College of Osteopathic Medicine. He completed a urology residency at SUNY Downstate Medical Center, as well as a fellowship in pediatric urology at Vanderbilt University Medical Center. Dr. Krishnan's specialty interests include reconstructive urologic surgery and minimally invasive robotic surgery for kidney, bladder and prostate cancer.

Jeffrey Donohoe, MD, joined the Glickman Urological & Kidney Institute as an associate staff member in the Department of Urology in 2014. Dr. Donohoe received his medical degree from New York Medical College. He completed a urology residency at SUNY Downstate Medical Center, as well as a fellowship in pediatric urology at Vanderbilt University Medical Center. Dr. Donohoe’s specialty interests include urinary tract reconstruction for congenital bladder defects; male and female genital reconstruction; and hydronephrosis and obstructive uropathy.

Upcoming Events — Save These Dates

April 24, 2015
Ambulatory Urology Symposium
Course Co-Directors: Edmund Sabanegh Jr., MD, and J. Stephen Jones, MD, FACS

May 14-16, 2015
2015 Nephrology Update
Course Co-Directors: Brian R. Stephany, MD, and Sankar Navaneethan, MD

October 23-24, 2015
Seventh Annual International Symposium on Robotic Kidney and Pelvic Urologic Surgery
Course Director: Jihad Kaouk, MD

Please visit ccfcmes.org for more details about these events.
2014 Glickman Urological & Kidney Institute Achievements

Appointments

Stuart M. Flechner, MD, FACS — Board of Directors of the United Network for Organ Sharing; representative of the American Society of Transplant Surgeons on the American Transplant Congress Program Committee

Lawrence S. Hakim, MD — Sexual Medicine Society of North America’s representative to the 4th International Consultation on Sexual Medicine

J. Stephen Jones, MD, FACS — Associate Editor of the American Urological Association’s new Urology Practice journal

Manoj Monga, MD — Secretary-elect of the American Urological Association


Emilio Poggio, MD, FASN — American Society of Nephrology’s Transplant Advisory Group

Edmund Sabanegh Jr., MD — President-elect, Society for Study of Male Reproduction

Daniel Shoskes, MD — American Urological Association’s representative to the United Network for Organ Sharing

James Simon, MD — American Society of Nephrology’s Training Program Directors Executive Committee

George Thomas, MD — American Society of Nephrology’s Hypertension Advisory Group

Leslie P. Wong, MD, FASN — American Society of Nephrology’s Dialysis Advisory Committee

Hadley Wood, MD — Associate Editor of the new Urologic Congenitalism Section of Urology

Eric A. Klein, MD — Presidential Citation from the American Urological Association for innovative research in molecular markers in prostate cancer, leadership of Society of Urologic Oncology and creating a center of excellence at Cleveland Clinic; received the Huggins Medal from the Society of Urologic Oncology for his distinguished and notable career in urologic oncology, important contributions to the understanding and treatment of prostate cancer, and mentorship of many urologic oncologists

Robert J. Heyka, MD — Kidney Foundation of Ohio 2014 Person of the Year for outstanding dedication and service to the foundation’s mission

Department of Nephrology and Hypertension — accredited by American Society of Hypertension as the first Comprehensive Hypertension Center in Northeast Ohio and one of only 12 nationally

Renal transplant team — received the National Kidney Registry’s Excellence in Teamwork Award for its participation in “Chain 221,” the second-longest paired donor kidney exchange in the history of renal transplantation

Ashok Agarwal, PhD, Rakesh Sharma, PhD, and Sajal Gupta, MBBS — received Case Western Reserve University School of Medicine’s Scholarship in Teaching Award for making a positive impact on medical education and students’ careers, and for being part of the School of Medicine’s legacy of educational excellence

Hannah Kerr, MD — selected as the inaugural Andrew Novick Award recipient for best presentation at the 2014 Urologic Society for Transplantation and Renal Surgery Annual Meeting

Lawrence Hakim, MD — named 2014 Clinician of the Year by Cleveland Clinic Florida

Nitin Yerram, MD, and co-authors — won the British Journal of Urology International’s 2014 Coffey-Krane Prize, awarded to authors of an outstanding paper published in the journal who are trainees based in the Americas

Honors and Awards

Urology program — ranked No. 1 and nephrology program No. 2 in the nation in U.S. News & World Report’s 2014-2015 Best Hospitals survey

Urology Residency Program — ranked No. 1 in America in an assessment by the online physician network Doximity in collaboration with U.S. News & World Report

Dr. Klein (left) receives the American Urological Association’s Presidential Citation from AUA President Pramod Sogani, MD.
By Edmund Sabanegh Jr., MD

In 2014, U.S. News & World Report named Cleveland Clinic the No. 1 medical center in the nation for urology care. Of course, we are thrilled and humbled at the same time.

This marks the third time since 1990 that we have received the honor, having hovered near the top of the rankings most other years. With so many excellent organizations in the urology field, competition within the Top 10 is tight. Moving from second place to first is a difficult feat.

What helped Cleveland Clinic make the gain is our Patients First philosophy. Each of our nearly 150 team members in the Department of Urology tries to keep a razor-sharp focus on outcomes, patient safety and patient satisfaction. Each of us acknowledges the pride that comes with taking superb care of patients.

Putting patients first is the foremost discussion topic when we interview potential new team members, not simply their national or international urological expertise. We listen to what candidates’ colleagues say about their demeanor and bedside manner. We spend extensive time talking about Patients First during our employee orientation process. We wear the motto on our lab coats. And we make sure our team members embody it, by regularly analyzing patient survey data.

While we are honored by the recognition from U.S. News & World Report, the judging we ultimately value comes from our patients and their families.

Keeping patients first for the long term requires developing the next generation of urological treatments and training the next generation of urology caregivers. Cleveland Clinic’s Urology Residency Program has been among the most competitive in the United States, and in September 2014 it was ranked the nation’s No. 1 urology training program, in a physician survey conducted by Doximity and U.S. News & World Report.

Led by Cleveland Clinic urologist Steven Campbell, MD, PhD, who has had a lifelong commitment to education, and a cadre of dedicated medical educators, our training program attracts smart, competitive trainees who engage in a partnership with their instructors. During their six-year residency, trainees dedicate one year to urology research. Cleveland Clinic is one of only a few programs to retain research as part of its urology training. We know research is vital to our success in caring for patients and to propelling the field.

In light of our top rankings, some have asked what proven practices we will carry forward. I tell them that, other than maintaining our Patients First focus, our one constant will be driving change. Being named No. 1 is certainly not the time to settle for the status quo.

Pushing the envelope is in the DNA of all of us at Cleveland Clinic. We will continue to develop new and better ways of treating urologic disease and providing the highest level of patient care.

Is it important for us to maintain our No. 1 ranking? I think it is more important to maintain what the ranking represents: putting patients first so that Cleveland Clinic continues to be the destination of choice for quality of care, urologic outcomes and patient experience.

Dr. Sabanegh is Chairman of the Department of Urology in Cleveland Clinic’s Glickman Urological & Kidney Institute. He can be reached at sabanee@ccf.org or 216.445.4473.

We’re No. 1 ... by Putting Patients First

Key Point

Putting patients first in every aspect of medical care delivery — from employee hiring and training to treatment and research focus — is the key to Cleveland Clinic’s superior national ranking in urology.
By Jay Krishnan, DO, MBA

In 2013, Cleveland Clinic’s Glickman Urological & Kidney Institute began offering the expertise and innovative care of the nation’s top urology program to the residents of Las Vegas.

Cleveland Clinic Urology, Las Vegas provides patients with access to the skills, technology, research and treatment capabilities of Cleveland Clinic’s Department of Urology, whose services are ranked No. 1 in America in U.S. News & World Report’s 2014-2015 “Best Hospitals” survey. Our staff has recently expanded, and our services are growing.

Our office opened in April 2013 with three providers: Scott Slavis, MD; Laurie Larsen, MD; and Jennifer Urena, PA-C.

Dr. Slavis has practiced urology in the Las Vegas area for 25 years and developed the renal transplant program at Sunrise Hospital & Medical Center. Dr. Larsen served as a captain in the U.S. Army Reserve Medical Corps and has practiced urology with Dr. Slavis since 1994.

I joined Cleveland Clinic Urology, Las Vegas in July 2014 after completing my fellowship in advanced laparoscopy and robotics at Cleveland Clinic. I previously served as a General Medical Officer in the U.S. Navy for four years with deployments to Japan, Kuwait, Iraq and Afghanistan. After my military service, I completed my residency in urologic surgery at the University of Medicine and Dentistry of New Jersey.

I am excited about joining the Cleveland Clinic Urology, Las Vegas team, which is dedicated to providing leading-edge care. We will now be able to treat advanced urologic cancers and address complex urologic reconstructive challenges.

We plan to offer minimally invasive treatment options for bladder, prostate, ureteral and kidney cancers. We will also perform the complete range of reconstructive urology procedures, including neobladder implantation.

By instituting regular combined comprehensive cancer conferences with our colleagues at Cleveland Clinic’s main campus, we will provide our patients the most up-to-date urologic oncology care. The cancer conferences are multidisciplinary and occur monthly.

We also offer multiparametric MRI/ultrasound fusion biopsies for the advanced detection of prostate cancer. This new imaging technology significantly improves the localization and characterization of suspicious lesions by enabling targeted biopsies rather than standard six- or 12-core biopsies.

In addition to our close relationship with colleagues at Cleveland Clinic’s main campus, we also collaborate with our neurology colleagues at Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas. The center provides diagnosis and ongoing treatment for patients with cognitive disorders.

Our two centers share an electronic medical records system, which allows us to provide seamless care for patients with overlapping neurologic/urologic conditions.

Cleveland Clinic Urology, Las Vegas offers patients immediate access to the highest level of care, modeled on the same-day appointment system in use at other Cleveland Clinic locations.

“Our goals are to improve the quality of urology care in Las Vegas, to offer technologies not currently available here and to assist the medical community in taking care of more difficult cases,” says Dr. Slavis.

**Key Point**

New treatment options, same-day appointments and access to the expertise and innovative care of the nation’s top urology program are available at Cleveland Clinic Urology, Las Vegas.

Dr. Krishnan is an associate staff member of Cleveland Clinic’s Glickman Urological & Kidney Institute, practicing at Cleveland Clinic Urology, Las Vegas. He can be reached at krishnj2@ccf.org or 702.796.8669.
From Inspiration to Commercialization: How a Prostate Cancer Test Gets to Market

Mark Stovsky, MD, MBA

In November 2013, Cleveland Clinic announced a new spinoff company, Cleveland Diagnostics (CDx), with the objective of providing an institutional platform for increasing the accuracy of diagnostic tests for many types of cancer.

As Chief Medical Officer of CDx, Science and Technology Innovations Officer of Cleveland Clinic’s commercialization arm, Cleveland Clinic Innovations, and a staff physician within the Glickman Urological & Kidney Institute, I have enjoyed a front-row seat for CDx’s journey from concept to market and have learned several lessons along the way. Above all: Trust in Cleveland Clinic Innovations (CCI) to lead the way.

A New Approach to Diagnosis

The idea for CDx originated in 2013 and stemmed from the work of researchers at Cleveland-based AnalizaDx LLC, as well as physicians at Cleveland Clinic, Case Western Reserve University School of Medicine and the VA Boston Healthcare System.

To diagnose or assess the risk of cancer, scientists for years have focused narrowly on changes in the concentration of a single protein in biological fluids such as blood or urine or, alternatively, on genetic mutations. However, the diagnostic accuracy of single or multiple protein quantification tests has suffered from relatively poor sensitivity, specificity and predictive values, which limit clinical utility, while tests that identify multiple genetic mutations associated with cancer are difficult to transform into actionable results. These shortcomings result in poor clinical performance, an ineffective allocation of diagnostic resources, and substantial patient anxiety and dissatisfaction.

Our idea was to build a breakthrough biomarker platform that focuses on changes in the structure of certain proteins circulating in blood or other biological fluids to indicate the presence or absence of cancer. Proprietary tests, based on the novel Solvent Interaction Analysis (SIA) technology, would evaluate the structure of protein biomarkers and differentiate those produced by cancer in comparison with benign cells.

We achieved the potential for commercial success with the completion of an initial validation trial of the SIA technology in the diagnosis of prostate cancer. In this multicenter trial, the technology demonstrated favorable preliminary results. When compared with standard serum total prostate specific antigen (PSA) testing, the proprietary PSA/SIA (today called IsoPSA) test showed 100 percent sensitivity with no false negatives and approximately 80 percent specificity. Those results compare favorably with those of the traditional serum PSA test.

Further analysis of data from serum appeared to show similar diagnostic accuracy for prostate cancer. Other preliminary results in breast and ovarian cancer detection demonstrated that SIA potentially could be used as a platform technology to diagnose a broad spectrum of cancers.

Strong Guidance and Rigorous Review

We knew we had a product that could have an immediate impact. But the research findings, as well as the intellectual property implications of a multicenter discovery, required significant commercialization guidance from experts. In fall 2013, Cleveland Clinic Innovations professionals assessed the concept, and the framework for a spinoff company was born. The newly formed CDx would mesh the intellectual property and technology expertise of AnalizaDx LLC, the clinical bandwidth of Cleveland Clinic, and the commercialization capability and know-how of CCI to commercialize the novel cancer testing platform.

With the strategy in place, CDx underwent a rigorous review to assess important factors including the company’s commercial potential, the funding necessary to support a successful venture, the competitive and regulatory environments, and the time frame for bringing products to market. After formal approval by Cleveland Clinic and CCI leadership as well as CCI’s advisory board (which consists of outside advisors), CDx received initial seed funding and became the 65th CCI portfolio company.

INVENT Nurtures Spinoffs

While CDx’s journey to commercialization has at times been challenging — as is the case for most new medical companies and products — CCI has helped minimize problems through the use of its new INVENT™ process.

INVENT stands for Idea submission, Need assessment, Viability assessment, Enhancement, Negotiation and Translation. The INVENT process guides an inventor from conception to commercialization.

At Cleveland Clinic, each institute, including the Glickman Urological & Kidney Institute, is assigned an innovation manager. The manager acts as the CCI point of contact as an
invention is assessed by institute peers and CCI professionals, is further developed in one of four incubators (Medical Devices, Therapeutics & Diagnostics, Health Information Technology and Delivery Solutions), and is licensed to an industry partner or transitioned into a Cleveland Clinic spinoff company.

CDx continues to benefit greatly from CCI’s ability to identify an opportunity with broad institutional platform appeal, assess the myriad factors involved in the technology development and commercialization process, and develop a plan to bring a potentially groundbreaking technology from bench to market.

As with CDx, it all starts with an idea.

Dr. Stovsky is a staff member of the Department of Urology in Cleveland Clinic’s Glickman Urological & Kidney Institute and Science and Technology Innovations Officer of Cleveland Clinic Innovations. He can be reached at stovskm@ccf.org or 216.445.4096.

Urology Residency Training at Cleveland Clinic: Striving for Excellence

Steven C. Campbell, MD, PhD; Drogo K. Montague, MD; and Kenneth W. Angermeier, MD

Cleveland Clinic’s Urology Residency Program is celebrating the 60th anniversary of its 1954 founding and was recently named America’s No. 1 urology training program in a national assessment by the online physician network Doximity in collaboration with U.S. News & World Report.

This ranking is based in part on nominations by board-certified urologists and represents a great honor for all involved with our residency program.

The residency has a strong heritage and its leaders take pride in its efforts to provide an enriched training experience. The program’s strengths include:

• Diverse subspecialty representation, with dedicated leaders in all branches of urology who serve as mentors and help trainees build a career in whatever subspecialty they choose.

• A wide variety of challenging medical and surgical referral cases reflecting Glickman Urological & Kidney Institute’s international reputation as a provider of innovative, effective care.

Key Point

Cleveland Clinic’s Urology Residency Program seeks to provide a superlative education by offering residents a diverse and challenging clinical, surgical and research experience in a supportive mentoring environment.

• A large clinical volume available on Cleveland Clinic’s main campus and through our community hospitals, and our philosophy of placing trainees in the best clinical and educational settings within our healthcare system, wherever that might be.

• An appropriate balance among the three domains of urologic surgery: endourologic, open and minimally invasive. Our minimally invasive surgical team performs more than 1,000 procedures per year and is at the leading edge of the field. Exposure to vascular and open surgical cases remains strong due to our renal transplantation service, which resides within the Department of Urology, and the urology patients who are referred to Cleveland Clinic for major surgical challenges that still require an open approach.

• A healthy service/education balance that is supported by urology-focused nursing teams and physician extenders who perform routine preoperative evaluations and other activities. This allows our residents at all levels to be in the operating rooms or clinics every day.

• Extensive exposure to “nuts and bolts” urology that is built into our residency through a rotation at the Louis Stokes Cleveland VA Medical Center during the third year, and outpatient and ambulatory surgery rotations that take place throughout the training experience.
Intracorporeal Hypothermia During Robotic Partial Nephrectomy Using Renal Ice Slush

Jihad H. Kaouk, MD; Homayoun Zargar Shostari, MD; and Jay Krishnan, DO, MBA

The application of robotic technology to partial nephrectomy has allowed surgeons to re-create the principles of open surgery via a minimally invasive approach. Even larger deeply infiltrative tumors, or hilar tumors, can be treated with robotic partial nephrectomy (RPN). Excision of such tumors in a bloodless field requires that the renal hilum be clamped as in open surgery. However, prolongation of clamp time in such scenarios may be detrimental to long-term renal parenchymal function.

An ice slush packed around the kidney can safely and effectively cool the renal parenchyma during robotic partial nephrectomy (RPN), thereby preserving long-term renal parenchymal function.

The ice slush technique of renal hypothermia may be especially advantageous when a prolonged clamp time is anticipated during RPN.

Long-term functional outcomes assessment is needed to establish the utility of this approach to cool the renal parenchyma during RPN.

Renal parenchymal cooling has been used in open partial nephrectomy (OPN) to protect against such detrimental effects. When renal parenchymal temperatures of 5 to 20 degrees Celsius are achieved, renal metabolism is suspended and the

More than 40 graduates of Cleveland Clinic’s Urology Residency Program are currently active in academic medicine, almost all in top urology programs. Many serve in leadership roles within their institution or subspecialty. Many others have successful community practices.

• A dedicated research year that provides the opportunity to participate in a wide variety of well-established National Institutes of Health-funded research. Residents learn the fundamentals of trial design, statistics, and writing and presenting research data during this year, with opportunities to publish and to compete for the best urology fellowships.

• Exposure to the Case Based Urology Learning Program (CBULP), a medical educational tool being developed by the Department of Urology along with colleagues at University Hospitals’ Rainbow Babies & Children’s Hospital (Cleveland). The CBULP provides cases representing the most common and important clinical scenarios a urologist will encounter during routine practice. The goal is to illustrate the disease process and the fundamentals of clinical evaluation and management. Each case can be reviewed within 10 minutes via mobile electronic platforms. More than 240 CBULP cases have been produced, and the portfolio will eventually be aligned with the American Urological Association’s core curriculum.

Dr. Campbell is Vice Chair of the Department of Urology in Cleveland Clinic’s Glickman Urological & Kidney Institute, Director of the Urology Residency Program, Associate Director of Graduate Medical Education, and Professor of Surgery at Cleveland Clinic Lerner College of Medicine. He holds the Eric A. Klein Endowed Chair in Urologic Oncology and Education in the Glickman Urological & Kidney Institute. He can be reached at campbes3@ccf.org or 216.444.5595.

Dr. Montague is a staff member of the Center for Genitourinary Reconstruction in Cleveland Clinic’s Glickman Urological & Kidney Institute, Professor of Surgery at Cleveland Clinic Lerner College of Medicine, and Associate Director of the Urology Residency Program. He can be reached at montagd@ccf.org or 216.444.5590.

Dr. Angermeier is a staff member of the Department of Urology in Cleveland Clinic’s Glickman Urological & Kidney Institute, Director of the Center for Genitourinary Reconstruction, and Associate Director of the Urology Residency Program. He can be reached at angermk@ccf.org or 216.444.0415.

Key Points

An ice slush packed around the kidney can safely and effectively cool the renal parenchyma during robotic partial nephrectomy (RPN), thereby preserving long-term renal parenchymal function.

The ice slush technique of renal hypothermia may be especially advantageous when a prolonged clamp time is anticipated during RPN.

Long-term functional outcomes assessment is needed to establish the utility of this approach to cool the renal parenchyma during RPN.
nephrons can withstand as much as three hours of ischemia without permanent damage.

Although various techniques have been devised to induce renal hypothermia during minimally invasive nephron-sparing surgery, technical difficulties, lack of reproducibility and lack of surgical proficiency have restricted their utility.

**Details of the Hypothermia Technique**

Based on the principle of using ice slush as a cooling medium, we have developed an easily reproducible technique to achieve renal hypothermia during RPN. Data from 22 consecutive patients undergoing RPN (transperitoneal or retroperitoneal) in which warm ischemia times of more than 20 minutes were anticipated were collected prospectively in our Institutional Review Board-approved database. A single surgeon experienced in RPN performed all procedures. Our standardized technique of RPN has been modified to encompass renal hypothermia using intracorporeal ice slush.

After patient positioning and placement of ports, sterile ice slush is created in an ice slush machine and is prefilled in multiple modified syringes for subsequent ice delivery. The ice is delivered via a lateral 12 mm accessory port placed directly above the kidney. The renal parenchymal temperature is measured with a needle temperature thermocouple.

Once the kidney and Gerota fascia are completely mobilized and the pedicle is dissected out, the ice is delivered into the abdomen and packed around the kidney. The renal artery and renal vein are sequentially clamped and more ice is introduced. Renal and core body temperatures are monitored during the procedure. More ice slush is introduced and the kidney is allowed to cool further to parenchymal temperatures of 20 degrees Celsius or less. At this point, the ice slush overlying the renal tumor is cleared and the tumor is resected. Renorrhaphy is then performed. The remaining ice is suctioned or placed along with the specimen in the entrapment sac.

**Initial Patient Experience and Conclusions**

Twenty patients were included in our analysis. Median operative time was 220 minutes with median estimated blood loss of 100 cc. The median cold ischemia time was 28 minutes, and the median time for introduction of ice slush was seven minutes. The median nadir parenchymal renal temperature was 17 degrees Celsius with minimal median change in core body temperature (0.35 degrees Celsius). Median time to achieve nadir renal hypothermia was eight minutes.

In our initial experience we did not observe any intraoperative complications or an increase in our surgical margin rate. Median short-term (one-month follow-up) preservation of estimated glomerular filtration rate was 81 percent. Importantly, we did not observe any delay in return of bowel function beyond two days or any postoperative complications. Our patients’ median length of hospital stay was two days.

From our preliminary study it appears that our technique of intracorporeal renal cooling is safe and reproducible. Short-term renal functional outcomes are promising, but longer-term functional outcomes need further assessment.

This technique is likely to have clinical utility in RPN cases involving a large or complex renal mass when prolonged clamp time is anticipated.

Our technique was reproducible for adoption in both retroperitoneal and transperitoneal RPN approaches, essentially replicating cooling during OPN, albeit with a minimally invasive technique.

**Figure 1.** (A) 20-cc syringe is modified by cutting off the nozzle ends of the barrels and removing the rubber seal on the end of each plunger. (B) The syringe is filled by successive insertions into an ice slush container. (C) Ice slush is delivered by pushing the plunger. (D) Left to right: inflation pump, balloon dissector, 12 mm blunt-tip trocar, inflating syringe (E) and (F) Balloon inflation with inflation pump and syringe, respectively (G) Port placement for intracorporeal hypothermia during retroperitoneal robotic partial nephrectomy using renal ice slush. The 12 mm camera port is placed at the tip of the 12th rib. The robotic port is placed along the posterior axillary line slightly cephalad to the camera port. Along the anterior axillary line, the robotic port is placed at the level of the balloon port, and the assistant’s 12 mm port is placed four finger-widths below the robotic port. (H) The robot is docked directly over the head of the patient, parallel to the spine. (I) Postoperative view of the port sites.
New Robotic System Designed for Single-Port Surgery: First Clinical Experience

Jihad H. Kaouk, MD

Since the inception of minimally invasive surgery, physicians have been inspired to push the limits of available technology by devising new methods and instruments.

The evolution of a single-site technique in robotic surgery has resulted in the development of a device intended specifically for use during urologic procedures appropriate for a single-port approach, including laparoscopic single-site surgery (LESS).

LESS has the primary goal of accelerating patient recovery and improving quality of life, but its role has yet to be determined due to inherent challenges compared with standard laparoscopic techniques.

Key Point

The single-port robotic system allows for a less invasive approach to single-site surgery, enabling intracorporeal triangulation while eliminating the challenge of instrument clashing as seen with other single-site techniques.

RLESS Is More

In 2009, Cleveland Clinic’s Glickman Urological & Kidney Institute reported the first series of successful robotic single-site surgeries.\(^1\) We found that combining LESS with the robotic platform (RLESS) greatly enhanced our surgical capability by offering increased articulation and stability for precise suturing and dissection.

Since the publication of our initial series, multiple institutions have adopted the technique and published series of
Although the da Vinci® robotic surgical system has substantially improved our ability to perform single-site surgery, it was not originally designed for this purpose. As a result, its manufacturer has developed an innovative device specifically designed for RLESS (da Vinci Sp Surgical System, Model SP999).

In contrast to the original robotic design that necessitated the use of multiple separate ports, the SP999 requires only a single port to introduce the instruments and camera.

**Advancing Minimally Invasive Surgery**

Our institution was one of the first to utilize the new single-port robotic system in a clinical series.² We performed single-site robotic surgery using this novel technology in 19 patients, including 11 who underwent single-site robotic prostatectomy and eight who underwent single-site robotic nephrectomy. (Four of those eight patients underwent partial nephrectomy.)

There were no conversions to open, contemporary robotic or laparoscopic technique. Functional outcomes during a three-year follow-up period were comparable to those using standard techniques.

This new single-port robotic technology represents a step forward in minimally invasive surgery. It is unique as it allows for intracorporeal triangulation while eliminating the instrument clashing that is observed with other methods of single-site surgery.

**References**


Robotic Radical Perineal Prostatectomy: Potential Advantages of a New Approach

Jihad H. Kaouk, MD; Kenneth Angermeier, MD; and Oktay Akca, MD

At Cleveland Clinic’s Glickman Urological & Kidney Institute, we have explored the feasibility of robot-assisted radical perineal prostatectomy (RPP) with its inherent advantages of more direct access to the prostate and a small incision.

Since Young first described it in 1905, open RPP remained the most common surgical approach for the treatment of prostate cancer until the mid-1970s.

Urologists discontinued common performance of RPP due to concerns about the perineal anatomy; urologists are not generally familiar with the perineum since they routinely operate in the retropubic space and may be uncomfortable when operating close to the rectum. Additionally, the perineum is a deep and narrow space compared with the retropubic route.

Millin initially described the retropubic technique in 1945. Walsh et al. redefined the anatomical approach, applying the techniques of cavernous nerve sparing in the 1980s. For open surgery, the retropubic approach currently represents the preferred technique of most urologic surgeons based on habit rather than on evidence-based medicine.

Although the most widely used approach for open radical prostatectomy is the retropubic approach, there are no randomized studies demonstrating its superiority over the...
perineal approach in terms of cancer control and continence rates. Reported advantages of the perineal approach include shorter operative time and hospital stay, lower cost, and lower rates of postoperative urethral anastomosis stricture and inguinal hernia, owing to the lack of dissection and incision of the dorsal vascular complex, less blood loss and a lower rate of transfusion.

Rethinking RPP

Robot-assisted laparoscopic radical prostatectomy (RALP) was first described in the early 2000s and currently represents the most commonly performed surgical approach for the treatment of prostate cancer in the United States. The increase in RALP can be attributed to its short learning curve and the advantage of its articulating design over laparoscopy.

We wondered whether similar advantages could exist when using the robot specifically for RPP, with the hypothesis that robotic instruments could overcome tricky points of open RPP, such as working in a deep and narrow surgical area.

We initially developed a cadaver model to examine the applicability of the da Vinci robotic surgical system for RPP. We completed all steps of the nerve-sparing radical prostatectomy operation using five cadavers.3

After obtaining Institutional Review Board approval for robotic RPP, we selected for the first procedures those patients diagnosed with localized prostate cancer and a risk for lymph node positivity of not more than 4 percent.

First Experience and Conclusions

The initial patient previously had undergone a total resection of his rectum to treat rectal cancer and had received pelvic radiotherapy. He was therefore living with an ileostomy. He also had mesh on the anterior abdominal wall owing to multiple hernia repairs.

Robotic RPP was completed successfully without complications, with an estimated blood loss of 50 cc. The patient was discharged on postoperative day one and was immediately continent when his urethral catheter was removed one week after surgery (Figures 1-4).

The potential technical advantages of robotic RPP over open RPP include the magnified view as well as the long, articulated robotic instruments, which may help minimize the difficulty of performing a procedure in such a narrow and deep surgical field.

In our initial patient, we were able to complete the procedure with an incision just large enough (4 cm) for specimen extraction. Minimizing the incision could also decrease postoperative pain and analgesia requirements.

In comparing robotic RPP with standard RALP, a perineal approach provides more direct access to the prostate than does the anterior abdominal wall, which allows for elimination of the first three steps commonly done in RALP (bladder mobilization, endopelvic fascia incision and dorsal vein complex dissection). Elimination of these steps could result in shorter operative time and less blood loss.

Robotic RPP eliminates risks of injury to abdominal organs and vessels, given its extraperitoneal nature. It might also be useful in those patients who have undergone a previous abdominal operation, similar to our initial patient and those who are severely obese.

In conclusion, the intersection of the da Vinci robotic surgical system and a natural anatomic approach to radical perineal prostatectomy might provide a new minimally invasive solution for patients diagnosed with localized prostate cancer.

Dr. Kaouk is Director of Cleveland Clinic Glickman Urological & Kidney Institute’s Center for Robotics and Laparoscopic Surgery and is the Urological & Kidney Institute’s Vice Chair for Surgical Innovations. He is Professor of Surgery at Cleveland Clinic Lerner College of Medicine. He can be reached at kaoukj@ccf.org or 216.444.2976.

Dr. Angermeier is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology and Director of the Center for Genitourinary Reconstruction. He can be reached at angermk@ccf.org or 216.444.0415.

Dr. Akca is a research fellow in the Department of Urology. He can be reached at akcao@ccf.org.
Figure 1. Exaggerated lithotomy position. Figure 2. Robot docking, approaching from head and passing between legs. Figure 3. Incision closure. Figure 4. Robotic RPP specimen.
Partial Nephrectomy: Saving as Many Nephrons as Possible

Steven C. Campbell, MD, PhD

One of the primary goals of partial nephrectomy (PN) is to preserve as much renal function as possible. This is particularly important in patients with imperative indications such as a solitary kidney or pre-existing chronic kidney disease (CKD).

Factors that can influence ultimate renal function after PN include the quality of the nephrons prior to surgery, the quantity of nephrons preserved, and the type (warm versus cold) and duration of ischemia.

A Flawed View of Ischemia Time’s Significance

The quality of the nephrons is determined by the patient’s age and the presence of comorbidities such as diabetes, and is essentially nonmodifiable. Early studies reported an association between warm ischemia time and increased incidence of CKD, and a cause-and-effect relationship was presumed, expressed by the catchphrase “every minute counts.” However, these studies were inherently flawed because they failed to incorporate all the potentially relevant contributing factors, most notably, the quantity factor, which is the volume of nephron mass preserved by the procedure. When this factor is included in the analyses, ischemia time loses all significance unless it is warm and prolonged (> 25 minutes).

Stated more simply, these studies have shown that almost all preserved nephrons recover completely from the ischemic insult as long as limited warm ischemia or hypothermia is applied. How can we optimize the quantity factor — the number of nephrons saved by the procedure?

Studying the Impact of Surgical Precision on PN Outcomes

The number of nephrons saved during PN is determined by the precision with which we excise the tumor and reconstruct the kidney. Some have argued that this precision is also a nonmodifiable factor because it is largely influenced by tumor size and location. Based on this line of reasoning, functional outcomes after PN would be mostly out of our control as surgeons, as long as we avoid extended warm ischemia. But is this really true?

We recently studied the precision of tumor excision and reconstruction in a series of 122 patients with conventionally clamped PNs at our center, including a representative mix of cases with cold ischemia (N = 50) and warm ischemia (N = 72). Forty-five patients (37 percent) had a solitary kidney.

Key Points

- The quality of the nephrons determines the baseline renal function and is essentially nonmodifiable.
- Ischemia can impact functional recovery, but only if warm and extended.
- The quantity of preserved nephrons correlates directly with functional recovery after partial nephrectomy.
- Precision of tumor excision and renal reconstruction to save as much vascularized parenchyma as possible is critically important and can be optimized through the use of high-quality preoperative and intraoperative imaging and meticulous surgical technique.

Volumetric computed tomography (CT) scans were used to measure the volume of vascularized normal parenchyma before and four to 12 months after surgery as previously described. We presumed that an “ideal PN” would be associated with the loss of an approximate 5 mm rim of normal parenchyma due to tumor excision (some parenchyma is removed along with the tumor to avoid a positive margin) as well as devascularization of a modicum of adjacent parenchyma (related to capsular closure to minimize the risk of postoperative leak and bleeding).

Figure 1 illustrates our estimate of the amount of parenchyma and tumor that would be lost during PN for an anteriorly located, intrinsic tumor, and includes some radially located tissue that would be compromised in this setting. After subtracting the volume of the tumor, the amount of parenchyma that would be lost with an ideal PN was then estimated. We defined precision of tumor excision and reconstruction as the amount of vascularized parenchyma actually saved divided by the amount that would have been saved with an ideal PN.

In our series, the median value for surgical precision was 93 percent, demonstrating that most PNs approximated the best-case scenario in terms of preservation of nephron mass. On univariate and multivariate analysis, the only factor that correlated with surgical precision was the presence of a solitary kidney, while tumor size and complexity, type and duration of ischemia, and other factors failed to correlate.

Surgical Precision Is Modifiable and Important

Our data suggest that precision was highest when it was at a premium (i.e., in patients with a solitary kidney), likely related to the recognized need to preserve as much renal parenchyma as possible given the absence of a contralateral kidney. In the end, surgical precision appears to be a modifiable factor, and it appears to be the most important factor for determining ultimate renal function after PN.
Our perspective is that high-quality preoperative imaging, intraoperative ultrasonography and operating within a bloodless field can all facilitate surgical precision.

Efforts to optimize surgical precision will be important moving forward. They could include energy-based resection and hemostatic agents that might preclude the need for capsular reconstruction; further improvements in perioperative imaging; and selective utilization of tumor enucleation.

Dr. Campbell is Vice Chair of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology, Director of the Urology Residency Program, Associate Director of Graduate Medical Education and Professor of Surgery at Cleveland Clinic Lerner College of Medicine. He holds the Eric A. Klein Endowed Chair in Urologic Oncology and Education. He can be reached at campbes3@ccf.org or 216.444.5595.

Figure 1. Volumetric CT to measure the amount of parenchyma that would be lost during an ideal PN for an anteriorly located, intrinsic tumor. The kidney is viewed from anterior and medial aspects. Summation of areas at 3 mm intervals is utilized to obtain volume estimates as previously described.
Robotic Radical Cystectomy with Intracorporeal Urinary Diversion: A New Horizon

Homayoun Zargar Shostari, MD; Vishnuvardhan Ganesan, BS; and Georges-Pascal Haber, MD, PhD

Despite the decline in morbidity and mortality of open radical cystectomy (ORC) during the past two decades, the high rate of perioperative complications remains a challenge for clinicians. After a rocky start with a technically challenging laparoscopic approach, the robot-assisted procedure offered a new horizon.

Expanding on the experience gained with robotic radical prostatectomy, robotic radical cystectomy (RRC) has gained momentum as an alternative to the open approach. Long-term oncologic outcomes with RRC are equivalent to those with ORC.

However, recent prospective data showed that RRC was not superior to ORC in terms of complications and was associated with increased cost. Even though the cystectomy was done robotically, the diversion was performed extracorporeally through an open approach, diluting the advantages of minimally invasive surgery.

Improving RRC Outcomes Through Standardization

Our experience with RRC and intracorporeal diversion has been encouraging.

Standardizing our technique and defining the steps for intracorporeal ileal conduit and intracorporeal neobladder have allowed us to improve both the intraoperative and postoperative outcomes.

Since the refinement of our technique, we have performed more than 70 RRCs with intracorporeal diversion. The median blood loss for our series is 300 cc. The overall 90-day complication rate is approximately 50 percent, with a 20 percent rate of high-grade complications (Clavien III/IV) and a 90-day mortality rate of 2 percent. The median time to full diet is 5.5 days, and median hospital stay is seven days.

In comparing the overall cost of our RRCs to ORCs, the overall cost is approximately $2,000 less for the robotic group, despite the higher direct operating room (OR) cost. The lower cost is mainly due to reductions in length of stay and in the rates of major complications and secondary procedures. Although OR time and minor perioperative complications were comparable between RRC and ORC, blood loss, transfusion rate, the rate of major perioperative complications, length of stay and the rate of readmissions were superior with RRC.

Reducing Paralytic Ileus Incidence

More recently, we have modified our perioperative care pathways for patients undergoing RRC. In an effort to further reduce the incidence of paralytic ileus, we have adopted a multimodal opioid-sparing approach to postoperative analgesia. In our early experience, the combination of intraoperative injectable liposomal bupivacaine, regular acetaminophen and ketorolac tromethamine has enabled us to minimize and in some cases eliminate the need for narcotic analgesia.

The minimally invasive approach is only one component of enhanced recovery after surgery (ERAS) for RRC. Robotic radical cystectomy in combination with other components of ERAS such as early feeding, early mobilization and opioid-sparing multimodal analgesia is likely to become the gold standard for performing RRC in the future.

RRC with intracorporeal urinary diversion has enabled us to decrease the morbidity associated with this major procedure without compromising oncologic outcomes. Its widespread use would not be a surprise but a natural evolution.

Key Points

- Oncologic outcomes with robotic radical cystectomy (RRC) with intracorporeal diversion are equivalent to those with open radical cystectomy while associated with reductions in the rates of morbidity and major complications and length of stay, resulting in lower cost.

- In an effort to reduce the incidence of paralytic ileus following RRC, an opioid-sparing approach to postoperative analgesia is often possible.

Dr. Zargar Shostari is a clinical fellow in Cleveland Clinic’s Glickman Urological & Kidney Institute. He can be reached at zargarh@ccf.org or 216.445.1172.

Mr. Ganesan is a medical student at Cleveland Clinic Lerner College of Medicine. He can be reached at ganesav@ccf.org.

Dr. Haber is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology. He can be reached at haberg2@ccf.org or 216.445.4781.
Figure 1. Intracorporeal reconstruction of the neobladder.

Figure 2. Intracorporeal ureteroileal anastomosis.
Emerging Technologies in Radiation Therapy May Improve Tumor Control in Prostate Cancer

Rahul Tendulkar, MD

During the past decade, two technologies have emerged that may change the future of external beam radiation therapy for prostate cancer: stereotactic body radiation therapy (SBRT) and proton beam therapy (PBT).

External beam radiation therapy has been utilized in the treatment of prostate cancer since 1904, less than a decade after radiation was first discovered by Wilhelm Roentgen in 1895.

Numerous technological advancements in therapeutic radiation were made in the ensuing decades, including the discovery of cobalt-60, the development of the linear accelerator, the invention of the computed tomography scan, the utilization of beam modulation to shape radiation dose away from normal organs, and the incorporation of image guidance with real-time tumor tracking.

Dose-escalated, intensity-modulated radiation therapy (IMRT) with daily image guidance, delivered during several weeks of treatment, has been established as the current standard of care based on numerous publications demonstrating a superior toxicity profile and tumor control rate compared with older techniques.

SBRT and PBT are forms of external beam radiation that have theoretical advantages over IMRT.

SBRT Reduces Treatment Time

As an alternate technique to deliver hypofractionated radiotherapy to the prostate, SBRT involves immobilization of the patient and the target to deliver high doses of precise radiation therapy. The treatment is typically delivered in five fractions, significantly shortening the overall treatment time compared with conventional IMRT, which can require as many as nine weeks of daily sessions.

The rationale for using SBRT is based on radiobiologic studies that suggest that most prostate cancers have a low “alpha/beta ratio” and an enhanced therapeutic ratio when higher daily doses are used. In addition, SBRT may be more cost-effective and convenient for patients.

Due to the relatively recent adoption of SBRT in clinical trials, long-term outcomes data are now emerging and suggest a favorably low rate of late toxicities and similar efficacy to IMRT or other treatments for early-stage prostate cancer. Unfortunately, no randomized trials have been conducted to compare SBRT with other modalities.

Theoretical Advantages, Barriers to PBT Use

PBT is a technology that has been used to treat prostate cancer since 1976. Protons are heavy charged particles with a very different radiation dose distribution compared with X-ray photon-based therapy.

Unique to PBT is the Bragg peak, which is the deposition of a burst of energy at the tail end of a proton’s range. This physical property allows for the relative sparing of the radiation dose to normal tissues beyond the Bragg peak, potentially reducing the toxicities to those organs.

Unfortunately, the theoretical advantages of PBT have not been clinically observed to date in the treatment of prostate cancer.

One large study utilizing the National Cancer Institute’s Surveillance, Epidemiology, and End Results database demonstrated that patients treated with PBT actually experienced more gastrointestinal (GI) toxicity compared with IMRT. This excess of GI toxicity may be explained in part by the lack of available methods to actively modulate the dose intensity of a proton beam (“active scanning”), which is yet another emerging technology itself.

Another potential barrier to the widespread adoption of PBT is the high acquisition cost of a proton beam unit, as well as the higher cost of a treatment course to patients and insurers. One study estimated the median Medicare reimbursement rate to be approximately 75 percent higher for PBT than for IMRT.

Fortunately, randomized trials comparing PBT with IMRT are underway, and these studies will be extremely valuable in determining the relative efficacy of each modality with regard to tumor control, toxicity, quality of life and cost.

In summary, both SBRT and PBT are encouraging technologies that will likely shape the future of radiation treatment delivery for prostate cancer. Ongoing clinical trials will be important to determine the relative value of these emerging technologies in the evolving healthcare economic climate.

Dr. Tendulkar is an associate staff member of Cleveland Clinic’s Department of Radiation Oncology. He can be reached at tendulr@ccf.org or 216.445.9869.

Key Points

- Stereotactic body radiation therapy (SBRT) and proton beam therapy (PBT) are emerging forms of external beam radiation therapy for the treatment of prostate cancer.
- A greater biologic dose of radiation, delivered in fewer sessions, is possible with SBRT, which may enhance disease control while lowering treatment costs compared with intensity-modulated radiation therapy.
- PBT has the theoretical advantage of reducing dose delivery to healthy tissue surrounding the prostate.
Use of Salvage Therapies in the Treatment of Radioresistant Prostate Cancer

By Nic Muruve, MD

The treatment of locally recurrent prostate cancer after radiation therapy is difficult, as an ideal option remains elusive. The current treatment options include surgical removal, additional radiation therapy, ablative therapies (cryoablation, high intensity focused ultrasound) or observation with androgen ablation. All these options carry significant morbidity that impacts patients' quality of life. The only option that minimizes functional complications is observation and expectant androgen ablation. This is not a curative choice, however, and if the patient is interested in eradication of the tumor, one of the other more invasive options must be undertaken.

Very little data exist on the optimal treatment. Most retrospective studies report a prostate specific antigen (PSA) control rate of approximately 50 percent at two years. As a result, most urologists tend to recommend what is perceived to be the least invasive treatment: ablative therapies.

Salvage prostatectomy was always considered the most invasive option, but the advent of robotics in surgery has greatly diminished complications.

Comparison of Prostatectomy and Cryotherapy Outcomes

We reviewed oncologic outcomes and toxicity in patients who underwent either salvage prostatectomy or cryotherapy treatments at Cleveland Clinic Florida to determine if robotic salvage prostatectomy could offer similar outcomes to cryoablation, a procedure that has been presumed to be less morbid than surgery.

We reviewed cases from January 2004 to June 2013 and identified a total of 23 salvage procedures. Six of those patients underwent salvage robotic prostatectomy while 17 underwent salvage cryotherapy.

Patients who were considered for salvage therapy had localized disease at presentation, a PSA < 10 at recurrence, life expectancy > 10 years at recurrence and a negative metastatic workup. Patients were followed postoperatively to observe for cancer progression and any toxicity of treatment or complications. The mean follow-up period for salvage cryotherapy patients was 14.1 months and for prostatectomy patients was 7.2 months.

The incidence of disease progression was 23.5 percent and 16.7 percent after salvage cryotherapy and prostatectomy, respectively. The overall complication rate also was 23.5 percent after salvage cryotherapy versus 16.7 percent after prostatectomy, with the most frequent complication after salvage cryotherapy being urethral stricture and after salvage prostatectomy being severe urinary incontinence.

There were no rectal injuries with salvage prostatectomy and only one rectourethral fistula in the cohort after salvage cryotherapy. Patients who underwent salvage cryotherapy were statistically older and had a higher incidence of hypertension than did the salvage prostatectomy cohort.

Review Identifies Advantages

Our outcomes review found that salvage procedures were generally safe and effective. Both salvage cryotherapy and salvage prostatectomy allow for adequate cancer control with minimal toxicity.

The complication rates for salvage robotic prostatectomy appeared no worse than for patients treated with salvage cryoablation. Robotic salvage prostatectomy potentially has fewer local complications (stricture disease) than does cryotherapy, and urinary incontinence can be managed with new options (e.g. artificial urinary sphincter implants), enabling us to treat patients’ disease while preserving their quality of life.

At Cleveland Clinic Florida we are further analyzing these encouraging results to determine if a definitive advantage of one procedure over the other exists. We believe this will lead to better management of patients diagnosed with locally recurrent prostate cancer after radiation therapy.

Dr. Muruve is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology who practices at Cleveland Clinic Florida. He can be reached at muruven@ccf.org or 954.659.5188.
Determining Biochemical Success Following Primary Whole-Gland Prostate Cryoablation

David A. Levy, MD; Ahmed El-Shafei, MD; and J. Stephen Jones, MD, FACS

Although whole-gland cryosurgical ablation to treat clinically localized prostate cancer is recognized as a safe procedure, there are no established biochemical standards defining treatment success, as exist for radiation therapy and prostatectomy.

We have conducted numerous studies during the past six years in an effort to identify an evidence-based definition of treatment success for prostate cryoablation. We have utilized the national Cryo On-Line Database (COLD) Registry as well as data from Cleveland Clinic patient populations to achieve our goal. A recent publication from the COLD Registry represents the culmination of our efforts to date.

Methodology for Evaluating PSA Endpoint

From the COLD Registry we reviewed hormone-naïve patients who underwent primary whole-gland cryoablation, all of whom had a minimum of five years of follow-up data. None of the cohort received adjuvant therapy of any kind during the follow-up period.

We studied variables of interest including age, prostate specific antigen (PSA) level at time of diagnosis, Gleason score, clinical T stage and all postoperative PSA values.

Patients were stratified according to the D’Amico risk criteria. We studied biochemical progression-free survival (BPFS) at 0.1 ng/mL PSA increments for the intermediate risk category (471 men), aiming to identify a statistically significant PSA endpoint of biochemical success. We plotted Kaplan-Meier estimates of five-year BPFS using the Phoenix definition. Cohort demographics are listed in Table 1. We determined hazard ratios (HR) based on 0.1 ng/mL nadir PSA increments and analyzed failure rates.

Results and Survival Impact

A total of 891 (74.25 percent) of 1,111 patients achieved a nadir PSA < 0.4 ng/mL, which correlated with five-year BPFS rates of 90.4 percent, 81.1 percent and 73.6 percent for low, intermediate and high risk, respectively (Figure 1).

As shown in Table 1, 24-month biochemical failure rates in patients who had a PSA nadir > 0.4 ng/mL were significant, regardless of risk group. Moreover, patients who had a nadir PSA < 0.3 ng/mL had similar outcomes compared with those who had a PSA nadir < 0.4 ng/mL, with five-year BPFS rates of 92.2 percent, 81 percent and 77 percent for low-, intermediate- and high-risk patients, respectively (Table 1).

Our analysis failed to reveal a statistically superior PSA nadir endpoint compared with the < 0.4 ng/mL value (HR 5.649 [95 percent confidence interval (CI) 4.33-7.38], p < 0.0001).

PSA Nadir Guides Ongoing Treatment

To the best of our knowledge, our results convey the first evidence-based study for definition of biochemical success in patients who underwent primary whole-gland cryoablation of the prostate. A nadir PSA < 0.4 ng/mL is the best cutoff point for biochemical success, with no statistical advantage of using a lower PSA nadir.

Patients with a nadir PSA > 0.4 ng/mL showed unacceptable biochemical progression at 24 months in all risk categories, which precludes using a higher-nadir PSA endpoint. Consideration of post-treatment biopsy in patients whose PSA fails to reach that nadir may help direct management to either salvage local therapy or evaluation of possible metastasis if local control is confirmed.

Key Points

Unlike radiation therapy and surgical extirpation for prostate cancer, cryosurgery has lacked an established biochemical standard that defines treatment success.

Utilizing the Cryo On-Line Database Registry and patient treatment data from our institution, we developed an evidence-based definition of biochemical success: nadir prostate specific antigen level < 0.4 ng/mL.

Biopsy should be considered for patients who fail to reach that nadir following cryosurgery, in order to inform ongoing treatment decisions.

Dr. Levy is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology. He can be reached at levyd3@ccf.org or 216.692.8900.

Dr. El-Shafei is a research fellow in Cleveland Clinic’s Education Institute. He can be reached at el-shaa@ccf.org.

Dr. Jones is President, Cleveland Clinic Regional Hospitals and Family Health Centers, Professor of Surgery at Cleveland Clinic Lerner College of Medicine and holds the Leonard Horvitz and Samuel Miller Distinguished Chair in Urological Oncology Research. He can be reached at joness7@ccf.org or 216.986.4421.
Reference

During the past five years, treatment options for men with advanced prostate cancer (PCA) have changed dramatically with the introduction of immunotherapy, novel adrenal and androgen receptor targeted agents, and the use of alpha emitters. Despite the uniqueness of some of these approaches, the role of chemotherapy in the management of this disease has gained momentum with the recent results from a large North American intergroup trial. ECOG 3805, also known as the ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED), evaluated the role of upfront chemotherapy in men with metastatic disease who need androgen deprivation therapy (ADT).2

The Evolving View of Chemotherapy in PCa

Historically, the use of chemotherapy in PCa has faced significant challenges. Among these, who should have responsibility for patient oversight has been the biggest one. Should patients with advanced disease be managed by urologists or medical oncologists? When should a urologist refer a patient to a medical oncologist? Although these questions can be answered in many ways, there is now recognition that men with advanced PCa benefit from a multidisciplinary treatment approach. Fueling the debate is the fact that chemotherapy has traditionally been reserved for men with advanced disease who become castration-resistant — a patient population managed by medical oncology.

Myths surrounding chemotherapy relate to its side effects and potential detrimental impact on quality of life (QOL), its supposedly questionable activity in PCa and the perception that it should be used as the last treatment choice after everything else has failed. It certainly did not help that trials in the late 1990s evaluating mitoxantrone-based chemotherapy in castration-resistant disease failed to show survival benefit.3,4

Chemotherapy Improves Overall Survival in Castration-Resistant Prostate Cancer

Perhaps one of the most important years in PCA was 2004, when two well-conducted randomized phase 3 clinical trials (SWOG 9916 and TAX327) evaluating docetaxel-based chemotherapy in men with metastatic castration-resistant prostate cancer (mCRPC) led to the Food and Drug Administration’s approval of this regimen for CRPC.

Treatment with docetaxel not only improved overall survival (OS) but led to effective tumor burden reduction, prostate specific antigen (PSA) declines and improvement in QOL in those men with symptomatic disease.5,6 In fact, the median OS in the long-term follow-up analysis for the TAX327 trial is 19.2 months for docetaxel-treated patients versus 16.3 months for those receiving mitoxantrone.7 As important was the fact that the side effect profile was manageable and similar to that of chemotherapy agents used to treat other solid tumors.

More recently, the utility of second-line chemotherapy with cabazitaxel, a semisynthetic taxane derivative developed for its activity in patients with resistance to docetaxel, was demonstrated in the international TROPIC trial. This phase 3 trial evaluated this novel taxane against mitoxantrone in mCRPC patients who have progressed on docetaxel. Men
treated with cabazitaxel had an increased OS compared with those treated with mitoxantrone (hazard ratio [HR] 0.70, 95% CI 0.59-0.83, median survival 15.1 versus 12.7 months).8

The results of these trials have clearly changed the thinking about systemic chemotherapy in CRPC and have debunked some of the myths that discouraged this approach for many years.

Now the issues we face are of even greater magnitude. An improved understanding of the biology of CRPC coupled with the availability of newer agents has challenged the approach that one treatment fits all. As a result, questions about patient selection, the appropriate timing for treatment, the mechanisms of resistance and the best treatment sequence are the focus of additional research.

**Should Chemotherapy Be a Last Treatment Choice?**

The simple answer to this complex question is NO. Some of the most dramatic findings ever published in PCa are the recent results of ECOG 3805, a randomized phase 3 study of androgen deprivation therapy (ADT) +/- 6 cycles of docetaxel chemotherapy in men with hormone-naïve metastatic PCa.2 Cleveland Clinic participated in the ECOG 3805 trial.

The rationale for the trial’s design was simple: Attack de novo testosterone-independent clones early, allowing ADT to keep PCa in remission longer.

More than 790 men with metastatic PCa in need of ADT were randomized to either ADT alone or chemotherapy and ADT. Patients were stratified based on extent of metastases (high versus low volume), age, Eastern Cooperative Oncology Group performance status, use of agents to prevent skeletal-related events (SREs), use of anti-androgens and prior adjuvant ADT. The primary endpoint of the study was OS. Standard secondary endpoints included rate of PSA undetectability at six and 12 months, time to CRPC, safety and QOL at 12 months

The OS for the entire cohort was 57.6 months versus 44 months favoring the docetaxel + ADT arm (HR 0.61; p = 0.003). Similarly the OS in men with high-volume disease (defined as visceral disease and/or four or more bone metastases with at least one beyond pelvis and vertebral column) was 49.2 months versus 32.2 months in favor of the chemotherapy + ADT arm (HR 0.60; p = 0.0006). Nearly twice as many patients achieved an undetectable PSA at six and 12 months in the chemotherapy arm (27.5 percent vs. 14 percent and 22.7 percent vs. 11.7 percent, respectively; p < 0.0001), and the time to CRPC was also greater for those in the combination arm (14.7 months vs. 20.7 months; p < 0.0001).

As one would expect, patients in the chemotherapy arm experienced more toxicities compared with those on ADT alone; however these toxicities were docetaxel-related and similar to those commonly observed when this agent is utilized in the CRPC setting.

These data continue to support the importance of chemotherapy in men with PCa. They debunk the myth that late treatment is better and clearly establish the use of upfront chemotherapy for selected men with advanced disease (even prior to the development of castration-resistant disease) as a new standard of care.

**Dr. Garcia is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology and of the Department of Hematology and Medical Oncology. He can be reached at garciaj4@ccf.org or 216.444.7774.**

**References**


A Progress Report on the Genomic Prostate Score and Its Impact on Risk Stratification and Active Surveillance Decisions

Eric A. Klein, MD

Despite the statistical improbability of dying from prostate cancer (PCa), more than 90 percent of men diagnosed with low-risk disease undergo immediate treatment with surgery or radiation. In many of those cases, active surveillance (AS) — employing serial monitoring with digital rectal exams, prostate specific antigen testing, imaging and biopsy, and undertaking curative intervention only if tumors progress — would be the appropriate course, thereby avoiding the needless cost and morbidity of overtreating biologically insignificant disease.

The resistance to widespread adoption of AS has stemmed from a lack of confidence in risk assessment and outcome forecasting. Specifically, AS acceptance has been hampered by the less-than-optimal ability of conventional pretreatment tests to predict indolent PCa and to estimate true tumor grade and stage.

The advent of genomic analysis of prostate tumors and the development of various diagnostic tests based on gene expression signatures have improved the potential to predict outcome in localized PCa. However, the frequent genetic variations that exist between regions in individual tumors, as well as the limits on tumor sampling imposed by needle biopsy, have persisted as challenges for accurate forecasting and, by extension, for increased confidence in AS.

Key Points

Oncotype DX® Genomic Prostate Score (GPS), a new 17-gene assay performed on prostate biopsies, has the ability to accurately predict prostate cancer aggressiveness.

Validation study results and initial testing in a clinical setting show that GPS has the potential to identify men with biologically indolent disease who are good candidates for active surveillance.

The year 2014 may mark a turning point in surmounting those challenges. Evidence of a new 17-gene assay’s ability to accurately predict PCa aggressiveness reached critical mass with publication of a second validation study by the test’s developers at Cleveland Clinic and the University of California, San Francisco. And our initial clinical evaluation of the assay, marketed by Genomic Health Inc. as the Oncotype DX® Genomic Prostate Score (GPS), verified its capacity to improve risk-stratification and aid decision-making in a real-world setting.

Development and Validation of the Test

The GPS is the result of a decade of investigative and developmental work intended to determine whether a common underlying biology that reliably predicts clinically aggressive PCa, regardless of biopsy sampling location within a heterogeneous tumor, could be identified.
The GPS’ 17-gene algorithm was derived from a progressively narrowed pool of candidate genes identified by analyses of tumor specimens and confirmed to be associated with aggressive PCa. The GPS’ final set of 12 genes in four gene groups representing four key PCa molecular pathways (plus five reference genes) is strongly linked with adverse pathology and, in an as-yet-unpublished third validation, with disease recurrence.

The latest validation study, published in *European Urology* in September 2014, used the GPS to assess biopsy tumor tissue collected from a cohort of 395 men with low- to low-intermediate-risk PCa who were potential candidates for AS, but who elected to undergo prostatectomy within six months of their initial diagnostic biopsy. The study evaluated the GPS’ ability to accurately predict the presence of adverse pathology (high-grade and/or non-organ-confined PCa) in the prostatectomy specimens.

The study determined that the GPS was a significant predictor of pathologic stage and grade at prostatectomy. Every 20-point rise in the GPS score (which ranges from 1 to 100) was associated with more than a doubling of the risk of high-grade PCa and a nearly doubled risk of malignancy beyond the prostate’s confines. We and our UCSF coauthors concluded that the independent molecular information the GPS results provide correctly reflects a tumor’s underlying biology throughout the prostate, including the cancer’s potential to invade and distantly metastasize.

**Assessment in Clinical Practice**

In the latter half of 2013 we undertook an inception cohort study to evaluate the GPS assay’s performance in a clinical setting. One hundred fifteen patients at Glickman Urological & Kidney Institute with National Comprehensive Cancer Network (NCCN)-graded very low- to intermediate-risk PCa who were candidates for AS underwent GPS testing on prostate biopsy specimens obtained within six months of study entry. We sought to assess how often GPS testing altered patients’ NCCN risk stratification, the effect of GPS scores on physician recommendations for disease management and the impact of GPS results on patients’ decisions regarding disease management.

GPS outcomes altered risk assignment in 21 percent of the study cohort, most often (in 18 patients) changing classification from NCCN low to GPS very low. Physicians recommended AS to 100 percent of patients with very low-risk GPS results, and to 87 percent of patients with low GPS results. Physicians recommended treatment to 78 percent of patients who the GPS stratified as intermediate-risk. All but one patient chose treatment when assigned by GPS results to a higher risk category. All patients whose GPS outcomes reassigned them to a lower-risk category chose AS.

More research is needed to fully establish how GPS results affect physician and patient confidence in choosing AS versus therapy. But these study outcomes show that the GPS clearly improves risk stratification at the time of PCa diagnosis, and that it has the potential to help resolve perhaps the most urgent and vexing issue in PCa — identifying men with biologically indolent disease who are good AS candidates — and providing the reassurance to move forward.

**Dr. Klein is Chairman of Cleveland Clinic’s Glickman Urological & Kidney Institute. He holds the Andrew C. Novick, MD, Distinguished Chair in Urology and is a Professor of Surgery at Cleveland Clinic Lerner College of Medicine. Dr. Klein is the principal investigator for Cleveland Clinic’s GPS development studies. He is a paid consultant for Genomic Health Inc. He can be reached at kleine@ccf.org or 216.444.5591.**

**References**


Multiparametric Magnetic Resonance Imaging Ultrasound (MP-MRI-US) Fusion Targeted Prostate Biopsy

By Andrew J. Stephenson, MD, FRCSC, FACS

Accurate localization/characterization of clinically important prostate cancer lesions among healthy men who are otherwise candidates for curative therapy is essential for successful active surveillance and focal therapy strategies.

Indeed, progression rates on active surveillance as high as 48 percent over short (<5 years) time intervals have been reported, and rates of advanced pathological features (Gleason score ≤ 4+3, extraprostatic extension, seminal vesicle invasion or lymph node metastasis) as high as 23 percent have been reported among men undergoing deferred radical prostatectomy.

The limitations of transrectal biopsy strategies to accurately characterize and localize prostate cancer are highlighted by the consistent 20 to 30 percent reclassification rate among low-risk men undergoing immediate repeat extended prostate biopsy (10 to 14 cores) on active surveillance protocols. Likewise, among men undergoing repeat saturation biopsy (≥20 cores) after one or two prior negative biopsies, we reported cancer detection rates of 33 percent and 19 percent, respectively. Among men with known low-risk prostate cancer undergoing three-dimensional transperineal mapping biopsy (3D-TPMB), a 20 percent negative biopsy rate has been reported despite 50- to 69-core sampling.

Imaging Advances Improve Diagnostic Accuracy

Advances in prostate imaging using multiparametric magnetic resonance imaging (MP-MRI) and the ability to apply this information to targeted biopsy strategies using transrectal ultrasound (termed MP-MRI-US fusion biopsy) have the potential to improve our ability to accurately localize and characterize individual prostate cancer lesions.

Advances in MRI such as improved anatomical resolution on T1- and T2-weighted images (T2WI) with the use of 3 Tesla (3T) magnets, and functional imaging sequences using diffusion-weighted imaging (DWI), dynamic contrast enhancement (DCE) and MR spectroscopic imaging (MRSI) enable better diagnostic accuracy for prostate cancer (Figure 1). DCE allows for the visualization of blood perfusion via a bolus injection of gadolinium contrast during rapidly repeated scanning. Evidence of early and intense enhancement and washout in lesions is associated with angiogenesis seen in prostate cancers. DWI quantifies free water motion, which is restricted in lesions with increased cellularity, as is seen in prostate cancers. MRSI measures levels of choline (increased in cancer) relative to creatine and citrate peaks, and increases the specificity of low-signal-intensity lesions seen on T2WI.

However, the incremental benefit of MRSI to DWI and DCE sequences appears limited. The use of MP-MRI for prostate cancer detection and characterization has been aided by a standardized grading system called PI-RADS that rates regions of interest on a scale of 1 to 5 based on the likelihood of clinically significant cancer. MP-MRI using the PI-RADS scoring system has shown a sensitivity and specificity for prostate cancer detection of 67 percent and 92 percent, respectively, with 85 percent diagnostic accuracy. The use of MP-MRI for targeted prostate biopsy has been limited by the time, expense and impracticality of performing biopsies under real-time MRI guidance in the MRI gantry. Likewise, the use of MP-MRI to perform targeted biopsies of suspected lesions using standard transrectal ultrasound (TRUS), or so-called cognitive recognition, has questionable accuracy.

Imaging Fusion Results in Better Biopsy

Technological developments now enable MP-MRI images to be “fused” with TRUS using specialized computer software to improve targeted biopsy of suspicious lesions. Various tracking systems have been described, including a 3-D US probe attached to a mechanical arm (Figure 2), and one that uses an electromagnetic (EM) field generator placed above the pelvis with a custom US probe embedded with a passive EM tracking sensor. The best approach has yet to be determined.

Using MP-MRI-US fusion targeted biopsy, cancer detection rates of 15 to 20 percent, 29 to 40 percent, and 50 to 71 percent have been reported among lesions classified as having a low, moderate, or high probability of cancer, respectively. Targeted biopsy strategies also appear to be as accurate as 3D-TPMB for detecting clinically significant cancers. On average, 6 to 13 additional biopsies are taken per patient when a targeted biopsy strategy is added to a standard 12-core biopsy.
MP-MRI-US fusion targeted biopsy has the potential to significantly improve the localization and characterization of prostate cancer when added to a standard 12-core biopsy. It is anticipated that this strategy will enable better selection and monitoring of patients who choose active surveillance and focal therapy as a management option. This technology may also be useful in patients with suspicion of prostate cancer despite one or more negative biopsies. In 2014, Cleveland Clinic began offering MP-MRI-US fusion targeted prostate biopsy to patients. We also plan to investigate its utility in active surveillance and focal therapy protocols.

Dr. Stephenson is Director of the Center for Urologic Oncology at Cleveland Clinic’s Glickman Urological & Kidney Institute and a staff member of the Taussig Cancer Institute. He can be reached at stephea2@ccf.org or 216.445.1062.

Figure 1. Prostate cancer lesion identified on (a) T2-weighted images, (b) diffusion-weighted sequences, (c) dynamic contrast enhancement sequences, and (d) whole-mount prostatectomy specimen. Reprinted from Natarajan S, Marks LS, Margolis DJA, et al. Clinical application of a 3D ultrasound-guided prostate biopsy system. Urol Oncol 2011;29(3):334-342. © 2011, used with permission from Elsevier.


Figure 3. MP-MRI-US fusion guided image from biopsy procedure. Prostate is outlined in red, suspected tumor in green and biopsy needle in yellow.
Brachytherapy Versus Other Radiotherapeutic Modalities for Prostate Cancer: Why the Bias?

By Jay Ciezki, MD

Cleveland Clinic recently performed its 4,300th prostate brachytherapy procedure. While most centers are reducing the number of prostate brachytherapy procedures they do in favor of other modalities, we have been increasing our utilization of this treatment. Our preference for prostate brachytherapy over competing radiotherapeutic modalities is due to several factors. The most influential are our patient outcomes, which we have continuously reviewed since the program’s inception in 1996. As explained below, those outcomes show a clear advantage for brachytherapy in terms of lower long-term toxicity.

All patients definitively treated at Cleveland Clinic for prostate cancer have been recorded and followed in an inception cohort study that includes radical prostatectomy, external beam radiotherapy and brachytherapy. Since 1996, those involved in treating prostate cancer patients within the institution and those with whom we have a close working relationship, such as the Veterans Administration medical system, are invited to a biannual meeting in which we share information on treatment effectiveness, toxicity and new research, and discuss ways to improve the prostate cancer program.

Long-term Outcomes Monitoring

Cleveland Clinic has been on the leading edge of prostate cancer treatment for many years. In 1998 we were one of the first medical centers in the country to employ intensity-modulated radiation therapy (IMRT) for the treatment of prostate cancer. Over the years we have monitored IMRT outcomes and compared them with the outcomes of brachytherapy and prostatectomy through our inception cohort study and biannual program review meetings.

Through this mechanism we came to appreciate the higher long-term toxicity rate of IMRT. As a team, we felt this toxicity was not balanced by IMRT’s efficacy, which continues to equal that of brachytherapy and prostatectomy across all risk groups. Further investigation by our group using the Surveillance, Epidemiology, and End Results (SEER) database has reinforced this opinion. (We presented our findings at the American Society of Clinical Oncology’s 2012 Genitourinary Cancers Symposium.) Figure 1 demonstrates the cumulative incidence of grade > 3 toxicity after treatment with brachytherapy, prostatectomy or external beam radiotherapy for this study.

Key Points

Though prostate brachytherapy use is declining at many medical centers in favor of competing radiotherapeutic modalities, particularly intensity-modulated radiation therapy (IMRT), Cleveland Clinic is increasing brachytherapy’s utilization.

This support is based on long-term institutional outcomes monitoring that shows an advantage for brachytherapy in terms of reduced toxicity.

Economic incentives may explain IMRT’s higher utilization rates at other institutions.

Possible Incentives for IMRT Use

Our rationale for preferring brachytherapy over IMRT is clear, given our internal review process results, but other centers have continued to choose IMRT over brachytherapy. Not knowing their internal review processes, one cannot determine if they have experienced better outcomes with IMRT, but a recent multi-institutional study in which we enrolled patients noted no evidence for lower toxicity with IMRT.

Beyond the medical evaluation of the various prostate cancer treatments, there are financial considerations that differentiate the procedures. Current reimbursement structures allow payment for IMRT and other external beam radiation techniques that are about twice as much as for prostatectomy or brachytherapy.

Moreover, external beam radiotherapy for prostate cancer qualifies for an in-office ancillary services exemption to the federal prohibition of self-referral that applies to other cancer treatments. This exemption enables urologists to own an interest in an external beam radiation treatment center to which they refer patients. There is clearly an association between these economic incentives and the preponderance of IMRT as a radiotherapeutic modality for prostate cancer.

Cleveland Clinic’s structure, in which there is no financial incentive for physicians to choose one treatment over another, permits us to offer therapy based on outcomes. This continuous evaluation of patient outcomes has allowed us to refine and tailor our treatment recommendations for patients. The prostate brachytherapy program at Cleveland Clinic is an example of the success of our method.

Dr. Ciezki is a staff member of Cleveland Clinic’s Department of Radiation Oncology and Department of Cell Biology. He can be reached at ciezki@ccf.org or 216.445.9465.
Figure 1. A) Cumulative incidence of gastrointestinal toxicity after therapy with external beam radiation quickly outpaces brachytherapy and prostatectomy. B) While prostatectomy has more initial genitourinary toxicity, external beam radiation again is seen to cause more toxicity with more follow-up. C) Despite the argument that the toxicity of modern external beam radiation (such as IMRT) is reduced because of its superior targeting, its toxicity exceeds standard, pre-IMRT radiotherapy.

References


Department of Nephrology and Hypertension Designated as a Comprehensive Hypertension Center

Robert Heyka, MD, and George Thomas, MD

Hypertension as the first Comprehensive Hypertension Center in Northeast Ohio, and one of only 12 nationally. This designation recognizes institutions that have demonstrated experience and expertise in the management of difficult hypertension cases.

Our Center for Blood Pressure Disorders is staffed with a team of experienced nephrologists certified as hypertension specialists by the American Society of Hypertension, and with medical assistants, physician assistants and clinical nurse practitioners.

The center has a dedicated hypertension laboratory with space and equipment devoted to evaluation and testing.

Monitoring Capabilities

Along with the standardized use of automated blood pressure devices in our outpatient clinics, we provide 24-hour ambulatory blood pressure measurements for a large cohort of patients to help assess different blood pressure patterns, in addition to assessment of therapy efficacy.

We utilize noninvasive impedance cardiography in patients with difficult-to-control hypertension to help guide treatment decisions and tailor therapy by assessing neurohumoral profiles and hemodynamic parameters.

Central blood pressures have been shown to correlate more strongly with vascular disease than do routine peripheral blood pressure measurements, and we have the ability to assess central blood pressure indices, including measures of pulse wave velocity and augmentation index.

The center also has expertise in the management of secondary hypertension, specifically related to the diagnosis and treatment of primary aldosteronism, pheochromocytoma and renal artery stenosis.

A Collaborative Care Model

The center uses a collaborative approach to diagnosis, care and monitoring of blood pressure disorders. We work closely with internists, cardiologists, endocrinologists and vascular medicine specialists to develop a diagnostic and management plan tailored to the individual patient.

An effective treatment program requires partnership between the patient and care providers. Our center supports patients with information regarding blood pressure monitoring guidelines, lifestyle changes and nutrition.

Dr. Heyka is Chairman of the Department of Nephrology and Hypertension in Cleveland Clinic’s Glickman Urological & Kidney Institute. He can be reached at heykar@ccf.org or 216.444.6771.

Dr. Thomas is a staff member of the Department of Nephrology and Hypertension. He can be reached at thomasg3@ccf.org or 216.636.5420.

Key Points

As a designated Comprehensive Hypertension Center, Cleveland Clinic’s Department of Nephrology and Hypertension has the capability and experience to evaluate and manage all forms of blood pressure disorders in collaboration with numerous specialties, and to engage patients to participate in their care.
Pulmonary Hypertension and Kidney Disease: A Deadly Duo

Sankar Navaneethan, MD

Pulmonary hypertension (PH) is a progressive, fatal pulmonary circulatory disease that accompanies left or right ventricular failure.

Several factors lead to the development and worsening of PH, and kidney dysfunction and volume overload are common occurrences in clinical practice that can lead to increased pulmonary artery (PA) pressure. This decline in kidney function could be transiently related to hemodynamic changes during the treatment of volume overload associated with PH. These hemodynamic changes could lead to chronic kidney disease (CKD) if the insults are persistent or the underlying disease continues to worsen.

Examining CKD-PH Relationships

Since kidney disease in itself is a significant risk factor for death, it is relevant to examine its effects in the population with PH. Therefore, we attempted to determine if the presence of pre-existing non-dialysis-dependent CKD is an independent risk factor for death in patients with PH of varying etiology.

We studied 1,088 adult patients diagnosed with PH based on mean PA pressure > 25 mm Hg at rest as measured by right heart catheterization performed at our institution between 1996 and January 2011. The primary outcome of interest was all-cause mortality, which was ascertained from our electronic medical record and linkage of our data with the Social Security Death Index.

Patients were followed from their date of right heart catheterization until October 31, 2011. Mean age of the study cohort was 60 ± 15 years; 66 percent were females and 81 percent were white. Mean serum and estimated glomerular filtration rate (eGFR) was 72.2 ± 29 mL/min/1.73 m². Mean PA pressure of the entire cohort was 47 ± 14 mm Hg. Among the 1,088 patients, 388 (36 percent) had evidence of CKD; 340 (31 percent) had stage 3 CKD and 48 (4 percent) had stage 4 CKD.

During the median follow-up period of 3.2 years (interquartile range 1.5 to 5.6 years), 559 (51 percent) of the total cohort died. Kaplan-Meier survival estimates at one year were 86 percent, 78 percent and 48 percent in those without CKD, with stage 3 CKD and with stage 4 CKD, respectively (log-rank p < 0.001; see Figure 1).

Key Point

The presence of chronic kidney disease is an independent risk factor for death in patients with pulmonary hypertension.

In the multivariable adjusted Cox proportional hazards model, the presence of eGFR < 60 mL/min/1.73 m² was independently associated with mortality. When eGFR was examined as a continuous variable, every 5 mL/min/1.73 m² decrease in eGFR was associated with a greater hazard for death (HR 1.05, 95% confidence interval [CI] 1.03-1.07). Presence of CKD did not seem to modify the associations between severity of PH and death.

Possible Explanations for CKD-PH-Associated Mortality

Pulmonary hypertension and CKD are disease states associated with poor outcomes. In this large cohort of patients with PH (based on right heart catheterization data), underlying CKD was highly prevalent. The observed association between CKD and mortality in our study could be explained by the higher prevalence of diastolic dysfunction and volume overload (resultant pulmonary congestion) in those with mild to moderate CKD.

In addition, other investigators have speculated on the potential influence of uremic toxins, bone mineral disorder and endothelial dysfunction on outcomes among those PH patients who are on dialysis. Particularly, these reports note that nitric oxide levels are reduced and release of nitric oxide is attenuated in patients on hemodialysis with PH. These deficiencies in nitric oxide often lead to increased pulmonary vascular tone, which in turn can promote arterial stiffness with resultant adverse consequences.

Whether such mechanistic pathways prevail in those with earlier stages of CKD, thereby causing higher mortality rates, is unknown and could be explored in CKD cohorts with longitudinal data relating to PH and left ventricular function. Our group is conducting these analyses, which might also help us identify novel risk stratification tools for our kidney disease patients.

Dr. Navaneethan is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Nephrology and Hypertension. He can be reached at navanes@ccf.org or 216.636.9230.
Reference


Figure 1. Survival based on eGFR in patients with pulmonary hypertension.
Erectile Dysfunction Is a Major Cause of Peyronie Disease: A Personal View

Drogo K. Montague, MD

Peyronie disease (PD) occurs in as many as 9 percent of middle-aged and older men. It is caused by plaque formation in the tunica albuginea, thought to result from repeated minor injuries to the penis during intercourse. The goal of treatment is to restore or maintain the ability to have intercourse.

As a prelude to the following discussion of PD, penile fractures are uncommon, dramatic injuries that occur during coitus in young men with fully rigid erections. If a large force is applied to these erections during sexual activity, there is sharp pain followed by penile swelling and ecchymosis. Surgical exploration reveals a tear in the elastic covering (tunica albuginea) of the erection chambers at the base of the penis. When the tear is surgically repaired, future erections remain straight. If surgical repair is not done, a palpable scar (plaque) develops at the base of the penis, and erections curve toward the side of this inelastic plaque.

PD has some things in common with penile fracture. Typically, men with PD still have erections suitable to initiate coitus; however, erectile rigidity is less than when they were younger, and the penis may be subject to bending during coital thrusting. The bending results in delaminating injuries to the tunica albuginea. In contrast to penile fracture, these less dramatic injuries are often painless and occur farther out on the shaft of the penis. Unlike penile fracture, there are no outward signs of injury. As healing takes place, scar tissue forms (Figure 1), causing loss of penile length and erectile deformity (Figure 2).

Ways to Avoid PD

As men’s erectile rigidity declines with aging, they can avoid developing PD by regularly using a phosphodiesterase type 5 (PDE5) inhibitor (sildenafil, vardenafil or tadalafil) to treat their mild erectile dysfunction (ED). Men should avoid excess bending of the penis during coitus, as well as sexual activity when erections might be weaker than usual due to fatigue or alcohol intake. If the penis slips out of the vagina, the man or his partner should use their hand to guide it back in. Avoiding coitus in which the partner is on top is also advisable because of greater forces often applied to the penis in this position.

At Cleveland Clinic, when men present to us with PD, we discuss this ED injury model and provide the above advice on how to avoid recurring injury. If coitus is already impaired or impossible, we consider surgical treatment.

Key Points

Mild erectile dysfunction (decreased erectile rigidity) is usually a causal factor in the development of Peyronie disease.

Peyronie disease can be prevented by advice to lessen the possibility of penile injury during coitus.

Men with Peyronie disease who have difficulty with or are unable to perform coitus usually require surgical therapy.

Surgery most often consists of either tunica albuginea plication of the penis or inflatable penile prosthesis implantation, depending on baseline erectile rigidity.

Surgical Options

To restore the ability to have sex safely without further injury, the penis must be reasonably straight and erections must be reliably firm. If curvature is the problem and erections after taking a PDE5 inhibitor are firm, then tunica albuginea plication of the penis is advisable. In this procedure, the normal tunica albuginea is shortened at the point of maximal curvature to match the penile shortening due to the inelastic scar on the opposite side. The length of the resulting erection will be approximately equal to the preoperative stretched penile length. With this procedure there should be no worsening of the underlying ED.

If the patient does not respond to PDE5 inhibitor therapy, we recommend inflatable penile prosthesis implantation. If cylinders are used that expand only in girth, prosthesis implantation usually results in satisfactory penile straightening. The prosthesis also provides a firm erection each time it is inflated. Men with PD invariably have lost penile length, and, as with tunica albuginea plication, the length of the erection after prosthesis surgery will be approximately equal to the stretched penile length prior to surgery.

Penile plaque excision or incision with autologous tissue grafts can be done to lengthen the scarred side of the penis (Figure 3). This extensive surgery straightens the penis and restores some of the lost penile length. With these procedures, however, there is a significant chance of worsening the underlying ED. If ED worsening occurs, a second procedure to implant an inflatable penile prosthesis is often necessary.

In conclusion, PD is the result of an often silent injury or recurrent injuries to the erect penis during sexual activity. Some degree of ED is usually an underlying factor. Occurrence or worsening of PD is avoidable by following commonsense advice. When PD makes coitus difficult or impossible, surgical intervention is indicated. The goal in treatment, provided erections are reliably firm, is correction of the deformity. If the degree of ED precludes a straightening procedure alone, inflatable penile prosthesis implantation is often the surgical choice.
Dr. Montague is a staff member of the Center for Genitourinary Reconstruction at Cleveland Clinic’s Glickman Urological & Kidney Institute and Professor of Surgery at Cleveland Clinic Lerner College of Medicine. He can be reached at montagd@ccf.org or 216.444.5590.

Additional Reading


Figure 1. On the bottom is a dense scar replacing the tunica albuginea in a patient with PD. The tissue on top is attached cavernous smooth muscle.

Figure 2. Dorsal curvature of the erection in a man with PD.

Figure 3. Excision of penile plaque and replacement with an autologous pericardial graft.
Staged Buccal Graft Urethroplasty for Difficult Strictures

Kenneth Angermeier, MD; Hadley Wood, MD; and Ryan Mori, MD

Although the majority of urethral strictures are repaired in a single operation, a two-stage approach is preferred in some situations. For example:

- Patients with recurrent stricture following hypospadias surgery often have insufficient genital skin for flap reconstruction, and may not have adequate dartos fascia to reliably support one-stage urethral reconstruction using a graft. In this setting, staged buccal graft urethroplasty has emerged as a reliable form of repair.

- A second group of patients who may benefit from this approach are those with anterior urethral strictures related to lichen sclerosus (LS), which are often long and associated with significant spongiformfibrosis. This group is known to have a higher stricture recurrence rate following surgery compared with other stricture etiologies. Although success with a one-stage operation has been reported, a staged technique has been shown to be a reliable form of reconstruction, especially in the presence of inflammatory obliteration of the glanular and distal penile urethra.

Previous reports of staged buccal graft urethroplasty have occasionally described the need for three or more operations to complete the reconstruction, and in some series, relatively low rates of progression to urethral tubularization have been noted with patients retaining a proximal urethrostomy.

These findings prompted us to review our experience with staged buccal graft urethroplasty during the past 10 years. We identified 78 men who have undergone the procedure, with hypospadias-related stricture present in 53 percent, LS in 40 percent and other conditions in 7 percent. Stricture was limited to the penile urethra in 63 percent of patients, and was multifocal or panurethral involving both the penile and bulbous urethra in 37 percent.

Details of the Surgery

The surgical procedure is initiated by opening the urethra from the distal end of the stricture (typically at the urethral meatus) and continuing the urethrotomy incision into healthy wide-caliber urethra for a distance of 1 to 1.5 cm.

At that site, a urethrostomy is created using adjacent penile or scrotal skin for part of the circumference when necessary. In the case of a particularly dense or obliterated area of stricture, which seems to occur most often within the glanular and distal penile urethra in men with LS, this segment may be completely excised.

Dartos fascia may be mobilized to cover the tunica albuginea adjacent to the urethral plate if needed to provide a good graft bed. Buccal mucosa is then harvested, either unilaterally or bilaterally, and sutured and quilted into place along either side of the urethral plate or across the midline in place of the urethra. A bolster dressing is applied for five days to promote graft take, and a urethral catheter is left indwelling for two to three weeks.

Second-stage tubularization is carried out when the graft has healed and softened, usually four to six months later. We strive for a healed urethral plate of approximately 3 cm in width to allow for adequate final diameter of the urethral lumen and to minimize the chance of recurrent stricture. The patient is informed that additional oral mucosa (either lingual or buccal) may be harvested to complete the repair if the plate is insufficient in a particular area. The urethra is closed and additional tissue layers are mobilized and brought together as available, or a tunica vaginalis flap may be raised to cover the repair if the dartos is inadequate. The repair is stented for three weeks, and the patient is then monitored in routine fashion.

Postoperative Complications and Conclusion

Postoperative results following staged buccal graft urethroplasty have been quite good. Recurrent stricture or urethrocutaneous fistula requiring intervention developed in 4 percent and 5 percent of patients, respectively (one patient had both). In five patients (6.4 percent), the glans closure opened to the level of the corona, and three requested a surgical revision as a result.

More than 95 percent of our patients returned for second-stage tubularization. Ninety-six percent of repairs were completed in two operations, with those needing a planned additional procedure having had a history of obesity and buried penis.
In summary, staged buccal graft urethroplasty is an effective procedure for patients with difficult anterior urethral strictures, particularly those with a history of hypospadias repair or LS. Although some patients in these two categories may be candidates for reconstruction in a single operation, one should not hesitate to use a staged approach if the status of local tissues is questionable, due to the high rate of success and acceptable morbidity.

Dr. Angermeier is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology and Director of the Center for Genitourinary Reconstruction. He can be reached at angermk@ccf.org or 216.444.0415.

Dr. Wood is a staff member of the Urological & Kidney Institute’s Center for Genitourinary Reconstruction and an Assistant Professor of Surgery at Cleveland Clinic Lerner College of Medicine. She can be reached at woodh@ccf.org or 216.444.2146.

Dr. Mori is a former genitourinary reconstruction and prosthetic surgery fellow in the Center for Genitourinary Reconstruction.

Figure 1. (A) First stage: Ventral urethrotomy and incision of glans penis. (B) Exposure for buccal mucosa harvest. (C) Buccal graft sutured and quilted onto recipient bed.

Figure 2. Bolster secured in place to immobilize graft for five days.

Figure 3. (A) Second stage: Well-healed buccal graft and urethral plate prior to procedure. (B) Tubularization of the urethra. (C) Immediate postoperative appearance.
Proteomics and the Future of Sperm Testing

Edmund Sabanegh Jr., MD, and Ashok Agarwal, PhD

Up to 15 percent of couples are infertile, with almost 50 percent of those having male factor as a contributing cause. For the past 50 years, semen analysis has been the mainstay of the male fertility evaluation.1

Although advances in semen testing have incorporated computer-assisted technologies, the test has remained fundamentally unchanged, with emphasis on the three main parameters: sperm count, motility and morphology. The most significant modifications have involved the redefinition of normal ranges of semen parameters as defined in five iterations of the World Health Organization’s reference values, most recently in 2010.2

Despite these updates, clinicians and patients remain frustrated with the low sensitivity and specificity of the conventional semen analysis. Many men with abnormal semen parameters will go on to achieve spontaneous pregnancies, and less than 50 percent of infertile men have a discernible etiology. The remarkable day-to-day and geographic variability in ejaculate quality further limits test utility.

### Key Points

- Examination of sperm function through proteomics has the potential to improve on conventional semen analysis in the workup of male infertility.
- Alterations in differentially expressed proteins (DEPs) are present in infertile men with bilateral varicocele; some of these proteins are involved in sperm function, sperm motility and other functions related to reproduction.
- DEPs may serve as novel biomarkers in the identification of bilateral varicocele and may help urologists identify better options for clinical management of infertile men.

### Examining Differential Expression of Key Spermatozoa Proteins

In a recent study, we examined how the etiology of bilateral varicocele-related male infertility might be affected by the differential expression of key proteins in spermatozoa that results in testicular dysfunction and impairment of male fertility potential. We also validated two differentially expressed proteins (DEPs) that have reproductive function. We examined the DEPs extracted from spermatozoa cells from patients with bilateral varicocele (N = 17) and healthy donors (N = 10).

Using genomewide profiling, we found more than 1,000 proteins in the fertile group and a similar number in the group with bilateral varicocele. We identified 73 DEPs, of which seven were unique to the bilateral group and 58 were differentially expressed (overexpressed or underexpressed) in either group (Figure 1A). Proteins were further classified according to their abundance (high, medium, low and very low) (Figures 1B and C). The abundance (both high and medium) of proteins observed in the group with bilateral varicocele again demonstrates their likely involvement in the etiology of the disease.

We have demonstrated for the first time the presence of DEPs and identified proteins with distinct reproductive functions that are affected in infertile men with bilateral varicocele. The majority of the DEPs were associated with metabolic processes, stress responses, oxidoreductase activity, enzyme regulation and immune system processes. The topmost network with the core function of lipid metabolism showed five overexpressed and seven underexpressed DEPs in bilateral varicocele samples. Seven DEPs were involved in sperm function such as capacitation, motility and zona-egg binding. Two proteins, Tekin-3 (TEKT3) and T-complex protein 11 homolog (TCP11), may serve as potential biomarkers for bilateral varicocele.
Potential Biomarkers to Identify Bilateral Varicocele

Additional proteomic analysis identified 12 DEPs annotated with distinct functional categories. Of these, seven were related to reproduction and/or spermatogenesis, including sperm tail filaments, sperm motility, sperm function and binding of sperm to zona pellucida.

Of the seven proteins involved in reproductive-related functions, four proteins were overexpressed in the bilateral varicocele group. These were outer dense fibers protein 2 (ODF2), TEKT3, TCP11 and protein-glutamine gamma-glutamyltransferase 4 (TGM4). Calmegin (CLGN) and mitochondrial import receptor subunit TOM22 homolog (TOM22) were underexpressed in the group with bilateral varicocele. Apolipoprotein A1 was unique to the fertile group only. The details of the gene name, protein name and spermatogenic function of the DEPs in the group with bilateral varicocele compared with the fertile control group are shown in Table 1.

For the first time, we have demonstrated significantly poorer sperm morphology and elevated levels of reactive oxygen species in men with bilateral varicocele. These abnormalities also translate into significant alteration and overexpression of DEPs ODF2, TEKT3, TCP11 and TGM4. In addition, men with bilateral varicocele had underexpression of CLGN and TOM22, which may be responsible for the severity of the disease and sperm dysfunction in these patients.

These DEPs may serve as useful biomarkers in the identification of bilateral varicocele and in helping urologists identify better options for clinical management of infertile men with bilateral varicocele.

While we continue to rely on conventional semen parameters in the evaluation of the subfertile male, proteomic analysis holds great promise as a diagnostic tool in the reproductive medicine armamentarium. With the identification of novel biomarkers through proteomic studies, clinical tests and treatments for sperm dysfunction may be developed to potentially help infertile couples.

Figure 1. (A) Venn diagram of differentially expressed proteins (DEPs). Eight proteins are uniquely expressed in the fertile control group, seven proteins are uniquely expressed in the bilateral varicocele group and 58 proteins are commonly expressed in both groups. (B) Protein abundance of DEPs that are overexpressed, underexpressed or uniquely expressed in the fertile control group versus bilateral varicocele group. (C) Comparison of high, medium, low or very low abundance of DEPs in fertile controls and men with bilateral varicocele based on the normalized spectral counts obtained from the proteomic profile and gene ontology annotations for DEPs. H = high, M = moderate, L = low, VL = very low.

Dr. Sabanegh is Chairman of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology. He can be reached at sabanee@ccf.org or 216.445.4473.

Dr. Agarwal is Director of the Department of Urology’s Center for Reproductive Medicine and the Andrology Center. He can be reached at agarwaa@ccf.org or 216.444.9485.
Table 1. Gene name, protein name and spermatogenic function of the DEPs in the group with bilateral varicocele compared with the fertile control group.

<table>
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<th>UniProt No</th>
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<td>Outer dense fiber protein 2</td>
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References


Renal Access for Percutaneous Nephrolithotomy: Where Are We Today?

Sri Sivalingam, MD, MSc, FRCSC

Percutaneous nephrolithotomy is the current gold standard for large renal stones > 2 cm. The initial step in this procedure is obtaining renal access, which is often the most challenging part of the procedure and can directly impact the safety and efficacy of stone removal.

The approach to obtaining renal access varies among endourologists who routinely perform this procedure. Often, interventional radiologists are asked to obtain the initial access prior to dilating the tract. Practically, this approach can be cumbersome and inefficient, as the patient must undergo two separate procedures, and the tract placement may not be ideal.

A recent survey of Endourological Society members found that the majority of endourologists (approximately 76 percent) obtained their own renal access, in contrast to a previous survey of members of the North Central Section of the American Urological Association, which reported that only 11 percent of urologists obtained their own access.

This disparity may be attributable to inherent biases within the surveyed populations. In the survey of endourologists, however, fellowship training in endourology was a significant determinant of whether urologists obtained their own access.

Majority in Survey Use Antegrade Approach

Obtaining the ideal access is paramount to successful stone removal, and over the years, the various techniques have been refined. At Cleveland Clinic, we have expertise in the full range of available techniques, including pure antegrade access, pure retrograde access and a combined antegrade-retrograde access.

According to the survey of endourologists, 68 percent established access using the classic antegrade approach, 19 percent utilized a retrograde approach and 12 percent utilized a combined approach (Figure 1). Patient positioning also varied, with the majority (85 percent) of endourologists favoring the prone position (Figure 2).

The classic antegrade approach begins with placement of a ureteral access catheter into the ipsilateral ureter while the patient is in supine position; subsequently the patient is repositioned in prone to establish percutaneous access. Renal access is obtained with a 21-gauge Chiba needle (Cook Medical; Bloomington, IN) under fluoroscopic guidance (triangulation/bull’s eye technique), and once the calyx is entered and access secured, tract dilatation is performed. Postoperative drainage is typically maintained via a nephrostomy tube.

We recently demonstrated safety and efficacy with a purely retrograde access technique. This technique is especially useful in a nondistended collecting system and precludes prone positioning. It is performed with the patient in a modified low lithotomy position with the ipsilateral flank wedged upward and prepped.

Cystoscopy and retrograde pyelography is performed, and a Lawson™ steerable catheter is advanced into the optimal calyx. A puncture wire is then advanced retrograde through the catheter under fluoroscopy until it emerges through the skin at the flank. An assistant then grasps and gently pulls the wire until the catheter emerges through the skin, and the puncture wire is removed. A stiff guide wire can then be placed antegrade for through-and-through renal access. A double-J ureteral stent is placed, which obviates postoperative nephrostomy tube placement. The patient is then gently repositioned in a lateral decubitus position, and tract dilatation and nephrolithotomy are performed.

Details of the Combined Approach

A third technique is a combined antegrade-retrograde approach. This begins with placement of a ureteral access sheath with the patient in prone position. An assistant performs ureteropyeloscopy and navigates the ureteroscope into the calyx of choice.

Key Points

- Percutaneous renal access is obtained by urologists in the majority of cases managed by endourology fellowship-trained surgeons.
- Renal access may be obtained safely by antegrade, retrograde or combined techniques.
- Antegrade access with prone positioning is the most commonly used approach by urologists in the Endourological Society, while expertise in all three access techniques is available at Cleveland Clinic.
- With outcomes data showing comparable safety for all three approaches, the choice of which to use should be based on surgeon experience and comfort.
The primary surgeon then utilizes an antegrade approach to obtain access, by which the 21-gauge Chiba needle is placed into the preselected calyx with the tip of the ureteroscope as the target, and needle entry is confirmed by direct visualization. A guide wire is then placed though the needle, and once visualized with the ureteroscope, the guide wire is grasped and brought out through the external urethral meatus, establishing a through-and-through access. The tract is dilated and nephrolithotomy is completed with the patient in prone position. A ureteral stent is often placed, without a nephrostomy tube, at the end of the procedure.

While each of these techniques has inherent advantages and disadvantages, the approach of choice must be based on surgeon experience and comfort. Although some variability in operative time, radiation exposure, patient positioning and postoperative drainage may exist, outcomes data show that all these approaches are safe. Further comparative evaluation of these techniques will help determine which is most efficacious in different clinical scenarios.

Dr. Sivalingam is an associate staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology. He can be reached at sivalis@ccf.org or 440.461.6430.

References


Figure 1. Percutaneous renal access approach for nephrolithotomy among endourologists.¹

Figure 2. Patient positioning for percutaneous nephrolithotomy among endourologists.¹
Knowledge of baseline risk factors for progression of pelvic organ prolapse (POP) can be used to help symptomatic women make treatment decisions. Unfortunately, data on progression of POP in symptomatic women are minimal.

Working with colleagues at the Sotero del Río Hospital and the Pontificia Universidad Católica de Santiago, Chile, and those in Cleveland Clinic Department of Urology’s Center for Female Pelvic Medicine and Reconstructive Surgery, we prospectively describe the natural evolution of POP in this group of patients, comparing the patients who developed progression with those who did not, and evaluating risk factors for progression.

Evaluation Process and Findings

We evaluated a prospective cohort of patients treated between 2008 and 2013. Women with symptomatic POP having two or more POP-Q examinations (a measure of degree of prolapse) during follow-up (still awaiting surgery or prior to surgery) were included. We defined changes of ≥ ± 2 cm in the POP-Q measurements of either points Ba, C or Bp (anterior, apical or posterior compartments) between initial and follow-up examinations as clinically significant. We analyzed risk factors for progression for both groups.

A total of 392 patients met the inclusion criteria. With a median follow-up of nine months, 47.5 percent of patients progressed (meaning prolapse worsened), 8.7 percent regressed and 43.8 percent did not change. Same-compartment progression was observed in 29.4 percent, 7.1 percent and 23 percent in the anterior, posterior and apical compartments, respectively. When the leading edge was the anterior compartment, 74 percent of the progressions involved the apical compartment.

We performed a baseline comparison between nonprogression (N = 206) and progression (N = 186). The groups were statistically significantly different at baseline in regard to the degree of anterior compartment descent and the presence of the leading edge of prolapse beyond the hymen (72.8 percent vs. 81.7 percent). There were no differences in terms of apical prolapse. More severe anterior POP and leading edge beyond the hymen were the only baseline factors that were associated with a statistically higher risk of progression.

We performed a multiple logistic regression analysis including the following variables for POP progression:

- History of hysterectomy
- Active tobacco use
- Leading edge beyond the hymen

The only variable that was statistically significant was leading edge beyond the hymen at baseline, which demonstrated a twofold increase in risk of progression.

Predictors of Pelvic Organ Prolapse Progression

Howard Goldman, MD, and Javier Pizarro-Berdichevsky, MD

Knowledge of baseline risk factors for progression of pelvic organ prolapse (POP) can be used to help symptomatic women make treatment decisions. Unfortunately, data on progression of POP in symptomatic women are minimal.

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- History of hysterectomy
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- Leading edge beyond the hymen

The only variable that was statistically significant was leading edge beyond the hymen at baseline, which demonstrated a twofold increase in risk of progression.

POP Evolution Has Treatment and Policy Implications

We describe for the first time the natural evolution of prolapse in patients actively seeking treatment. The evolution of symptomatic POP is progression in 47.5 percent of patients. When the leading edge is the anterior compartment, 74 percent of the patients’ progression involves the apical compartment. When the leading edge is beyond the hymen, the chance of progression is doubled.

In summary, our research has demonstrated that almost 50 percent of women with symptomatic POP who are actively seeking treatment will have prolapse progression within a year. This information can be used to counsel symptomatic women regarding the chance that their POP will worsen. It also has public policy implications, given the increasing number of women at risk for POP as the baby boomer generation ages. In the coming decades, treatment of POP in this population will require increased resources and trained professionals.

Dr. Goldman is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology. He is also the Urological & Kidney Institute’s Vice Chair for Quality and Patient Safety, and a Professor of Medicine at Cleveland Clinic Lerner College of Medicine. He can be reached at goldmah@ccf.org or 216.445.5121.

Dr. Pizarro-Berdichevsky is a clinical fellow in the Department of Urology. He can be reached at pizarrj@ccf.org.

Key Points

- The risk of progression of pelvic organ prolapse in women seeking treatment approaches 50 percent.
- A leading edge of prolapse beyond the hymen is associated with a twofold increased risk of progression.
Delivery of stem cells may someday represent a treatment option for childbirth injury and related disorders, such as pelvic organ prolapse (POP). First, it must be determined whether stem cells home preferentially to pelvic organs after injection. POP is the downward descent of the pelvic organs that results in a protrusion of the uterus, vagina or both. It is a problem that affects adult women worldwide across different cultures and races.

About 12.6 percent of women will undergo surgery for POP by the age of 80 in the United States. Although not life-threatening, POP can be devastating to one’s quality of life.

There is increasing agreement that the strongest risk factor for lifetime development of POP is vaginal childbirth, which can injure the nerves, muscles and supportive tissues responsible for maintaining pelvic support. Obesity, diabetes mellitus and advanced age are other major risk factors for development of POP. With obesity on the rise, the incidence of POP is expected to substantially increase.
Stem Cell Upregulation After Delivery

Stem cells participate in normal repair processes and therefore have the potential to be harnessed to facilitate repair of childbirth-related injuries. Cytokine gradients produced by the injured tissues attract or home circulating stem cells to sites of injury, where they facilitate the repair process, sometimes via the same receptor-mediated mechanisms involved in homing.

Cleveland Clinic research fellows Javier Pizarro-Berdichevksy, MD, and Bruna Couri, MD, from the Section of Female Pelvic Medicine, together with Howard B. Goldman, MD, and a research group led by Margot S. Damaser, PhD, of the Department of Biomedical Engineering and Cleveland Clinic’s Glickman Urological & Kidney Institute, have shown that a lysyl oxidase like-1 (LOXL1) knockout (KO) mouse develops POP that increases with parity and age, as in humans.

Our research also demonstrates that stem cell homing cytokines, particularly those that attract adult mesenchymal stem cells (MSCs), are upregulated after delivery in the pelvic floor tissues of LOXL1 KO female mice. These mice serve as a valuable animal model to study pelvic floor disorders. Homing of stem cells has been described in other animal injury models but not in LOXL1 KO mice after delivery. We are conducting a study to verify stem cell homing in this POP model using an in vivo and ex vivo cell tracking system (the IVIS® Lumina system; PerkinElmer, Waltham, MA) that measures radiance emitted by cells that express luciferase.

Cell Tracking Shows Preferential Homing

In vivo cell tracking demonstrated a three- and 6.5-fold higher radiance one and four days after vaginal delivery and injection, respectively, indicating preferential stem cell homing to the pelvic region after pup delivery in these mice.

Ex vivo imaging demonstrated 5.8 and 3.3 times higher homing of cells in the vagina and urethra, respectively, four days after the stem cell injection. There were no differences in cell homing in other organs four days after injection compared with nulliparous animals. No differences were noted one day after injection.

After vaginal delivery, bone marrow-derived MSCs that were delivered intraperitoneally home preferentially to the vagina and urethra. This preferential homing suggests that the vagina and urethra are injured by parturition and secrete injury-related cytokines, as we have previously confirmed.

A semilocal cell delivery route such as intraperitoneal injection may enable a regenerative therapy to reach areas of injury not accessible by a local delivery mechanism. Assuming a diffuse injury provoked by the parturition process, our results could be relevant for future stem cell-based therapies for delivery-related disorders, such as POP.

Dr. Goldman is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute's Department of Urology. He is also the Urological & Kidney Institute’s Vice Chair for Quality and Patient Safety, and a Professor of Medicine at Cleveland Clinic Lerner College of Medicine. He can be reached at goldmah@ccf.org or 216.445.5121.

Dr. Pizarro-Berdichevksy is a clinical fellow in the Department of Urology. He can be reached at pizarroj@ccf.org.

![Figure 1. In vivo imaging comparing preferential homing of bone marrow-derived mesenchymal stem cells one and four days after injection in nulliparous and vaginal-delivery mice.](image-url)
Chronic kidney disease (CKD) remains a formidable health problem affecting 26 million American adults. Millions more are at risk due to type 1 diabetes mellitus or hypertension, the primary causes of CKD.

Hemodialysis, a therapeutic technology pioneered by Cleveland Clinic with the establishment of the nation’s first program in 1950, has extended the lives of many patients with end-stage renal disease (ESRD).

Kidney transplantation, which Cleveland Clinic surgeons were among the first to perform beginning in 1963, has provided additional survival and quality-of-life benefits for ESRD patients.

A Half-Century of Achievement

More than 4,340 patients have received kidney transplants during the program’s half-century of operation. We celebrated 50 years of success in October 2013. One of the attendees was a former patient who received a kidney as a teenager in 1968 from her mother, making her kidney 91 years old.

Our most recent one-year and three-year graft and patient survival statistics show expected or better-than-expected outcomes compared with predictive statistical models representing similar transplant patients nationwide.

Though the availability of donor organs continues to be a limiting factor for all transplant programs, our volume remains substantial. In 2013 our Center for Renal Transplantation at Cleveland Clinic’s main campus performed a record 184 kidney transplants, a 12 percent increase from the previous year, making us the busiest program in Ohio for the calendar year.

This growth in transplantation is due, in part, to an increase in the number of living donor procedures. In 2013, 44 percent of Cleveland Clinic’s kidney-only transplants involved living donors.

The acquisition of these organs is largely the result of a relationship begun in 2011 with the National Kidney Registry (NKR) to facilitate paired donations. In 2013 Cleveland Clinic was the seventh largest NKR participant by volume among 75 hospitals. This collaboration has enabled us to perform more than 20 living-donor transplants that otherwise would not have occurred. Through this program, an incompatible donor’s kidney is procured in Cleveland and shipped to a matching donor elsewhere in the United States. In return, Cleveland Clinic has received organs from as far away as Los Angeles. Locally unmatched altruistic donors make it possible for extended chains of transplants to occur; in 2013 Cleveland Clinic transplant surgeons participated in the second-largest paired kidney exchange to date, involving 56 donors and recipients and 19 hospitals.

More than 90 percent of our living donor nephrectomies were performed laparoscopically — a technique we have employed in more than 1,000 patients since 1997, including the first single-port kidney removal in 2007 and the first robotic transvaginal nephrectomy in 2012.

To further assist with the organ shortage, our transplant program has extended the use of the deceased donor pool via pediatric en bloc and dual adult kidney transplantation. We also are conducting research intended to improve pretransplant prediction of risk of rejection and acute and chronic allograft injury. We have instituted a waitlist intravenous immunoglobulin desensitization program to enhance transplant opportunities for highly sensitized patients.

Wait-Time Improvements

We have streamlined the assessment process for transplant candidates, resulting in a significant reduction in the time from patient referral to evaluation and evaluation to listing in the United Network for Organ Sharing (UNOS) registry. The entire process is now completed in less than 80 days. We have refined the pretransplant monitoring and preparation regimens as well, contributing to our center’s 36.3-month median wait time to transplant, compared to the UNOS Region 10 and national averages of 40.7 months and 54.3 months, respectively, for patients listed between 2007 and 2012 (Figure 1).

Analysis of post-transplant data had shown that delayed graft function was a major factor in determining length of stay in prior years. Improved management of the transition from hospital to outpatient enabled us to decrease patients’ mean length of stay in 2013 to less than six days, the shortest duration in the past four years (Figure 2).
Expanding Transplant Services

Cleveland Clinic has extended the reach and impact of the renal transplant program well beyond our main campus (Figure 3), beginning in 1987 with the alliance of our Glickman Urological & Kidney Institute and West Virginia’s Charleston Area Medical Center, where more than 1,000 transplants have been performed. A similar collaboration with St. Vincent Indianapolis Hospital in 2009 has resulted in more than 200 transplants to date. Renal transplantation began at Cleveland Clinic-managed Sheikh Khalifa Medical City in Abu Dhabi in 2007, and at Cleveland Clinic Florida in August 2013. Our transplant program is truly a global resource.

Figure 1. Time to kidney transplant for waitlist patients.

Figure 2. Hospital mean length of stay for kidney transplant patients.

Dr. Klein is Chairman of Cleveland Clinic’s Glickman Urological & Kidney Institute and Professor of Surgery at Cleveland Clinic Lerner College of Medicine. He can be reached at kleine@ccf.org or 216.444.5591.
The diagnosis of low testosterone (T) and the risks and benefits of testosterone replacement therapy (TRT) remain controversial. While established guidelines for TRT do exist, the past several years have seen an explosion in prescriptions for TRT, with the majority of men lacking the clinical and laboratory testing necessary to guide safe and effective treatment. The surge in TRT has led to a backlash from physicians and payers against TRT use, especially for the stereotypical aging male trying to regain lost youth.

By contrast, there are at-risk patient populations with low T in whom TRT has the potential to both improve and prolong life. Low T is particularly common in men with HIV/AIDS, type 2 diabetes and end-stage renal disease, and is associated with poor survival in those with these diseases.

Indeed, for men on dialysis, low T is independently associated with death within three years. In type 2 diabetes, TRT has been shown to improve glucose control and prolong life.

**Querying the Chronic Kidney Disease Registry**

Few studies have looked at TRT in renal failure and disease. To explore the impact of low T in men with renal disease (but who are not yet on dialysis), we used the Cleveland Clinic Chronic Kidney Disease (CKD) Registry, focusing on men with CKD stages 3-4 (estimated glomerular filtration rate [eGFR] 15 to 59 mL/min/1.73 m²).

We identified 2,633 such men in the database who had a serum T measurement. Low T was identified in 54 percent and was more likely with lower eGFR, diabetes and a higher body mass index. In a multivariable Cox analysis, when compared with the highest quintile (T 512 to 7,469 ng/dL), the two lowest quintiles of T (100 to 225 ng/dL and 226 to 301 ng/dL) were associated with significantly higher mortality (HR 1.70, 95% confidence interval [CI] 1.21-2.39, and HR 1.56, 95% CI 1.12-2.19, respectively).

**Examining Low T’s Effect on Survival**

The next obvious question is whether low T is a marker of other illness or disease burden or whether it is actually a mechanistic target that can be treated with TRT to improve survival. This is still an open question.

Following successful kidney transplant, men with low T commonly have their T levels normalize. Many do not, however, especially if they are diabetic.

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**Key Points**

In men with renal disease, reduced levels of serum testosterone are associated with an increased mortality risk compared with higher testosterone levels.

A low serum testosterone level following kidney transplant predicts an increased risk of death and graft loss.

Whether low serum testosterone in these settings is a target for treatment with testosterone replacement therapy requires study.

Given the negative impact of low T on survival in renal disease, we next wished to study the effect of low T on renal transplant patient survival and graft survival. We utilized a quick and convenient resource: All patients have serum collected and frozen on the day of their transplant for use if needed in future immunologic testing.

We identified such samples in male patients transplanted six to 10 years ago, and were able to measure T and retrospectively correlate it with the clinical outcomes during the subsequent five years.

There were 197 male renal transplant recipients with sufficient serum to run the assay. Patients ranged in age from 14 to 75 years (mean 48.9 years). There were 100 living and 97 deceased donors, and 53 (27 percent) of the recipients were diabetic. Serum T ranged from 48 to 2,013 ng/dL (mean 477 ± 251.3) and was low (< 220 ng/dL) in 24 patients.

**Low T’s Disease Marker Potential**

Low T transplant recipients had worse one-year patient survival (75 vs. 95 percent, p = 0.003), three-year patient survival (62.5 vs. 86.1 percent, p = 0.008), one-year graft survival (62.5 vs. 92.4 percent) and three-year graft survival (50 vs. 76.3 percent, p = 0.01) than those whose T had normalized.

Survival curves showed significantly worse patient survival (p = 0.004) and graft survival (p = 0.02) for low T (Figures 1 and 2). In multivariable analysis, low T was independently associated with patient death (HR 2.27, 95% CI 1.19-4.32) and graft loss (HR 2.05, 95% CI 1.16-3.62).

As we have shown in these two studies, there may be a unique opportunity to study low T and TRT in men with renal dysfunction and renal transplantation, both as a marker for disease severity and as a target for TRT.

**Dr. Shoskes is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology and of the Transplant Center. He is a Professor of Surgery at Cleveland Clinic Lerner College of Medicine. He can be reached at 216.445.4757.**
Figure 1. Renal transplant patient survival comparing low and normal T levels.

Figure 2. Renal transplant graft survival in patients with low and normal T levels.
Kidney stone disease or nephrolithiasis is common, with nearly 1 in 11 individuals in the United States experiencing a stone event at some point in their lives. In addition, at least 50 percent of individuals experience another stone within 10 years of the first occurrence.

A small subset of these patients has identified metabolic abnormalities that cause a wide spectrum of stone events ranging from the spontaneous passage of small stone debris or gravel, causing minor symptoms, to frequent, painful calculi that do not pass easily, sometimes resulting in sepsis and loss of renal function.

The etiology of these metabolic stone diseases includes calcium oxalate, cystinuria, renal tubular acidosis, calcium oxalate and uric acid, and medullary sponge kidney. The more severely afflicted patients require frequent radiologic imaging of the urinary tract plus a variety of urologic interventions including ureteral stents, nephrostomy tubes and percutaneous nephrostolithotomy, extracorporeal shock wave lithotripsy, ureteroscopy with lithotripsy, or open surgical extraction of stones. Some patients report passing more than 70 stones during their lives.

For many of these patients, standard treatments will be inadequate to control the burden of their stone-related symptoms. Such patients may become dependent on chronic narcotics for pain relief, and for many, the metabolic stone burden becomes the driving force in their lives, interfering with daily activities, family life and well-being.

Surgery Alters Anatomy to Pass Stones

To address the problem of intractable metabolic stone disease with narcotic dependence, we offer patients a surgical option of replacing their ureter, which is the narrow point in the urinary tract that causes most of the symptoms during stone passage. We remove the kidney and all visible stones, perform a renal autotransplantation, and create a bladder tube, or modified pyelovesicostomy, to permit subsequent passage of stone debris (Figure 1).

It was anticipated that the procedure would result in (1) renal denervation to reduce pain, (2) near complete removal of stone debris while the kidney was ex vivo, (3) replacement of the ureter with a wide channel for future stone passage and (4) creation of an easier route to the kidney with endoscopic instruments if needed. In theory, vesicorenal reflux to wash out small stone granules would also likely occur over time.

Although this surgical approach alters the anatomy and ability to pass subsequent stones, it would not alter the metabolic derangements that cause stone formation.

Candidates for this procedure undergo the following assessments (Figure 2):

- Rigorous evaluation of prior treatments and metabolic testing
- Renal function testing
- Assessment of vascular and urologic anatomy
- Pain management evaluation with attempts to perform nerve blocks and confirm the visceral localization of the chronic pain
- Transplant psychiatric assessment to confirm any substance abuse, depression or psychiatric conditions, and to quantify the degree of psychological disruption caused by the intractable nephrolithiasis

Patients are selected for this approach only if there is a high likelihood of successful rehabilitation and future medical compliance and follow-up.

Autotransplantation Resolves Pain, Reduces Treatment Rate

During the past nine years, we have autotransplanted 28 kidneys in 22 patients (six bilateral), with resolution or improvement in chronic pain in all. About half of these patients continue to pass stone gravel that is usually painless. About one-third have had a subsequent procedure to remove a stone during a five-year interval. However, the stone treatment rates, even in those with cystinuria, were dramatically reduced from as many as 10 procedures a year to less than one every few years. The preoperative mean estimated glomerular filtration rate was 77.2 cc/min; postoperatively it was 73.5, 71.9 and 79.2 cc/min at 12, 36 and 60 months, respectively.

None of these procedures was performed for the sole purpose of stone removal. This aggressive surgical approach should be limited to carefully selected patients who meet strict criteria and for whom success can be reasonably predicted. Proper selection requires a team approach for the evaluation of candidates, including urologic surgeons,
physicians, nurses, pain management specialists and psychiatrists.

Renal autotransplantation and pyelovesicostomy can offer patients with intractable metabolic stone disease the opportunity to improve their quality of life and decrease daily narcotic use.

Dr. Flechner is a staff member of Cleveland Clinic’s Glickman Urological & Kidney Institute and of the Transplantation Center. He is a Professor of Surgery at Cleveland Clinic Lerner College of Medicine. He can be reached at flechns@ccf.org or 216.445.5772.

Dr. Noble is Surgical Director of Stone Disease at the Glickman Urological & Kidney Institute. He can be reached at noblem@ccf.org or 216.445.8501.

Additional Reading


Figure 1. Renal autotransplantation to the iliac fossa and creation of a modified pyelovesicostomy for subsequent stone passage.

Figure 2. Evaluation of patients with intractable nephrolithiasis.
Dialysis Therapies and Cleveland Clinic: Bringing Patients Back Home

Sheru Kansal, MD, and Leslie Wong, MD

Home dialysis therapies, which include peritoneal dialysis (PD) and home hemodialysis (HHD), have traditionally been underutilized in the United States. The majority of American patients with end-stage renal disease (ESRD) — about 92 percent — are treated with center-based intermittent (thrice-weekly) hemodialysis (IHD), compared with 6 percent for PD and 2 percent for HHD.

Worldwide, PD utilization is almost twice that of the United States.

Myths and Realities of Renal Replacement Therapies

Misconceptions are partially to blame for this underutilization of home therapies. Historically, PD has been viewed as the therapy of choice for the young and otherwise healthy, since patients are responsible for performing the dialysis themselves. Also, patients with diabetes have typically been advised to avoid PD since it involves increased glucose exposure.

Similar misconceptions have hampered the growth of HHD, particularly the notion that patients require a high level of intelligence to be successful on HHD, as well as the fear of catastrophic complications. Although observational studies lend credence to some of these notions, the reality of renal replacement therapy in the United States is that 80 percent of patients who start on IHD use a central venous catheter. These catheters are associated with numerous complications and contribute markedly to morbidity and mortality. (On p. 56 of this issue of Urology & Kidney Disease News, we outline an innovative new program being implemented at Cleveland Clinic to help decrease the use of central venous catheters through increased utilization of PD.)

Another reality of renal replacement therapy is that the model of thrice-weekly hemodialysis is fraught with issues that increase morbidity and mortality. Aggressive ultrafiltration (which is common for patients on IHD) is associated with myocardial stunning and increased mortality. Also, the seven-day week necessitates a two-day skip every week, which is associated with increased mortality compared with the rest of the week.

Bolstering the Utilization of Home Dialysis Therapies

The realities described here underlie a growing movement to get more patients on home therapies for ESRD. In fact, the Centers for Medicare & Medicaid Services has changed reimbursement for dialysis providers to incentivize home therapies.

Through various educational programs and care coordination, Cleveland Clinic has been able to increase its utilization of home therapies significantly in the past few years. Our HHD program, established in 2010, is the largest in Northeast Ohio and offers patients the options of short daily therapy or frequent extended hemodialysis. We have trained 18 patients during the past four years, of which 13 remain on therapy to date.

Our PD program has also seen extraordinary growth during the past couple of years. Currently, Cleveland Clinic’s Department of Nephrology and Hypertension provides care to almost 60 patients on PD, spread across three units. One of these units, Ohio Home Dialysis, is the single largest PD unit in the region.

Our successes are largely due to our commitment to patient education. Studies suggest that patients who undergo education about the different hemodialysis modalities are more likely to choose home therapies. Our department is well ahead of the curve in referring patients to dialysis modality education — almost 50 percent of patients who begin dialysis in our care have undergone modality education prior to starting, compared with about 20 percent nationally.

Furthermore, when patients attend dialysis education, they are more likely to actually start on PD. In the first half of 2014, 65 percent of patients who attended modality education actually started on PD, compared with about 20 percent nationally.

With a preponderance of evidence to suggest that dialysis education is imperative to good outcomes, we have taken further steps to educate our patients. We invite those who have expressed interest in home therapies to a quarterly seminar. During these seminars, patients meet the home therapy staff and are exposed to aspects of home therapies that are unavailable during educational classes.

More important, they are able to talk to patients currently on home therapies. This discussion provides an invaluable opportunity for patients to ask questions and receive insight from those with hands-on experience.

Key Points

- Misconceptions about home hemodialysis have hampered its acceptance in the United States.
- Education about hemodialysis modalities and opportunities to interact with patients on home therapies play a large role in facilitating home hemodialysis as a choice and optimizing outcomes.

More articles online at ConsultQD.clevelandclinic.org/urology-nephrology
Leslie Wong, MD; Sheru Kansal, MD; and Dustin Thompson, MD

Patients with end-stage renal disease (ESRD) who present to the hospital and require urgent initiation of dialysis (defined as the need for dialysis within two weeks of presentation) almost always begin treatment with a central venous hemodialysis catheter.

Use of central venous hemodialysis catheters is strongly associated with bloodstream infection and reduced survival in ESRD. Despite these known risks, there is usually no alternative to a central venous catheter and hemodialysis in this setting.

**PD Averts Infection Risk but Normally Requires Wait**

Peritoneal dialysis (PD) is a viable but underutilized treatment for patients who require urgent initiation of dialysis. Unlike hemodialysis, PD does not involve use of a central venous catheter and is largely free of risk for bloodstream infection.

PD is performed by inserting a silicone PD catheter into the abdominal cavity, where a sterile dialysis solution is instilled and drained to remove waste products and excess fluid via ultrafiltration across the peritoneal membrane.

Traditionally, a minimum wait period of two weeks after PD catheter insertion is required to allow healing of the catheter exit site to avoid dialysis fluid leakage and infection. The availability of operators skilled or interested in placing PD catheters is limited.

The wait requirement to start dialysis and the lack of support for timely PD catheter insertion at many hospitals have discouraged PD use despite its potential to avoid bloodstream infection.

**Urgent-Start PD Is Promising but Faces Barriers**

Recently, a modified technique known as urgent-start PD has gained interest in the United States as a means to break the cycle of reliance on central venous hemodialysis catheters to treat ESRD patients who require unplanned dialysis initiation.

Urgent-start PD involves the timely placement of a PD catheter instead of a hemodialysis catheter, followed by supine, low-volume PD to reduce the risk of dialysis fluid leakage and complications.

This approach has been employed in Europe for many years and has recently been successfully adopted by some U.S. centers. Widespread adoption of urgent-start PD is limited, however, by infrastructure barriers and lack of experience with and knowledge about PD at many institutions.

Led by nephrologists at Cleveland Clinic, a multidisciplinary task force was created that included interventional radiology, surgery and nursing stakeholders interested in reducing the use of central venous hemodialysis catheters for ESRD patients.

Using established best practices in PD catheter placement and dialysis care as guidelines, the task force created a protocol to identify and educate patients and provide them with the option of urgent-start PD instead of default hemodialysis via a central venous catheter.

This protocol includes clear steps that outline the process of referral, patient selection and communication between different caregiver teams. Additionally, the protocol includes explicit roles and responsibilities for interventional radiologists and surgeons involved in PD catheter placement and care. Order sets and a visual urgent-start PD guide were developed to facilitate education and understanding by nursing staff and physicians about the desired process of care.

PD nurses from Fresenius Medical Care (FMC), a national dialysis provider affiliated with Cleveland Clinic, were given hospital vendor privileges to facilitate planning for transitioning patients from the hospital to the outpatient PD setting in a safe and appropriate manner.
A Defined Protocol for Urgent-Start PD Care

Instead of relying on central venous catheters, patients needing urgent dialysis who meet defined selection criteria can now be offered urgent-start PD.

Candidate patients are identified and referred to a core team of expert physicians and nurses for evaluation. If the patient has no contraindications, the core team approves initiation of the urgent-start PD protocol. Specialists in interventional radiology place the PD catheter, and a standard supine PD prescription and exit site care pathway are implemented. Patients and their families receive additional education and support to help them adjust to dialysis.

If the PD catheter malfunctions, the surgical service is consulted for timely revision. After patients have been stabilized, they are discharged to an affiliated FMC dialysis unit to continue urgent-start PD treatment until the PD catheter site has healed sufficiently for standard home dialysis training.

We recently implemented the Cleveland Clinic urgent-start PD program and created a PD research registry to track patient outcomes. Our experience suggests that through a dedicated multidisciplinary approach, efforts to promote PD in appropriate patients will help reduce use of central venous hemodialysis catheters and their associated complications.

Dr. Wong is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Nephrology and Hypertension. He can be reached at wongl@ccf.org or 216.445.0673.

Dr. Kansal is a staff member of the Department of Nephrology and Hypertension. He can be reached at kansals2@ccf.org or 216.444.0026.

Dr. Thompson is an associate staff member of Cleveland Clinic’s Department of Diagnostic Radiology. He can be reached at thompsd9@ccf.org or 216.444.2136.
The past 12 years have seen several paradigm shifts in the management of children with febrile urinary tract infections (UTI) and vesicoureteral reflux (VUR), including but not limited to:

- The use of continuous antibiotic prophylaxis (CAP) and the emergence of antimicrobial resistance (AMR).
- The use of minimally invasive endoscopic techniques such as dextranomere/hyaluronic acid.
- The use of laparoscopy and robotic surgery.
- Reconsideration of whether a voiding cystourethrogram (VCUG) should be employed after a first febrile UTI in an infant.

Historically, children with febrile UTIs underwent a VCUG to determine if they had VUR. The purpose of this practice was to identify children who were at risk for progressive renal scarring, hypertension and, ultimately, renal demise from reflux nephropathy.

Children thus diagnosed were subsequently placed on CAP to keep the urine sterile while the tincture of time determined whether the VUR would resolve spontaneously during a defined period.

Many concerns have been raised regarding CAP, the most pertinent of which pertains to its inappropriate use leading to AMR.

The advent of endoscopic treatment with the copolymer dextranomere/hyaluronic acid (Deflux®) provided a minimally invasive outpatient procedure that could correct the reflux, thus avoiding reconstructive surgery and precluding the use of CAP.

However, long-term success rates of Deflux do not consistently match those of open surgery. In addition, peculiar long-term sequelae are related to the Deflux implant, the significance of which has not been clearly determined (i.e., chronic intramural bladder calcifications).

Should Low-Grade VUR Be Diagnosed?

Also called into question is whether all children with VUR, particularly low-grade VUR, should have been diagnosed in the first place. Some believe that since low-grade VUR is more likely to resolve spontaneously, perhaps we should not treat or even diagnose low-grade VUR, considering the potential for long-term antibiotic use to lead to AMR.

Key Points

An individualized approach to managing pediatric vesicoureteral reflux (VUR) considers the history of renal scarring and risk of VUR to guide diagnostic study. The individualized strategy can reduce the number of unnecessary voiding cystourethrograms performed and may identify those who require continuous antibiotic prophylaxis and subsequent definitive surgical treatment.

Antibiotic prophylaxis for VUR should be reserved for children at increased risk of developing pyelonephritis and renal scarring.

This concern led to the 2011 American Academy of Pediatrics policy statement regarding VUR, which states that children with a first febrile UTI do not require VCUG and that a renal ultrasound can be obtained instead. If further UTIs ensue, VCUG may then be warranted. Primary care practitioners were inclined to follow such guidelines because parents abhorred VCUGs, and they and the practitioners were concerned about prophylaxis-related AMR.

Without an early VCUG, urologists were concerned that they would not identify renal infections in a timely fashion, leading to progressive renal scarring, and thus reverting to a time when children presented with hypertension and chronic renal failure due to reflux nephropathy.

Meta-analysis of VUR studies further indicated that perhaps not all VUR patients initially require antibiotic prophylaxis unless additional confounding factors, such as bladder and bowel dysfunction, abnormal renal sonograms, or pre-existing medical conditions are present. This is especially true for lower grades of non-dilating VUR, which are at reduced risk of causing progressive renal scarring and are more likely to resolve spontaneously.

A more recent study known as the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial has concluded that the use of antibiotic prophylaxis does prevent recurrent UTIs but does not necessarily prevent renal scarring.

Individualized VUR Treatment Plans

At Cleveland Clinic’s Glickman Urological & Kidney Institute, pediatric urologists employ a specific individualized treatment plan for each VUR patient. It is based on information gleaned from meticulous history-taking, including a detailed bladder and bowel elimination history; specific information about the urine culture results, including the actual organism and how the culture was obtained; and the clinical scenario regarding the first febrile UTI.
We reserve the option to start CAP in infants and children younger than 2 if it is likely that they presented with pyelonephritis. We believe that by employing this individualized clinical approach, we can exclude false positives, reduce the number of unnecessary VCUG studies and perhaps correctly identify those who do require CAP and subsequent definitive surgical treatment as necessary.

We consider a top-down approach in which a VCUG is performed only if a prior dimercaptosuccinic acid (DMSA) study confirms renal scarring and only in subsets of patients who we believe are at reduced risk of having VUR but whose clinical scenario compels us to perform a diagnostic study.

We also believe that antibiotic prophylaxis should be reserved for children at increased risk of developing pyelonephritis and renal scarring: those with dilating grades of VUR (grades 3-5) of those with low-grade reflux in children who have bowel/bladder dysfunction or abnormal renal sonograms. Through judicious use of CAP, we aim to lower the potential for the development of AMR. We consider Deflux as a tool for children with low to moderate grades of VUR in whom medical therapy with CAP has failed and who cannot undergo definitive surgical repair.

We advocate an open ureteral reimplant, either intra- or extravesical, as the primary mode of treatment in patients who have breakthrough UTIs despite medical therapy with CAP. By employing precise surgical techniques to achieve an obliquely traversing, sufficiently long, intramural ureter, using coaptation of the intramural ureter via a flap valve mechanism, we can definitively prevent VUR and progressive renal scarring. Despite the considerable advances in laparoscopic robotic surgery, we adhere to the standard of a ureteral reimplant performed via an open extraperitoneal approach through a 5 cm Pfannenstiel incision, which significantly reduces potential morbidity.

Using a Tactical Approach

The treatment of VUR remains somewhat nebulous. Urologists for the past 12 years have fluctuated on a treatment spectrum because they are not truly sure which patients are being helped, even with newly available treatment techniques. Although guidelines have been instituted by our governing bodies, these do not truly identify those patients who are at increased risk.

We have carefully reviewed and considered present guidelines and recommendations, which cannot be used to manage unique patients, and we are mindful of the past, when reflux nephropathy presided. We believe that a tactical individualized approach brings Cleveland Clinic pediatric urologists to the forefront in identifying patients at increased risk for long-term sequelae of VUR, and in providing definitive treatment.

Dr. Donohoe is an associate staff member in Cleveland Clinic Glickman Urological & Kidney Institute’s Department of Urology. He can be reached at donohoj@ccf.org or 216.636.9483.

Dr. Rhee is an associate staff member of the Department of Urology and of Cleveland Clinic Children’s and the Pediatric Institute. She can be reached at rhea@ccf.org or 216.636.9483.

Additional Reading


Defects in the genitourinary tract are among the most common congenital problems. Affected children can have problems such as abnormal size, shape or location of their genitals or lack of proper function. They may be missing reproductive organs or have duplicates of an organ. Patients with neurological conditions such as cerebral palsy or spina bifida often have substantial urological comorbidity.

During youth and adolescence, these patients typically are treated by pediatric specialists, including pediatric urologists, who primarily focus on renal deterioration, incontinence and genital appearance.

Improvements in pediatric care have enabled more patients with genitourinary defects to survive into adulthood and have a higher quality of life. As they grow older, many patients are better served by being transitioned into adult-centered care. Such a transition can allow physicians to focus on the medical, psychosocial and educational aspects of these patients’ unique maturation issues, such as sexuality, fertility or post-pubertal genital function and appearance.

Timing of the Transition

Pediatric specialists have an integral role in deciding when to begin transitioning patients and helping them make the change. In some cases, they remain an important part of the patient’s healthcare team even after transition has occurred.

I am often asked when transition should begin. My typical answer: “When everyone is ready.” Transition requires agreement from all parties involved — the patient, his or her personal caregivers and the providers. The process can take several years, so starting as early as age 12 allows ample time for full readiness by age 18 to 20. Many pediatric facilities do not permit patient admission beyond the age of 24 or 26, so this often represents the upper age limit for transition.

Transition typically involves a stepwise process in which pediatric providers regularly assess their patient’s readiness. Factors to consider include a patient’s cognitive level and ability to assist in his or her care, as well as whether the patient’s urological issues are of an adult nature, such as those relating to sexual activity or pregnancy.

Pediatric providers should document their readiness assessment findings and initiate conversations with all involved about the optimal timing for transition. They should help the youth identify an appropriate adult provider and, after obtaining consent, communicate with that provider about the pending transfer of care and share medical records.

Key Points

Improvements in pediatric treatment are enabling more children with congenital genitourinary defects to survive into adulthood, raising the need for an eventual transition to adult-centered medical care.

Transition can take several years and requires agreement of all parties involved, coordination, and readiness and needs assessment.

The adult-centered urologist who assumes oversight of a young patient with congenital genitourinary anomalies must be prepared to deal with complex and wide-ranging medical issues.

After the patient has begun seeing the adult provider, pediatric providers should follow up to confirm the transfer of care has occurred, answer any questions and offer ongoing consultation services as needed.

Forgoing Transition Can Be a Mistake

Simply transferring these patients into any adult urology practice can be a mistake, as adult providers often do not have specialty expertise in congenital anomalies or the clinical resources to treat these very complex patients. Transitional urology and urological congenitalism often require an approach more akin to geriatrics or palliative medicine, since the patient has many competing medical issues that must be considered to achieve optimal outcomes.

Diagnoses that fit into this category include:

- Myelomeningocele (spina bifida)
- Exstrophy
- Hypospadias
- Disorders of sexual differentiation (intersex)
- Posterior urethral valves
- Pediatric cancer
- Problems such as muscular dystrophies that affect the urological system with progression of age

These patients are not typical new consults. Initial examinations can be difficult and may need to be conducted under anesthesia to define the anatomy thoroughly. These patients often have been heavily dependent on family members for daily care, so taking a history may require two interviews: one with the caregivers present and one with them outside the exam room. As these patients begin to assume a decision-making role after a lifetime of others being in charge of their care, be aware that the change may cause some tension for patients and their caregivers.
Assessing Patients’ Needs, Goals

Patients often present with a single focus of interest, such as erection quality, whereas I may be more concerned with other urological issues that seem more critical, such as worsening hydronephrosis. Addressing both takes time and, sometimes, careful negotiation.

After gathering a full medical history, I perform a thorough baseline assessment of patients’ urological health and ask about their goals and how their urological issues affect their quality of life. Together, we begin to map out treatment plans.

These are a few highlights of what transitional urology offers and how it can be a valuable resource for pediatricians and pediatric urologists with young adult patients whose needs have expanded beyond those of childhood. Pediatric providers are a key component in making the transition a success, by helping lay its groundwork, perceiving the patient’s readiness for the change, and connecting the patient with the right provider for the next phase of his or her life.

Dr. Wood is a staff member of Cleveland Clinic Glickman Urological & Kidney Institute’s Center for Genitourinary Reconstruction and an Assistant Professor of Surgery at Cleveland Clinic Lerner College of Medicine. She can be reached at woodh@ccf.org or 216.444.2146.

### CONDITIONS THAT TRANSITIONAL UROLOGISTS TREAT

- Urinary incontinence
- Catheterization problems, including stomal stenosis or urethral strictures
- Penile curvature with erections
- Abnormalities of penile appearance
- Problems resulting from abnormal vaginal development
- Renal insufficiency due to kidney scarring
- Kidney stones
- Increased bladder cancer risk
- Male and female infertility
- Hernias from prior surgeries
- Chronic constipation from neurogenic bowel

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**Figure 1.** Relative importance of urologic and health issues throughout the life span of a patient with myelomeningocele.
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The Cleveland Clinic Way
By Toby Cosgrove, MD, CEO and President, Cleveland Clinic
Great things happen when a medical center puts patients first. Visit clevelandclinic.org/ClevelandClinicWay for details or to order a copy.

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Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,000 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 75 northern Ohio outpatient locations (including 16 full-service family health centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

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

Daniel Shoskes, MD
Glickman Urological & Kidney Institute
Medical Editor, Urology

Sankar Navaneethan, MD
Glickman Urological & Kidney Institute
Medical Editor, Nephrology

John Mangels
Managing Editor
mangelj@ccf.org

Barbara Ludwig Coleman
Graphic Designer