Cleveland Clinic Excels in Latest U.S. News Rankings

Urology ranked No. 2 in the nation; Kidney disorders ranked No. 3

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

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

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

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Center for Robotics & Image Guided Surgery
Chairman’s Report

The Global Reach of the Glickman Urological & Kidney Institute

We are pleased to bring you another edition of Urology & Kidney Disease News. Like prior volumes, this edition is intended to keep you abreast of activities in the Glickman Urological & Kidney Institute (GUKI) by introducing our newly hired physicians, sharing the recognition our physicians and nurses have earned from external organizations, providing an overview of a busy schedule of hosted educational conferences, and outlining the latest advancements in research and clinical care.

The underlying theme of this issue is the global impact of the institute’s expertise on patient care. GUKI physicians practice in 17 locations in Northeast Ohio, as well as in Indianapolis, Charleston, W.Va.; and Weston, Fla. In 2009 we evaluated and treated patients from 81 of the 88 counties in Ohio, 43 states and 13 countries on four continents. Some of our patients traveled from as far as South America, Africa and Asia. In the last three years we also have hosted 175 visiting physician observers from all over the world for as long as three months to share our approaches to learning and delivering medical care and, in turn, we have learned about diverse and far-flung social and medical cultures. Through a new relationship with an experienced provider in Toronto, high-intensity focused ultrasound (HIFU) is now available at Cleveland Clinic Canada for select patients with localized prostate cancer.

This publication contains highlights from one of our satellite programs, including an overview of our renal transplantation program at St. Vincent’s Hospital in Indianapolis (see page 7). We also highlight important scientific contributions from the Department of Urology at Cleveland Clinic Florida (see articles on pages 44 and 73).

GUKI has a long tradition of leveraging technology for patient benefit. Current efforts include the development of technology for virtual monitoring of hypertension (see article, page 65) and expanded indications for robotics in the management of renal and bladder tumors (see the articles on pages 34-55), including new developments in single-port robotic surgery (page 36). Another way we have extended our expertise is through the launching of a remote surgical telementoring program, a first-of-its-kind program that allows inexperienced robotic surgeons performing urologic procedures at remote sites to be mentored by our faculty in Cleveland in real time through Internet-based bi-directional audio, video and telestration capability. Since inception, we have performed live mentoring for nine cases. A description of the program can be found on page 8.

Finally, we believe GUKI embodies the best of the institute model of research and patient care at Cleveland Clinic, as evidenced by the scope of multidisciplinary programs in both spheres. On page 64 is a description of our chronic kidney disease registry, a combined effort of GUKI nephrologists, the Quantitative Health Sciences team and the eResearch team in the Information Technology Division to track the management of CKD over the entire care spectrum and explore the role of the electronic medical record in identifying and managing CKD patients throughout our health system. And on page 14 we include an update on XMRV, a novel retrovirus associated with prostate cancer and chronic fatigue syndrome, discovered and characterized by investigators in GUKI and Cleveland Clinic’s Lerner Research Institute.

I hope you enjoy the rich material in this issue.

Eric Klein, MD
Staff Awards and Appointments

Steven Campbell, MD, PhD, was named secretary/treasurer of the Society of Pelvic Surgeons.

Howard B. Goldman, MD, received the Inter-Institutional Subaward between Case Western Reserve University and Cleveland Clinic Lerner College of Medicine from the National Institutes of Health, National Institute of Neurological Disorders and Stroke for his research: Multi-functional Neuropathic Systems for Restoration of Motor Function.


Jihad H. Kaouk, MD, was promoted to Full Professorship at Case Western Reserve University in August 2010.

Jihad H. Kaouk, MD, is the first to hold the distinguished Zegarac-Pollock Family Foundation Endowed Chair. The chair is supported by a $2 million gift from the Zegarac-Pollock Family Foundation. The new chair supports research by Dr. Kaouk, who was the first surgeon at Cleveland Clinic to perform laparoscopic surgery through a single, small incision through the navel. He is among only a handful of surgeons across the nation pioneering single-port laparoscopy and robotic applications.

Michael C. Lee, MD, was awarded The Society of Laparoendoscopic Surgeons Award for Best Poster at the 19th SLS Annual Meeting and Endo Expo 2010 for “Tumor in Solitary Kidney: Laparoscopic partial nephrectomy versus laparoscopic cryoablation,” September 2010.

Andrew Stephenson, MD, was selected for an American Cancer Society Institutional Research Grant entitled, “Using Decision Analysis to Facilitate Decision-Making Regarding Prostate Cancer Screening.”

James Ulchaker, MD, has been named the 2011-2012 AUA Gallagher Scholar.

Christina Ching, MD, won the 2010 John D. Silbar Award for outstanding resident from the North Central Section of the American Urological Association.

Christina Ching, MD, and Mary Katherine Samplaski, MD, each won the 2010 Traveling Fellowship Award from the Society for the Study of Male Reproduction.

Kiranpreet Khurana, MD, won the 24th Annual Graduate Level-one Award 2010, presented by the Cleveland Clinic Alumni Association.

Amit R. Patel, MD, was awarded 2010 Outstanding Laparoendoscopic Resident Award by the Society of Laparoendoscopic Surgeons.

Upcoming Conferences

May 11 - 13, 2011

Health Care Quality Innovation Summit
Optimizing Value and Securing a Future of Innovation and Quality
InterContinental Hotel and Bank of America Conference Center, Cleveland, Ohio
Register Today! www.ccfcme.org/Quality11

June 3 – 4, 2011

3rd Annual Single Port Laparoscopy, Robotics and NOTES Surgery
Course Director: Jihad Kaouk, MD
A multidisciplinary two-day course, which includes educational insight and hands-on lab designed for physicians and surgeons from various specialties interested in the minimally invasive techniques of single-port laparoscopy, robotics and NOTES including gastroenterology, urology, nephrology, gynecology, colorectal surgery, bariatric surgery and general surgery.
Please visit ccfcme.org for more details on this conference as they become available.
New Staff  The Glickman Urological & Kidney Institute welcomes the following new staff members:

Urology

Prem S. Jawa, MD, received his medical degree at the University of the Punjab in India. He received his postgraduate training from the Medical College Hospital in Rhotak, India, and received his general surgery training at the Royal College of Surgeons in Edinboro. Additionally, he completed a urology residency and gained board certification in urology at Huron Hospital. Dr. Jawa also received board certification in urology from the Royal College of Physicians and Surgeons of Canada.

Dr. Jawa serves as the Glickman Urological & Kidney Institute’s Inpatient Medical Urologist, providing urology consults from other departments. He also completes follow-up with patients in the Glickman Tower outpatient clinic. His primary interest is general urology.

Omar Ortiz-Alvarado, MD, received his medical degree and underwent postgraduate training from the University of Puerto Rico School of Medicine. He completed his fellowship training at the University of Minnesota.

Dr. Ortiz-Alvarado’s specialty interests include urologic oncology, renal stone disease, general urology, and laparoscopic and endourology surgery.

Raj Ramanathan, MD, earned his medical degree at the Christian Medical College, Vellore, India. He underwent postgraduate training at the Postgraduate Institute of Medical Education and Research in Chandigarh, India, and the Sanjay Gandhi Postgraduate Institute of Medical Sciences in Lucknow, India, and has completed fellowships in robotics and laparoscopic urology at the University of Massachusetts Medical Center and at the University of Miami Medical Center.

Dr. Ramanathan’s specialty interests include general urology surgery, minimally invasive surgery, laparoscopic and robotic surgery, and endourology.

Alok Shrivastava, MD, MBBS, MCh, earned his medical degree at the M.G.M Medical College in Indore, India, and underwent postgraduate training at the Sanjay Gandhi Postgraduate Institute of Medical Science in Lucknow, India. He completed his urology residency and robotic urology fellowship training at the Vattikuti Urology Institute, Henry Ford Health System in Detroit. Dr. Shrivastava heads the section of Urologic Oncology at Cleveland Clinic Florida. He is also Affiliate Associate Professor at Florida Atlantic University.

Dr. Shrivastava’s specialty interests include robotic radical prostatectomy with or without vein nerve sparing, robotic partial and radical nephrectomy and robotic radical cystectomy.

Richard D. Levin, MD, FACS, received his medical degree and underwent postgraduate training at George Washington University School of Medicine in Washington, D.C. He completed fellowship training at the National Cancer Institute, National Institutes of Health in Bethesda, Md.

Dr. Levin’s specialty interests include laparoscopic and endourology, microsurgery and infertility, female urology, incontinence, trauma, perineal surgery, impotence, infertility and urologic stone disease.

Manoj Monga, MD, received his medical degree from the Chicago Medical School and underwent postgraduate training at Tulane University School of Medicine in New Orleans.

Prior to joining Cleveland Clinic, Dr. Monga was the Joseph Sorkness Endowed Professor and Vice Chair of the Department of Urologic Surgery at the University of Minnesota, where he was the Residency Program Director from 2005-2008. Dr. Monga also served as the Co-Director of the Center for Systematic Reviews in Urologic Surgery for the Minneapolis Veterans Affairs Healthcare System.

Manoj Monga’s specialty interests include nephrolithiasis, endourology and medical device design and innovation. He was awarded the Arthur Smith Young Innovators Award in 2007 by the Endourology Society and is currently the President of the Engineering & Urology Society.

Dr. Monga’s specialty interests include nephrolithiasis, endourology and medical device design and innovation.
Saraswathi Gopal, MD, received her medical degree from Madras Medical College and Research Institute in India. She underwent postgraduate training at Beth Israel Medical Center in New York.

Dr. Gopal’s specialty interests include hemodialysis and peritoneal dialysis, chronic kidney disease and renal transplantation.

Sheru Kumar Kansal, MD, received his medical degree from the State University of New York at Buffalo. He underwent postgraduate training at The Mary Imogene Bassett Hospital in New York, Western Pennsylvania Hospital in Pittsburgh and the University of Pittsburgh Medical Center.

Dr. Kansal’s specialty interests include chronic kidney disease, bone disease associated with CKD and renal replacement therapies.

Jonathan J. Taliercio, DO, received his medical degree from the New York College of Osteopathic Medicine and went through postgraduate training at Cleveland Clinic. He has a bachelor’s degree in sports medicine from the University of North Carolina at Chapel Hill.

Dr. Taliercio’s specialty interests include acute kidney injury.

George Thomas, MD, earned his medical degree at Bharati Vidyapeeth’s Medical College in India. He underwent postgraduate training at the Johns Hopkins University School of Public Health in Baltimore, St. Elizabeth’s Medical Center (Tufts Medical Center) in Boston and Cleveland Clinic.

Dr. Thomas’s specialty interests include hypertension, acute kidney injury and chronic kidney disease.

Updates from Cleveland Clinic’s Indiana Partner: Urologic Advancements at St. Vincent Indianapolis Hospital

Alvin Wee, MD

- Since first offering kidney transplants in 2009, our St. Vincent-Indianapolis program has performed 60 procedures through the end of August 2010. The first report by the U.S. Scientific Registry of Transplant Recipients (ustransplant.org) recently reported our program showed a one-year, 100% graft and patient survival. We have 65 patients on the waiting list and are evaluating new potential recipients and living donors weekly with collaborative support from transplant coordinators and nephrologist Mahendra Govani, MD, FRCP.

- In May 2010 we performed the first multi-organ transplant completed at St. Vincent, a combined heart-kidney transplant. Both graft and patient are doing excellent due to great cooperation between cardiac and renal transplant services.

- The first single-port radical nephrectomy was completed by Alvin Wee, MD, in July 2010. The procedure included simultaneous repair of umbilical hernia with the patient discharged in less than 24 hours.

- Vascular access and general surgery is offered by Paul W. Nelson, MD, Director of Transplant Services at St. Vincent.

- Drs. Wee and Nelson hope to begin pancreas transplantation before the end of 2010.
Transferring Skill through Telementoring:
The Glickman Urological & Kidney Institute’s Global Reach

The Cleveland Clinic’s global reach has continually grown over the last six years through forged partnerships in Austria, Egypt and the United Arab Emirates. To further emulate and expand on these far-reaching efforts, The Glickman Urological & Kidney Institute is now performing remote real-time surgical observations and mentoring of laparoscopic and robotic surgery through telecommunication technology to assist, guide and educate urologists at a distance.

Based on the principle of providing access to one of the world’s largest experience in urologic laparoscopic and robotic surgery through telementoring, our center uses advances in imaging technologies, virtual reality and teleconsultation to transfer surgical applications, improve training and decrease morbidity to trainees and their patients thousands of miles away. Due to the complexities of urological laparoscopic procedures and the advanced skill required through a steep learning curve, familiarity with laparoscopic anatomy related to urological organs for both transperitoneal and retroperitoneal access are essential. While hands-on mentoring in the OR is critical to train for these procedures, this approach often hinders access due to the additional effort of time, travel and extra resources required.

Telementoring

We are bridging these gaps through two telementoring approaches. The first, and primary method, uses advanced communications technology to allow a second surgeon in an operating room anywhere in the world to observe various types of laparoscopic and robotic surgeries, also known as teleconferencing. Not limited to one observer for each surgery, several remote sites can be scheduled to log on from offices or homes to view state-of-the-art procedures, such as robotic partial nephrectomy, single-port radical nephrectomy and single-port radical prostatectomy. By controlling the field of view through five cameras, the remote surgeon’s screen presents details such as the patient’s position, a global view of the operating room, the exact position of the organs, the positioning of the surgeon on the da Vinci® Surgical System (Intuitive Surgical, Sunnyvale, Calif.), and where the patient is being cut and sutured.
Telestration

Our second telementoring approach allows us to view a remote surgeon’s robotic procedure through on-site cameras, bringing their OR onto computer screens at Cleveland Clinic. Through telestration, an illustrative technique that uses a tablet laptop computer, we can indicate suggested surgical approach corrections on the operating surgeon’s video monitor. The computer-linked illustrations enable us to offer guidance, such as where to make an incision, or to highlight a tumor mass, in addition to offering experienced approaches to each case.

“Telementoring provides a unique approach to share our experience with many due to technology that wasn’t available before,” says Jihad Kaouk, MD, Director, Center for Robotics & Image Guided Surgery. “We are currently scheduling a variety of surgeries with physicians from remote sites around the country and the world to observe.”

A modern-day approach that continues to grow, telementoring is allowing us to share knowledge and techniques with our colleagues around the nation and the world through critical assistance and training. While the future for this technology is endless, the goal remains the same: to offer easy access to advanced urologic laparoscopic and robotic procedures through a cost-effective tool, which benefits both the surgeon and their patients.

“This program is another way we are leveraging state-of-the-art technologic advances for improving patient care,” says Eric A. Klein, MD, Chairman, Glickman Urological & Kidney Institute.

The Glickman Urological & Kidney Institute is bridging distances in urologic surgery around the world through its telementoring efforts. Having one of the largest experiences in urologic laparoscopic and robotic surgery, we are transferring this skill through technology to surgeons and their operating rooms throughout the United States, and those in far-off countries, including South America, Europe and the Middle East.
A significant number of men who undergo prostate biopsy (PBx) may harbor cancer in the gland that simply eludes identification. This is especially likely when inadequate biopsy strategies (sextant) were employed, when a side fire biopsy probe sampled only the posterior portion of the gland, or when high-grade prostatic intraepithelial neoplasia (HGPIN) or atypia were identified. It is widely assumed, but unproven, that rising PSA following negative prostate biopsy is more likely to indicate prostate cancer (PCa). However, no data support this assertion and there is no consensus on management of this heterogeneous population. Studies indicate that approximately one-fourth of all patients undergoing a second biopsy will be found to have prostate cancer.

Although missing small low-grade cancers might actually allow the patient to avoid unnecessary treatment, some of these are high grade so identification may offer the ideal scenario for curative therapy. MRI and template-guided biopsy have been proposed, but not validated in this setting, and data on their accuracy are largely absent.

We and other centers have identified that the anterior “horn” of the apex is the most likely site where cancer is missed on any biopsy. Additionally, it has now been clearly shown that the sextant biopsy scheme is unacceptable and the standard is to perform at least a 10-core biopsy using periprostatic nerve block initially allowing for painless biopsy including transrectal saturation biopsy in the office setting. Based on experience, we believe a 14-core biopsy with an additional core on each side of the “very apex” (as termed by Katsuto Shinohara) offers the best alternative for initial biopsy. It has become more clear over time that anterior prostate cancers are more common than previously believed, based most likely on these cancers having eluded biopsy during routine approaches that typically under sample the anterior gland.

Early in our experience it became clear that saturation prostate biopsy (sPBx) does not improve cancer detection in the initial biopsy setting, but we recently showed that repeat 20-core transrectal saturation biopsy had a significantly higher detection rate when compared to extended PBx (ePBx) (33% vs. 22.4%, p < 0.0001). For patients with completely normal initial biopsy, sPBx demonstrated an almost 50% improvement (31.7% vs., 21.6%, p < 0.0002.) For the higher risk population with HGPIN or atypical small acinar proliferation (ASAP) on initial biopsy, PCa detection rate was higher with sPBx (34.6% vs. 21.7%, p=.08 for PIN and 44.4% vs. 30.6%, p=.124 for ASAP). The tradeoff is that 38.3% of patients with positive biopsy had clinically insignificant cancer (41.2% sPBx vs. 34.6% ePBx, p= 0.178). Thus, repeat biopsy has a substantial chance of finding significant cancer, but the potential to identify clinically insignificant cancer is also higher than during initial biopsy. Accordingly, we partner our thorough detection program with an aggressive active surveillance program, successfully and safely managing approximately 25% of all patients in the author’s practice.

Counterintuitively, extended and saturation biopsy protocols do not result in increased complications unless general anesthesia is used, which we believe explains the approximately 10% rate of urinary retention in patients undergoing “template” biopsy in the operating room. To address this phenomenon, we perform all 20-core transrectal saturation biopsies in an office setting with periprostatic nerve block.

Interest is high in improving the decision on whether a second biopsy is justified, with the development of nomograms and other prediction models by our team, as well as others. However, utilization of all indicators is limited by a number of factors, most significant being that they only give a prediction of the percentage of patients in such setting that will have a positive biopsy. Unfortunately, no model to date can dichotomize patients into a group that will almost surely have either a positive or negative repeat biopsy, so the clinician must still help the patient decide whether to undergo biopsy.

Recently, a number of adjunctive modalities have been proposed, including several urinary and serum based markers. The only one to become available for routine clinical practice is prostate cancer antigen 3 (PCA3), a urine-based marker that has received much attention recently. We offer PCA3 testing for men with an initial negative biopsy based on its ability to define whether a patient is at higher or lower risk of having undiagnosed prostate cancer compared to the risk suggested by PSA alone. However, the actual impact of PCA3 findings is limited, and, like PSA, actually creates only...
an artificial separation between men who do or do not have clear indication for repeat biopsy. In fact, we and others have published that percent-free PSA as a proportion of the total value is actually a better predictor of prostate cancer risk; in the very low ranges, such as 12% or lower, its positive predictive value is very high and suggests clear indication for repeat biopsy. These and other urine- and serum-based markers continue to improve prediction of the risk of undiagnosed cancer, but to date none has proven capable of showing that a patient does not have significant cancer without performing a repeat biopsy to address suspicion of undiagnosed prostate cancer.

In summary, a negative biopsy does not assure absence of malignancy and at least 1/3 of those patients have unrecognized prostate cancer, the majority of which will not fit any widely used definition of “clinically insignificant.” Template biopsy is intuitively appealing, but supported by little data at present and is associated with higher complications. Extended transrectal biopsy is adequate for initial biopsy, but office-based transrectal saturation biopsy significantly improves cancer detection during repeat biopsy, with the caveat that more cases of clinically insignificant cancer will be detected. To address these challenges, we continue to strive to find the significant cancers and to observe those that carry limited risk to the patient unless they demonstrate signs of progression or harm. Furthermore, we and colleagues throughout the world continue to seek noninvasive approaches to evaluate these concepts.

Repeat Saturation Biopsy Scheme. As medial biopsies have proven to show low yield on repeat biopsy, the number of parasagittal cores is reduced in each sector. However, it is still important to obtain at least one core in each sector as rare cases may present with cancer in these areas.
Science, Patient Care and Healthcare Reform:
A nephrocentric perspective

When Bob Dylan wrote the song, “The Times They Are a Changin” in the early 1960s, I suspect he did not envision this anthem of change for the moment would strike a note in the healthcare environment in 2010. Yet in healthcare today, the only constant for the future is the pattern of continued change both on how we practice and the metrics applied to judging the value of research. Today, the most important force seemingly responsible for reshaping current U.S. healthcare may be the federal debt. Reigning in healthcare spending will both directly and indirectly affect medicine, whether it be in the actual models of care delivery that evolve, how professionals, providers and payers band together to address evolving quality metrics or how the public sector and government agencies chart out the increased expectations for funded research.

On March 23, 2010, President Obama signed into law the biggest expansion of federal healthcare guarantees in more than four decades. These changes were proposed to ensure healthcare coverage and access to all treatment options for patients with chronic disease. From a nephrocentric perspective, the traditional reimbursement structure of fee for service payment practice has not nurtured continuity of care and cost containment, but rather fosters disjointed and costly care with suboptimal outcomes for a significant percentage of patients with chronic kidney disease (CKD) and end stage renal disease (ESRD). Medicare reimburses hospitals through Part A and dialysis through Part B; in actuality, quality advances in dialysis can lower Part A costs and yet there is no incentive or cost sharing benefit to the dialysis centers.

On July 26, 2010, the Centers for Medicare and Medicaid Services (CMS) issued a final rule that redefined how Medicare pays for dialysis services for Medicare beneficiaries who have ESRD. In addition, CMS issued a proposed new pay for performance rule (starting January 1, 2012) that would establish a quality incentive program (QIP) linking payment with quality performance standards. CMS adopted three quality measures that will be utilized in the initial implementation of the QIP: Hemoglobin <10 or >12, and a urea reduction ratio (URR) >65%. Payments will be reduced by up to 2% if a facility fails to meet specific performance scores for these quality measures.

Moving forward, Accountable Care Organizations (ACOs) are being proposed as a model that will have a potential impact on kidney disease management as providers (hospitals, dialysis organizations, etc.) and doctor groups (primary care physicians, specialists) join together to accept responsibility to manage large numbers of patients to achieve better outcomes/quality and control costs. It remains unclear how smaller groups will adjust to this trend since they may not have the infrastructure to effectively assess or manage specific disease population data. Healthcare systems like the Cleveland Clinic Health System (CCHS) will need to examine how ACOs will change the historic regional alignment of providers and physician groups to achieve measurable quality improvements.

While substantial federal funds were allocated last year for comparative effectiveness research, it is imperative that the healthcare reform framework draw on the results of such research to establish a process for treating patients; it was disappointing that this mindset did not carry over to immunosuppressive medication coverage for kidney transplant recipients when the coverage provision was dropped from the Affordable Healthcare for Americans Act. Our department of Qualitative Health Sciences has linked with the Department of Nephrology & Hypertension to leverage systemwide and national data sets in developing predictive risk models for transplantation. We believe this methodology is transferable to predicting outcomes and future cost burden in other disease states.
Improving systems to ensure the delivery of optimal care to all patients in need, appears to be the main driver in today’s healthcare agenda. Yet, increasingly, the sense is that technological advancements must yield dramatic, and in some settings, unrealistic increases in efficacy to do more good than could be achieved by just improving how we deliver current care. Despite these observations, continued advances in technology are critical to the stature U.S. medicine has historically enjoyed worldwide.

Scientific initiatives and innovation are critical to providing the hope that all patients seek when they travel to facilities like Cleveland Clinic. Biomedical research in the United States increased $75.5 billion in 2003 to $101 billion in 2007; overall funding from the National Institutes of Health (NIH) and industry increased by 14% during this interval (compound annual growth rate of 3.4%). However, this rate is substantially less than the 7.8% annualized growth rate from 1994-2003. At Cleveland Clinic, the total research funding for 2009 totaled $272 million which represented a 34.6% increase over 2005 and a 5% increase from 2008. In the Department of Nephrology and Hypertension there are 53 active research projects (9 corporate, 17 federal, 1 professional societies and 26 Institution Review Board matching funds). Those currently funded research initiatives focus on five different theme areas: CKD, Hypertension, Renal Diseases, Transplantation and Dialysis. The areas of future accelerated basic science growth will focus on polycystic kidney disease (PCKD) and stem cell directed kidney repair and regeneration.

In this tough economy, underinvestment in preventive care and health education to decrease behaviors will continue to increase the risk for chronic disease (responsible for two-thirds of U.S. deaths) and remains a continued critical concern in nephrology fields. The electronic medical record (EMR) within CCHS (8 hospitals, 15 family health centers and the main campus) can be utilized to link prevention and treatment strategies to achieve the very best patient outcomes; currently there are more than 57,000 CKD patients in the EMR. Newer areas of research will continuously leverage the EMR as we explore in depth characteristics of disease populations, medication effectiveness, costs and physician behavior. In other cites and regions, an EMR linking ACOs with significant population numbers can provide invaluable patterns of care, which may provide increased understanding regarding morbidity and mortality in high-risk populations.

Our ongoing interest and support of advancing science can be seen in the development of the bioartificial kidney project, in addition to the success of our effort to expand virtual hypertension monitoring technology. As a department, we are keenly aware of the increased level of scrutiny that the current healthcare policies and economic downturn have on reshaping both the delivery of care for disease populations at Cleveland Clinic and how future research funding will be focused on both cost and the value of technology and research productivity. More than ever before, the times... they truly are changing.

For a list of research projects from the Department of Nephrology & Hypertension, please email the editor.
Animal Studies Shed Light on the Biology of XMRV Infection: Prostate Epithelium is an Early Viral Target

François Villinger, PhD², Jaydip Das Gupta, PhD¹, Prachi Sharma, PhD², Nattawat Onlamoon, PhD², Gerald Schochetman, PhD³, John Hackett Jr., PhD³, Robert H. Silverman, PhD² and Eric A. Klein, MD¹

1 Cleveland Clinic, 2 Emory University, 3 Abbott Diagnostic

Xenotropic murine leukemia virus-related virus (XMRV) is a novel gammaretrovirus initially discovered in men genetically predisposed to prostate cancer and subsequently in some patients with chronic fatigue syndrome. XMRV is related to a family of murine leukemia viruses (MLVs), which are known to cause neuroimmune diseases and/or cancer in mice and other mammals. Although likely derived from mice via zoonotic infection, XMRV will not infect common lab strains of mice due to mutations in its receptor (XPR1). We recently teamed with researchers from the Yerkes National Primate Research Center at Emory University and Abbott Diagnostic to study the infectivity, kinetics of infection and tissue localization of XMRV in primates.

XMRV was injected intravenously in five Rhesus macaque monkeys. Blood and other biologic samples were obtained at defined intervals after injection, and the monkeys were sacrificed at one week, five months or 9.5 months after injection. Acute viremic infection was detected in two of the three monkeys tested, initially apparent at day four and persisting for approximately two weeks. XMRV provirus was detected in the WBCs of all three monkeys as early as seven days after injection and persisted for up to one month. Flow cytometry detected XMRV primarily in CD4+ and CD8+ T cells and NK cells, suggesting that lymphocytes are a reservoir for viral replication and suggesting a potential mechanism of immune modulation by the virus.

Tissue studies demonstrated that XMRV establishes a chronic and disseminated infection after IV injection. Remarkably, autopsy of two monkeys at one week demonstrated intense expression of XMRV proteins by immunohistochemistry in the prostatic epithelium from which prostate cancer arises. Also remarkable is the pattern of expression seen at five months in one of the post-mortem examinations. In this monkey, XMRV was only detected in prostatic stromal fibroblasts and not in the epithelium, consistent with our prior studies in human prostate cancer at the time of radical prostatectomy. The results suggest that prostatic epithelium is an early target after viral infection, and that with time the virus is cleared from the epithelium and persists in adjacent stromal cells. Examination of other tissues showed XMRV detectable in a wide variety of organs in the early phase (including lymphoid tissue, lung, pancreas, and lower genital tract). A persistent infection was noted at 9.5 months in the spleen, gut-associated lymphoid tissue (GALT), and the lower genital tract, including the vagina and cervix of the one female monkey included in the study.

This study established for the first time that XMRV is infectious in primates, allowing this model to be used for further exploration of its potential to cause disease, immune responses and potential therapies.
High-Intensity Focused Ultrasound (HIFU) Treatment of Organ-Confined Prostate Cancer

William L. Orovan, MD
Dr. Orovan is President and Medical Director of Maple Leaf HIFU, exclusive distributor of Ablatherm® HIFU in Canada. Maple Leaf HIFU has a medical office at Cleveland Clinic Canada in Toronto.

High-intensity focused ultrasound (HIFU) offers a noninvasive, ambulatory treatment alternative for patients suffering from organ-confined prostate cancer. This technology has been available in Western Europe for more than a decade and in Canada since 2004 when it was approved by Health Canada. A clinical trial in the United States intended to achieve approval by the Food & Drug Administration (FDA) has ceased accrual, allowing data to mature over the next two years at which point application will be made for approval in the United States.

Ablatherm® HIFU is now available at Cleveland Clinic Canada in Toronto and is offered by Maple Leaf HIFU, a limited Cleveland Clinic-Canadian partnership. Treatment is a single session, typically two hours in duration, and is performed on an ambulatory basis. Spinal anesthetic and intravenous sedation is preferred, and patients require an indwelling urethra Foley for a minimum of two weeks.

Data generated by Maple Leaf HIFU on 303 primary treatment patients in the low- and medium-risk category document biochemical progression free survival (BPFS) of approximately 80% in the low-risk category and 70% in the medium-risk category with longest follow-up being five years. These data are comparable to those produced in Western Europe where published studies with follow-up of up to 10 years are now available.

In addition to being a primary treatment modality, HIFU can also be used in those patients who have failed radiation therapy and can, as well, be repeated in patients who have failed initial HIFU treatment.

To qualify as a candidate for HIFU, patients must have prostate volume less than 40 grams and no evidence of regional or distant spread of disease. Where initial prostate volume exceeds 40 grams prostate size reduction can be done utilizing androgen-deprivation therapy either in the form of luteinizing hormone-releasing hormone (LHRH) agonists or 5 alpha reductase inhibitors. Transurethral resection of the prostate (TURP) can be used and is regularly utilized in the European treatment model, but has not been a common factor in North American treatment protocols.

Common post-treatment sequelae to HIFU include delayed return to normal voiding as a result of post-treatment edema, tissue slough or both, which may impede urine passage in the early weeks post HIFU. Later complications including urethral stricture formation occur in some patients and may require urethral dilatation or transurethral visual urethroty.

Physicians interested in learning more about HIFU are invited to contact the Glickman Urologic & Kidney Institute at Cleveland Clinic’s main campus, 216.444.5600.
Role of Radical Prostatectomy for Prostate Cancer in 2011: Update from the Glickman Urological & Kidney Institute

Andrew J. Stephenson, MD

Recently, minimally invasive approaches (specifically, robotic prostatectomy) have been utilized increasingly over radical retropubic prostatectomy based on the public perception of less morbidity, quicker recovery and superior outcomes. Yet, benefits of the robotic approach remain unproven. Several recent publications from high-volume centers and the Surveillance-Epidemiology and End Results (SEER) Medicare database suggest that robotic prostatectomy is associated with similar, and in some cases inferior, outcomes compared to the conventional open approach. At Cleveland Clinic, we are conducting a prospective study to determine if differences exist between the two approaches in terms of quality-of-life outcomes. The skill and approach of the individual surgeon exist between the two approaches in terms of quality-of-life outcomes. The procedure may be unnecessary, as a similar cancer-specific survival may have been achieved without immediate radical therapy. Due to many different developing variables, we bring forward the impact new technology, the PSA era, adjuvant radiotherapy and active surveillance have on radical prostatectomy’s use for prostate cancer treatment.

Key Point:

A proven approach for long-term cure rates, radical prostatectomy’s role is being questioned due to the evolution of alternative techniques and the reality of its necessity. For instance, our large multicenter analysis shows that men with organ-confined and/or pathological Gleason score 2-6 cancers (particularly the latter) have a negligible risk of death from prostate cancer after radical prostatectomy. Yet, the procedure may be unnecessary, as a similar cancer-specific survival may have been achieved without immediate radical therapy. Due to many different developing variables, we bring forward the impact new technology, the PSA era, adjuvant radiotherapy and active surveillance have on radical prostatectomy’s use for prostate cancer treatment.

PSA recurrence universally antedates clinical recurrence and prostate cancer-specific mortality (PCSM), it is an imperfect proxy for these endpoints due to its variable natural history. Within 10-15 years, men are as likely to die from competing causes as they are from prostate cancer. PSA, pathological stage, surgical margin status and Gleason score are established prognostic factors for PSA recurrence. However, few studies have analyzed the association of these parameters for PCSM among contemporary patients treated by radical prostatectomy in the PSA era.

Investigators from Cleveland Clinic, Johns Hopkins University, Memorial Sloan-Kettering Cancer Center and the University of Michigan recently conducted an analysis of long-term (15+ years) outcome of radical prostatectomy among 24,000 patients treated at these centers since 1987 (the year the PSA test became widely available). The overall 15-year PCSM was 7%. The 15-year PCSM for patients with pathological Gleason score 2-6, 3+4, 4+3, and 8-10 was 1%, 7%, 8%, and 49%, respectively. PCSM risks were 2%, 7%, 29%, and 23% for organ-confined cancer, isolated extraprostatic extension, seminal vesicle invasion, and lymph node metastasis. Only three of 9,388 patients with organ-confined and Gleason score 2-6 died from prostate cancer. Primary and secondary Gleason grade 4-5 and seminal vesicle invasion were the only significant clinical predictors of PCSM. The 15-year PCSM among men with positive and negative surgical margins was 10% and 6%, respectively, and positive surgical margins were not significantly associated with PCSM. This study provides important information about the natural progression of treated prostate cancer in terms of the significance of key prognostic factors and cancers that pose the greatest (and least) threat to survival.

A separate recent randomized trial demonstrated that adjuvant radiotherapy versus observation significantly improves the survival of men with pT3N0 disease after radical prostatectomy, and men with seminal vesicle invasion appear to derive the greatest relative benefit. Given the association of seminal vesicle invasion and Gleason score 8-10 with PCSM, it is appropriate to consider these patients for adjuvant radiotherapy. There is controversy regarding the role of adjuvant radiotherapy for men with isolated positive surgical margins and/or extraprostatic extension. Only a minority of these patients is at risk for developing PSA recurrence and the long-term PCSM is 7-10%. It is also uncertain whether immediate adjuvant radiotherapy is associated with improved cancer control compared to close observation and salvage radiotherapy at the earliest signs of PSA recurrence. Some have advocated for adjuvant radiotherapy for those patients with extensive and/or multiple positive surgical margins based on the belief that these patients are at a higher risk of recurrent cancer. However, a recent study of 7,160 patients treated at Cleveland Clinic, Memorial Sloan-Kettering Cancer Center and the University of Michigan showed that the sub-classifications of positive surgical margins (extensive vs. focal, multiple vs. solitary, apical vs. other location) did not enhance the ability to predict PSA recurrence more ac-
Prostate brachytherapy has been available for the treatment of prostate cancer since 1905, according to filings at the U.S. patent office, and has changed dramatically over the years to improve treatment delivery. Cleveland Clinic has pioneered the advancement of brachytherapy while continually assessing patient outcomes to guide our refinement of the treatment of prostate cancer.

Possibly our greatest innovation has been the biannual, internal review of our brachytherapy program, which has occurred since the program’s beginnings in 1996. While this sounds simple, it is unique to our institution because we involve all medical specialties participating in the brachytherapy program including radiation oncology, urology and medical oncology. It is through this process that we identified problems with the brachytherapy technique most widely used, such as the separation of the planning process from the implantation. When the two are combined into one procedure, the logistics are simplified for the patient by lessening the number of visits for treatment, and the parameters of implant quality are improved. We continue to hone our approach to prostate cancer through this review. For example, our identification of a problem with the method widely used to measure outcomes from prostate cancer treatment caused us to change how we determine success after treatment. We noted an obvious dependence on PSA testing frequency and the success rates reported by most institutions. For a patient to have a good measure of treatment success as measured by PSA values, PSA tests must be completed on a regular basis throughout life. This is simple and obvious: if disease is not monitored, it will not be detected.

The effect of PSA testing frequency on some outcome measures is profound. As a result of this recognition, we began to direct our focus on “hard” measures of treatment outcome, such as prostate cancer-specific survival and overall survival. We were the first institution to present such an analysis among all major treatment modalities for prostate cancer in 2007. This analysis shows that patients treated with prostate brachytherapy and radical prostatectomy at Cleveland Clinic are equivalent in prostate cancer survival at 12 years post-treatment and have a 98% success. Since then, other centers have followed our lead in reporting “hard” endpoints.
Avoiding Androgen Deprivation Therapy for High-Risk Prostate Cancer: The Role of Radical Prostatectomy as Initial Treatment

Ranko Miocinovic, MD, Ryan K. Berglund, MD, Andrew J. Stephenson, MD, J. Stephen Jones, MD, FACS, Amr F. Fergany, MD, Jihad Kaouk, MD, and Eric A. Klein, MD

Men with high-risk localized prostate cancer have multiple options for therapy. Level 1 datum support the use of combined androgen deprivation therapy (ADT) plus external beam radiotherapy (EBRT) versus EBRT alone in this setting, though no randomized trials of ADT plus EBRT versus radical prostatectomy (RP) have been successfully conducted. However, new concerns associated with use of ADT and its effect on the increased risk of cardiovascular disease have once again raised the question of optimal therapy for high-risk localized prostate cancer. Given that some of the negative effects of ADT may occur within the first three months of therapy and that optimal treatment of high-risk prostate cancer with EBRT requires three years of therapy, patients with high-risk disease may achieve a greater benefit from surgical treatment to delay or escape the adverse effects of ADT. More recent studies of surgery as the primary treatment modality for locally advanced disease suggest excellent short-term local control and acceptable complication and biochemical failure rates, as compared to the previously published combined ADT and EBRT studies.

We studied 267 patients presenting with high-risk disease as defined by clinical stage >T2b, and/or preoperative PSA >15 ng/mL, and/or Gleason score ≥ 8, who underwent RP with pelvic lymph node dissection (PLND) between January 1998 and June 2004. The primary endpoints of the study were freedom from use of ADT, freedom from biochemical recurrence (BCR), freedom from distant metastasis (DM), prostate cancer specific death (PCSD), and overall survival (OS). Biochemical recurrence was defined as two consecutive detectable PSA levels (greater than 0.2 ng/mL), and time to failure was marked by the time of the initial detectable level. The mean follow-up was 6.7 years (range, 1-146 months). Biochemical recurrence (BCR), distant metastasis (DM) and death from prostate cancer were observed in 112 (42%), 28 (10%) and 15 (6%) patients, respectively. Salvage treatment was performed in 95 (85%) of 112 patients with BCR. Only 71 (27%) of 267 men were subjected to ADT. Overall, 10 year probabilities of freedom from BCR, DM, death from prostate cancer, and ADT were 59% (95% CI, 53-65), 89% (95% CI, 85-92), 94% (95% CI, 91-97), and 73% (95% CI, 68-79), respectively.

This series confirms the feasibility and acceptable oncologic outcomes of RP in patients with high-risk prostate cancer in the post-PSA era. We have previously reported similar surgically related short-term complication rates for RP in those with low versus high-risk features. Yet, current data suggests long-term benefits of RP as initial therapy in the high risk group, notably escaping the initial ADT and the potentially associated cardiovascular and metabolic side effects. In the current series of patients, approximately 70% of men would have been exposed to ADT unnecessarily. Furthermore, patients without BCR, metastasis, or cancer-specific death at five-year follow-up appeared to have durable cancer specific outcomes.
TMPRSS2-ERG Gene Fusion: Expression in Prostatic Adenocarcinoma

Donna E. Hansel, MD PhD, and Eric A. Klein, MD

For years, the molecular mechanisms underlying prostatic adenocarcinoma development have been elusive. Recently, however, the discovery of a recurrent gene fusion between the 5’ untranslated region of TMPRSS2 and the ETS transcription factors ERG or ETV family members has revolutionized the study of this disease. Initially identified via a bioinformatics approach, TMPRSS2-ETS gene fusions primarily involve gene fusion with ERG in greater than 90% of cases when present and with ETV family members ETV1, ETV4 and ETV5 in the remainder. As such, significant work has been performed on the contribution of TMPRSS2-ERG to prostate cancer pathogenesis.

Fusion of TMPRSS2 (21q22.3), which encodes a transmembrane serine protease, and ERG (21q22.2), a proto-oncogene, may occur through either a small deletion of chromosome 21 or via translocation. As a result of this gene fusion, the androgen-response elements of the TMPRSS2 promoter drive the overexpression of ERG, which has been hypothesized to promote prostate cancer growth. TMPRSS2-ERG gene fusions have been identified in up to 80% of prostatic adenocarcinomas, including peripheral and transition zone cancers, as well as numerous morphological variants of this disease. Furthermore, gene fusions have reported high-grade prostatic intraepithelial neoplasia (PIN), supporting a role in early pathogenesis of this disease.

Originally considered to be a marker of aggressive prostate cancer growth, TMPRSS2-ERG gene fusion has been recently studied in minute foci of prostatic adenocarcinoma, defined as ≤0.5 cm³ cancer, Gleason score ≤7 and organ-confined tumor on radical prostatectomy. Gene fusion was identified in 47% of all cases examined, which did not appear significantly different from non-minute prostatic adenocarcinoma matched for grade. This recent evidence suggests that further evaluation of the role of TMPRSS2-ERG as a marker of aggressive tumor behavior is warranted and that gene fusion signature may reflect simply an early step in prostate cancer pathogenesis.

For references, please email the editor.
Successful thermal therapy of solid organ tumors is reliant upon achievement of lethal tissue temperatures that envelop the tumor to accomplish complete tumor necrosis. When considering cryoablation, lethal tissue temperatures are finite in distribution with respect to distance from the working cryoprobe. Therefore, the size of the prostate gland and proximity of neoplastic cells in relationship to the cryoprobe are critical elements for treatment outcomes. Thus, prostate gland volume may have an impact on outcomes due to the finite size of ice that can be generated within the gland.

To examine this concept, we queried the Cryo Online Data (COLD) Registry in an effort to identify whether prostate volume in addition to other potential prognostic factors might impact upon favorable biochemical outcomes (PSA < 0.6 ng/ml), as communicated by our group in previously published reports.

We identified 2,685 patients treated with primary prostate cryoablation from the COLD Registry. The cohort was stratified based on prostate gland volume > 10 cm³ - < 50 cm³ (n = 2,316) and > 50 cm³ - < 70 cm³ (n = 369) at the time of treatment as well as D’Amico risk criteria. This volume cutoff was chosen based on the finite amount of ice that can be generated within tissue using current technology. An approach that is widely accepted and taught as part of our own, as well as other proctors recommendations, it is not formally validated. No patients had prostate volumes greater than 70 cm³. Available 60-month follow up data were analyzed.

Univariable and multivariable logistic regression was completed for prediction of favorable PSA outcomes and assessment of risk factors.

### Key Point:

After reviewing 2,685 patients treated with primary prostate cryoablation identified in the Cryo On-Line Data (COLD) Registry, we found that prostate volume is not a statistically significant factor in PSA outcomes following primary whole gland cryoablation. As in other types of prostate cancer intervention, PSA at diagnosis, Gleason score, clinical stage and risk category are prognostic indicators of favorable PSA outcomes following primary cryoablation of the prostate.

### Table 1. Univariate statistical analysis for impact of demographic factors for initial post cryoablation PSA < 0.6 ng/ml based on prostate gland volume > 10 - < 50 cm³ and > 50 cm³ - < 70 cm³.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vol (&gt; 10 – &lt; 50 cm³) (n = 1858)</th>
<th>Vol ( &gt; 50 - &lt; 70 cm³) (n= 308)</th>
<th>Odds Ratio (95% confidence interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean) (SD)</td>
<td>69.8 (7.2)</td>
<td>71 (6.45)</td>
<td>0.993 (0.979 – 1.006)</td>
<td>0.292</td>
</tr>
<tr>
<td>Volume</td>
<td>1855</td>
<td>308</td>
<td>1.238 (0.924 – 1.660)</td>
<td>0.153</td>
</tr>
<tr>
<td>PSA ddx&lt; 10</td>
<td>1481 (79.7%)</td>
<td>220 (71.4%)</td>
<td>0.993 (0.987 – 0.999)</td>
<td>0.02</td>
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<tr>
<td></td>
<td>364 (19.5%)</td>
<td>86 (27.9%)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>13</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA ddx&gt; 10</td>
<td>1190 (64%)</td>
<td>206 (66.8%)</td>
<td>0.866 (0.706 – 1.062)</td>
<td>0.167</td>
</tr>
<tr>
<td></td>
<td>668 (36%)</td>
<td>102 (33.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT stage &lt; T2b</td>
<td>1,128 (60.7%)</td>
<td>193 (62.7%)</td>
<td>0.794 (0.729 – 0.865)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>503 (27%)</td>
<td>83 (26.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>212 (11.4)</td>
<td>29 (9.4%)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gl Score &lt; 6</td>
<td>1,128 (60.7%)</td>
<td>193 (62.7%)</td>
<td>0.794 (0.729 – 0.865)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>503 (27%)</td>
<td>83 (26.9%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>212 (11.4)</td>
<td>29 (9.4%)</td>
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</tr>
<tr>
<td></td>
<td>15</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gl Score 7</td>
<td>522 (28.1%)</td>
<td>76 (24.7%)</td>
<td>0.682 (0.599 – 0.778)</td>
<td>0.385</td>
</tr>
<tr>
<td></td>
<td>791 (42.6%)</td>
<td>143 (46.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>545 (29.3%)</td>
<td>88 (28.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gl Score &gt; 8</td>
<td>522 (28.1%)</td>
<td>76 (24.7%)</td>
<td>0.682 (0.599 – 0.778)</td>
<td>0.385</td>
</tr>
<tr>
<td></td>
<td>791 (42.6%)</td>
<td>143 (46.4%)</td>
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</tr>
<tr>
<td></td>
<td>545 (29.3%)</td>
<td>88 (28.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk (D’Amico) Low Intermediate High Missing</td>
<td>522 (28.1%)</td>
<td>76 (24.7%)</td>
<td>0.682 (0.599 – 0.778)</td>
<td>0.385</td>
</tr>
</tbody>
</table>
Prostate volume was not a statistically significant factor in achieving a PSA < 0.6 ng/ml, on univariate, (p = 0.153, Table 1) or multivariate (p = 0.101, Table 2) analysis. A favorable initial post cryoablation PSA (< 0.6 ng/ml) was achieved in 80% (1,858/2,316) of patients with prostate volumes < 50 cm3 (range > 10 cm3 – < 50 cm3) and 83% (308/369) of patients with prostate volumes > 50 cm3. On univariate analysis, PSA at diagnosis (p = 0.02) and Gleason score (p = < 0.0001) proved to be statistically significant predictors of achievement of favorable PSA for individuals with prostate volumes less than 50 cm3 (Table 1), while clinical stage (p = < 0.0001) and D’Amico risk category (p = < 0.0001) were statistically significant predictors of favorable PSA outcomes by multivariate analysis (Table 2). An initial post-cryoablation PSA < 0.6 ng/ml was associated with a 60-month biochemical progression free survival (bPFS) (Phoenix definition) of 89% low, 77% intermediate and 64% high risk, respectively (Figure 1). An initial post cryoablation PSA > 0.6 ng/ml was associated with significantly worse (61.5%) 24-month bPFS regardless of risk category (Figure 2). At 12 months, there was no statistical difference in incidence of incontinence (3.3% vs. 2.1%), retention (1.1% vs. 2.6%), potency (30.3% vs. 32.2%) or fistula (0.6% vs. 0.2%) based on prostate volume < 50 cm3 compared to those individuals with volumes > 50 cm3.

Prostate volume is not a statistically significant factor in PSA outcomes following primary whole gland cryoablation. As in other types of prostate cancer intervention, PSA at diagnosis, Gleason score, clinical stage and risk category are prognostic indicators of favorable PSA outcomes following primary cryoablation of the prostate.

Continued on next page

Table 2. Logistic regression analysis for PSA < 0.6 ng/ml, multivariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio 95% Confidence Interval</th>
<th>P value Chi Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>1.288 (0.952 – 1.741)</td>
<td>0.101</td>
</tr>
<tr>
<td>PSA ddx</td>
<td>0.996 (0.992 – 1.000)</td>
<td>0.0668</td>
</tr>
<tr>
<td>cT stage</td>
<td>0.524 (0.406 – 0.676)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gl score</td>
<td>0.937 (0.844 – 1.041)</td>
<td>0.226</td>
</tr>
<tr>
<td>Risk (D’Amico)</td>
<td>0.587 ( 0.485 – 0.711)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Figure 1. Risk stratified Kaplan Meier 60-month biochemical progression free survival curve based upon Nadir + 2 criteria for 1,858 patients with initial post cryoablation PSA level < 0.6 ng/ml, (vol. > 10 - < 50 cm³). Blue - Low risk: n = 522, Green - Intermediate risk: n = 791, Gold - High risk: n = 545.

* Numbers of evaluable patients at specified time intervals are color coded below graph.

Post treatment PSA < 0.6 ng/ml: Volume > 10 cm³ - <50 cm³

Figure 2. Risk stratified Kaplan Meier 60-month biochemical progression free survival curve based upon Nadir + 2 criteria for 309 patients with initial post cryoablation PSA level < 0.6 ng/ml, (vol. > 50 - < 70 cm³). Blue - Low risk: n = 76, Green - Intermediate risk: n = 143, Gold - High risk: n = 88.

* Numbers of evaluable patients at specified time intervals are color coded below graph.
Editorial

Take ‘Anti-Cancer’ Supplements with a Grain of Salt:

Warren (Skip) Heston, PhD

Many men, encouraged by media spin on epidemiological data, are taking various supplements to ward off prostate diseases. However, there have been a number of studies showing that supplements are not helpful in preventing cancer; what’s more, taking mega-doses may be harmful.

A recent major clinical trial examining the role of supplements containing selenium or vitamin E was halted because interim analysis showed that the use of these supplements did not decrease the risk of prostate cancer.

Problems in taking vitamin supplements were further demonstrated in a study in which patients who had a colorectal polyt removed were asked to take either aspirin or folic acid, and to participate in a three- to five-year follow-up study of the prevention of benign colorectal tumors. This trial was based on published literature indicating an association between the supplements and reduced incidence of cancer. However, while aspirin had no effect, the participants taking folic acid actually had a significant increase in the number of colorectal polyps.

Given the strong evidence of a positive effect of dietary folate, this outcome was thought to be a statistical fluke. The participants were then asked if they would continue, and the majority did. However, the association between supplemental folic acid and increased colorectal polyt formation persisted. Furthermore, the results also showed that folic acid supplements were associated with a three-fold increase in the probability of being diagnosed with prostate cancer in a 10-year period.

The above clinical trial using folic acid raises questions concerning the doses and form of folate. The participants took a 1 mg daily dose of folic acid, which is comparable to the dose found in many vitamin supplements. While folates are naturally found in leafy green vegetables, the total folic acid being consumed by most people in the United States is increasing due to flour being supplemented with folic acid as a preventive against neural tube birth defects.

By examining men who did not receive the folic acid supplement in the above trial, it was determined that those with higher folate intake from natural food sources tended to have a lesser incidence of prostate cancer. Donald Jacobsen, PhD, of the Institute’s Department of Cell Biology, points out that a molecule called N5-methyltetrahydrofolate, not folic acid, is the form that is found in natural foods and transported in the body. This raises an interesting question: Should N5-methyltetrahydrofolate be used in supplements instead of folic acid? Would it decrease the risk of cancer development yet sustain the benefits regarding neural tube defects? The other question is whether there are other protective factors in leafy green vegetables: is folate by itself protective, or does it require some as yet unknown co-factor that’s present in natural foods?

Given that colon, breast and prostate cancers are major health issues in the United States and Europe, and that these cancers are not directly associated with well-established cancer risk factors such as cigarette smoking, will there be a significant increase in these cancers because of increased folic acid supplementation of foods?

Furthermore, what is the cancer potential of folic acid supplementation? Joel Mason, MD, at Tufts University, points out the good and bad aspects of folic acid supplementation. While folic acid can be metabolized to N5-methyltetrahydrofolate during its absorption, folic acid supplementation can overwhelm this system. He also points out that a recent study of 25,000 post-menopausal women receiving 853 μg/day folic acid supplements demonstrated a significantly increased risk of breast cancer.

Suffice to say, TV ads that would have us believe that buying vitamin supplements will save us from cancer should be taken “with a grain of salt.” Negative vitamin and supplement trials are summarized in a recent commentary by Alan R. Kristal, DPH, of the Fred Hutchinson Cancer Research Center, and Scott M. Lippman, MD, of the University of Texas MD Anderson Cancer Center, in which they underline how hard it will be to obtain money for funding large trials in the future, especially given that our culture is for the most part not nutritionally deprived. We will need excellent evidence with clear, measurable endpoints and solid rationale for the forms and doses of agents for use in cancer prevention.

As for me, I’ll have a leafy green vegetable or two, a cup of green tea in the morning and a glass of red wine at night.

For references, please email the editor.
High-grade prostatic intraepithelial neoplasia (HGPIN) as a finding on prostate biopsy remains a source of ongoing confusion. Although original reports suggest that it may actually be a precursor lesion for prostate cancer, some recent studies have suggested that HGPIN might be relatively unimportant.

We have long believed that scheduled “delayed interval biopsies” approximately every three years were the most reasonable approach to this conundrum, based on reports from New York University that found prostate cancer in almost one-quarter of HGPIN patients at both three- and six-year intervals. Using our prostate biopsy database, we recently compared risk of cancer on repeat prostate biopsy in men with or without HGPIN. A 42.2% greater number of our patients with HGPIN were diagnosed with prostate cancer on delayed interval biopsy compared to those with an initial completely benign diagnosis (Hazard ratio 1.89, 95% CI 1.39 to 2.55). Thus, the risk of developing prostate cancer predicted by HGPIN appears to persist at least through a six-year timeframe, and may develop well beyond that point. For this reason, prevention strategies using Toremifene, dietary manipulations, or 5-alpha reductase inhibitors (5-ARI) are important investigations.

Nevertheless, the literature continues to reflect controversy regarding whether HGPIN is truly premalignant, and urology textbooks now recommend not performing repeat biopsy based on this sole criterion. In order to elucidate this controversy, we have performed sub-analysis based on the extent of HGPIN. We found that the impact of HGPIN on cancer detection was almost exclusively in patients with multifocal disease. Our Kaplan-Meier curve estimated cancer rates of 3.6%, 12.5% and 22.4% for patients with initial biopsy benign diagnosis, 4.4%, 14.7% and 26.1% for patients with unifocal HGPIN and 9.1%, 29.0% and 47.8% for patients with multifocal HGPIN at 1, 3 and 5 years respectively. Thus, our data confirm that immediate repeat biopsy solely for the indication of unifocal HGPIN is unnecessary, and the risk of de novo cancer development over time is only minimally increased in men with unifocal HGPIN. However, multifocal HGPIN more than doubles the risk of de novo cancer development at both three (12.5% compared to 29.0%) and five years (22.4% compared to 47.8%), which makes delayed interval biopsy a highly logical approach in this select population.

Thus, HGPIN does not define a homogeneous population. It appears that unifocal disease may truly have limited significance, whereas multifocal HGPIN is a significant precursor to the development of prostate cancer. Therefore, we suggest a conservative approach to patients with unifocal HGPIN, reserving repeat biopsy for those that have independent indication of disease development, such as rising PSA levels or low percent-free PSA. By contrast, we now strongly recommend repeat “delayed interval” biopsy be performed approximately every three years for patients with multifocal HGPIN for as long as the patient’s overall health would warrant treatment for prostate cancer.

Key Point:
Based on our sub-analysis of high-grade prostatic intraepithelial neoplasia (HGPIN) as a predictor to future prostate cancer development, we conclude that HGPIN’s impact on cancer detection was almost exclusively in patients with multifocal disease. These results suggest a conservative approach to patients with unifocal HGPIN, with a strong recommendation for repeat “delayed interval” biopsy approximately every three years for patients with multifocal HGPIN.
Renal cell carcinoma (RCC) most commonly occurs in the 6th, 7th and 8th decades, and we are now seeing many elderly patients presenting with this malignancy. Traditionally, we have managed localized disease in an aggressive manner, mostly with radical nephrectomy (RN), even in the elderly. Although early detection has increased over the past decade, cancer-specific mortality has not declined, suggesting that this paradigm of aggressive treatment of early stage disease should be reassessed. This is particularly true in the elderly, who commonly have competing causes of death and limited life expectancy.

With these concerns in mind, we recently analyzed our outcomes with various management strategies in the elderly, defined as those > 75 years of age. A total of 979 patients from Cleveland Clinic between 2000 and 2006 met the study criteria. Kaplan-Meier estimates of overall 5-year survival rates for patients with stage T1a, T1b, and T2 cancers were 74%, 66% and 51%, respectively, with many patients dying of non-cancer related causes. In contrast, the overall 5-year survival rate for elderly patients with urothelial cancer was only 42%. Cancer-related deaths were infrequent in patients with stage T1 RCC (7%), yet much more common in patients with more advanced RCC (stage ≥T2) or upper tract urothelial cancer accounting for 51% and 46% of deaths, respectively. This suggests that aggressive treatment should continue to be offered to these patients.

We then focused on a subgroup of 537 elderly patients with localized clinical T1 renal tumors. Management was by RN (27%), nephron-sparing interventions (53%) such as thermal ablation or partial nephrectomy (PN), or active surveillance (AS) in the remaining 20%. The unadjusted Kaplan-Meier estimates of overall survival at 5 years for these patients were 72% with RN, 76% with nephron-sparing interventions, and 58% with AS. As expected, substantial selection bias was observed – the group managed with AS was older with more comorbidities than the active treatment groups. On multivariate analysis, comorbidity and age were the most powerful predictors of overall survival. In contrast, management type was not associated with overall survival after adjusting for age, comorbidity and other relevant variables.

The second main finding of our study was that cardiovascular events, not malignancy, were the leading cause of death, and pretreatment for renal dysfunction and comorbidity were significant predictors of cardiovascular deaths. Pre-treatment for chronic kidney disease (CKD, grade 3, defined as GFR < 60 ml/min/1.73 m2) was common in this elderly population and was greatly exacerbated by RN. CKD was present in 45% of patients prior to management of any type, and 86% of patients managed with RN were found to have CKD after surgery, much higher than after AS or nephron-sparing approaches. New diagnosis of CKD was found in 47% of patients managed with RN, compared to 25% after nephron-sparing management or 5% associated with AS. The Kaplan-Meier estimate of the incidence of cardiovascular death at 5 years was 15% versus 6% for patients with or without CKD, respectively, reflecting the known relationship between CKD and risk of morbid cardiovascular events.

In summary, RN is still necessary in some elderly patients with renal cancers that are potentially life threatening, such as locally advanced RCC and most high-grade urothelial cancers. However, loss of a kidney leaves most elderly patients with CKD and predisposes to cardiovascular morbidity and mortality. The paucity of cancer-related deaths in the elderly reflects the limited biological aggressiveness of most clinical T1 renal tumors and competing causes of death. At our center, nephron-sparing approaches are strongly preferred, and PN remains an important option for patients with good physiologic status. Treatment should be individualized based on physiologic age and comorbidities, with strong consideration given to AS for those with limited life expectancy. Further research will focus on the role of renal mass biopsy with molecular profiling or advanced imaging to facilitate rational patient management.

For references, please email the editor.
Renal Ablation for Small Renal Masses

Rajan Ramanathan, MD

Because sectional imaging is now routinely employed to evaluate patients with other abdominal conditions, an inadvertent “screening effect” has resulted in an average increase in the detection rate of small renal masses (SRM) from 2 to 3% per year, with its associated stage migration and an increase in the rates of surgical intervention.

Renal ablation (RA) uses the cell-killing properties of extreme temperature (hot or cold) to bring about apoptosis or immediate cell death in cancer cells. An ideal ablative treatment should be able to destroy all cancer cells, without affecting normal tissue and the zone of treatment should be under the physician’s control. RA is expected to destroy the same volume of renal tissue that would be excised in a partial nephrectomy and is performed using radiofrequency ablation (RFA), microwave therapy (MW) or high intensity focused ultrasound (HIFU).

It is known that cells die when exposed to a particular temperature for a given time. A time-temperature relationship for RFA shows that exposure to 60° C for even a few seconds is lethal. Ablation, unlike random tissue destruction by diathermy, however depends on the development of a controlled tissue-based thermodynamic equilibrium. This is dependent on the rate of delivery of thermal energy, tissue thermal conductivity and the rate of dissipation via the “heat sink” phenomena. (Figure 1). Thus, adequate energy needs to reach the tissue with a gradual buildup of temperature for adequate cell kill. When the heat delivery is rapid and exceeds dissipation by the heat sink, charring and carbonization will occur, producing a suboptimal ablation zone.

Heat sink mechanisms affect both radiofrequency and cryoablation zones. One of the main reasons for heat dissipation is tissue vascularity within and surrounding the renal tumor, which has an impact on the volume of the ablated area. Adjacent blood flow may dissipate heat making it more challenging to achieve target temperatures for the requisite duration in highly-vascularized lesions or lesions adjacent to large blood vessels. Adjunctive selective embolization, or clamping the renal artery prior to RA in order to decrease the heat sink effect may sometimes be required. If properly performed, RA can destroy the same extent of tis-

Figure 1: Thermodynamic equilibrium: the energy delivered must exceed the energy dissipated by such a magnitude that the temperature buildup is steady. If the energy delivery is much lower, target temperatures will not be reached. If energy delivery is disproportionately higher, rapid rise in temperature will cause carbonization and insulation and loss of conductance during RA. With RFA, this phenomenon is seen as an impedance roll over.

Figure 2: Ablation zone: It is important to match tumor size and geometry with appropriate probe size or number. Tumor A may be treated appropriately with 1 probe, but tumor B is larger and may need 2 or even 3 probes used synchronously or 1 probe used in 2-3 deployments.

Key Point:
Both heat-based and cold ablation techniques have been shown to be safe and efficacious for treatment of renal masses, with the laparoscopic approach resulting in higher success rates than those cases performed percutaneously. As technology and medical navigation systems improve, this difference may decrease and the urologist may find increasing use of percutaneous interventional techniques and RA may become an acceptable primary treatment option alongside partial nephrectomy for the treatment of SRM.
sue that is excised during partial nephrectomy. RA is usually done without hilar clamping and the risk of perioperative complications due to warm or cold ischemia is eliminated.

Both RFA and cryoablation are good tools for RA and success may be a function of patient selection and technique, and not the ablation technology. While cryoablation failures may be related to improperly performed freeze thaw cycles, RFA failures may reflect improper selection of patients (larger tumors, or tumors nearer large blood vessels, rapid heating causing tissue charring, and non-uniform heating of tumor). It is essential to use appropriate probe selection, and match it for tumor size. For example, a 2.5 cm tumor could be treated with one probe, but a 4 cm tumor would require two or even three probes.

Our experience shows RA is most useful in patients with multiple renal tumors, patients with renal tumors having renal impairment, or those patients unsuitable for surgical treatment. It may also have a significant role in the management of benign lesions, such as in patients with angiomyolipomas who have a high risk of developing a bleed.

RA may be performed percutaneously (PRA) using image guidance or laparoscopically (LRA). Anterior tumors (Figure 3) are easily approached by a standard anterior transperitoneal route (anterior to line B Figure 3, triangle A Figure 4). More laterally placed lesions (behind line B Figure 3, or in triangle B Figure 4) can still be accessed laparoscopically but some renal mobilization will be required. Posterior

Continued on next page
renal ablations are best done percutaneously (Triangle C Figure 4), although retroperitoneoscopic approaches may also be an option. In a typical tumor (Figure 5), the possible approaches are shown.

The ureters, surrounding bowel, nerves (genitofemoral and ilioinguinal nerves coursing along the psoas muscle) and muscle are at risk for thermal injury and the surgeon needs to be cognizant of their presence. The proximity of the adrenal gland must also be taken into consideration, as damage during renal ablation can lead to an acute hypertensive crisis.

During PRA, hydro-dissection with a non-electrolyte solution like D5W or pneumodissection using CO2 has been described to protect adjacent structures by creating an insulating envelope, yet both CO2 and D5W can dissipate or undergo resorption, and the actual displacement of the organ may not always be predictable.

In situations where bowel or ureteral injury is a concern, LRA would be a better option and this can sometimes be combined with adjunctive ureteral cooling using cooled dextrose 5% in water (D5W) solution instilled by retrograde pyeloperfusion for centrally located tumors within 1.5 cm of the ureter.

LRA is performed with the patient positioned as for a standard transperitoneal laparoscopic renal surgery. Intraoperative ultrasound should be used in all cases (Figure 6). Intraoperative ultrasound is also useful to monitor ice ball formation during cryoablation, but vaporization (gassing out) during RFA, causes the ultrasound image quality to deteriorate very rapidly. Real-time temperature monitoring, therefore, may be a better surrogate for identification of end points during RFA.

Once the tumor is localized, peripheral temperature sensor probes and ablation probes are placed in such a way as to follow the principles of ablation. Special effort is taken to match the 3-D configuration of the tumor with the expected ablation zones. (Figure 7).

Our experience shows LRA to have better technical success rates than the percutaneous approach. In a meta-analysis involving 47 studies representing 1,375 kidney lesions comparing RFA with cryoablation, RFA was found to be more often performed percutaneously (94% vs. 35% for cryoablation), and had higher rates of repeat ablation (8.5% vs. 1.3%; P < .0001), local tumor progression (12.9% vs. 5.2%; P < .0001) and metastasis (2.5% versus 1.0% (P<0.06).
When using the percutaneous approach, the surgeon must rely heavily on technology. Probe placement and ablation require active image guidance in order get the spatial bearings of tumor accurately. Inaccuracies of a few millimeters or angle changes of a few degrees can get amplified based on the distance of the target from the skin, since the pivot of the needle trajectory is on the skin surface. (Figure 8). Imprecise targeting can cause imprecise needle placement, and this can have an impact on procedure time, and the consequent need for multiple needle repositioning can increase the risk of bleeding or pneumothorax.

Long-term results using RA are as yet unavailable. However, the techniques have been shown to be safe and efficacious. Success rates with LRA are better than PRA, but as technology and medical navigation systems improve, this difference may decrease and the urologist may find increasing use of percutaneous interventional techniques. In the past, RA was used primarily for patients unsuitable for a surgical excision of renal tumors. However, as technology becomes more refined and results match other nephron-sparing options, RA may become an acceptable primary treatment option alongside partial nephrectomy for the treatment of SRM.

Figure 7: LRA: Note large tumor and the use of 3 probes. Tumor destruction is evident at the end of the ablation.

Figure 8: Effect of targeting error during PRA: a deviation by 15-20 degrees (lower pane) can result in an inadequate ablation and residual tumor (arrows).
New ASCO Guidelines: Use of Serum Tumor Markers for Germ Cell Tumors in Men

Timothy Gilligan, MD

The American Society of Clinical Oncology (ASCO) recently published its first guidelines on the use of serum tumor markers for germ cell tumors in adult males. Based on a systematic literature search and review of published studies, the evidence-based guidelines were developed by an expert panel of U.S. oncologists and provide recommendations for the use of tumor markers in all aspects of germ cell tumor diagnosis and management. Errors in the management of germ cell tumors can have grave consequences in terms of failure to cure or side effects from unnecessary treatment. Serum tumor markers play an important role in the management of germ cell tumors and it is hoped that the ASCO guidelines will result in more consistently appropriate use of serum human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH) levels in men with suspected or diagnosed germ cell tumors.

Several hundred adults will develop extragonadal germ cell tumors in 2010, most of which occur in the retroperitoneum or anterior mediastinum. Regardless of whether the cancer is testicular or extragonadal, the serum level of ß-hCG, AFP and LDH play a critical role in the medical management. Normal levels in adult males are less than 1.5 mIU/mL for beta-hCG, less than 15 ng/ml for AFP and assay-dependent for LDH.

According to the ASCO guidelines, tumor markers AFP and ß-hCG should be checked frequently in men with germ cell tumors with the initial monitoring taking place prior to orchiectomy with a suspected cancerous testis mass. The rationale is that pre-orchiectomy marker levels can help interpret post-orchiectomy marker levels and clarify whether markers are falling or rising. Moreover, an elevated AFP level precludes a diagnosis of pure seminoma because these tumors do not make AFP. However, there is no evidence to support using these markers to screen for testis cancer or to distinguish whether a patient has orchitis, epididymitis or a testis cancer.

The only two settings in which testing marker levels was recommended for patients without a histopathological diagnosis are: (1) men with a suspicious testis mass who are undergoing orchiectomy, and (2) extremely rare cases with a testis mass and bulky metastatic disease whose poor condition warrants immediate treatment without waiting for a pathological diagnosis. In the latter scenario, highly elevated AFP or hCG, in conjunction with the distribution of disease can justify a diagnosis of metastatic germ cell tumor. In contrast, in men with a histopathologic diagnosis of carcinoma of unknown primary site, the ASCO panel did not recommend measuring germ cell tumor serum marker levels because they found no evidence that using such levels to determine therapy resulted in better outcomes. Although some patients with carcinomas of unknown primary can achieve durable complete remissions with germ-cell-tumor chemotherapy, serum tumor marker levels do not appear to be helpful in identifying those men most likely to benefit from such treatment.

Post-orchiectomy tumor markers play an important role in staging germ cell tumors. Men with persistently elevated hCG or AFP following orchiectomy are presumed to have metastatic disease even in the absence of radiographic abnormalities and are treated as stage III patients unless there is a persuasive alternative explanation. Because LDH has low specificity, diagnosing metastatic testis cancer solely on the basis of an elevated LDH is not recommended.

In addition to checking post-orchiectomy marker levels in men who had elevated pre-orchiectomy markers, marker levels should be drawn on or immediately prior to the first day of chemotherapy because the degree of elevation of AFP, hCG and LDH may help determine the prognosis of metastatic germ cell tumors and influence the intensity and duration of treatment. More specifically, men with metastatic germ cell tumors who, at the time chemotherapy is started, have an AFP level above 1000 ng/ml, a ß-hCG level above 5000 mIU/mL or an LDH level more than 1.5 times the upper limit of normal are considered to have intermediate or poor risk disease (depending on the degree of eleva-
tion) and are generally treated more aggressively, i.e. with four rather than three cycles of bleomycin, etoposide and cisplatin. However, it is the marker levels when chemotherapy is started rather than the marker levels before or immediately after orchiectomy that should be used to determine how much chemotherapy to administer.

The ASCO guidelines also endorse using serum tumor markers AFP and ß-hCG to monitor the response to treatment. Tumor markers may rise during the first week of chemotherapy as a result of tumor lysis, but should decline thereafter. In patients with elevated markers, a rising AFP or ß-hCG level after the second week of the first cycle of chemotherapy generally indicates cisplatin-refractory disease and justifies a change in therapy. Slowly declining markers, however, are not indications to change treatment even though they portend a lower probability of cure. LDH levels may rise due to chemotherapy toxicity and are thus not generally used to monitor response to treatment.

One of the most valuable uses of serum tumor markers AFP and hCG for germ cell tumors is during relapse surveillance. For nonseminomas, elevated markers are often the earliest sign of relapse in men with stage I, II or III disease and marker levels should be checked at every surveillance visit. In contrast, although hCG is often elevated at the time of relapse for men who have been treated for disseminated seminoma, the ASCO guideline panel found no compelling evidence that tumor marker levels are useful for monitoring men with stage I seminoma for relapse. Stage I seminoma relapses are almost always detected by means of radiographic imaging or, less often, physical examination. The ASCO guidelines therefore recommended measuring serum AFP and hCG levels for men with a history of stage II or III seminoma, but not for men with stage I seminoma.

In order to interpret and respond to elevated serum tumor marker levels appropriately, clinicians must be aware of the potential for false positive tumor marker results and conditions other than germ cell tumors that can cause true marker elevations. Serum AFP levels may be elevated as a result of benign liver disease, pregnancy and a number of other cancers including hepatocellular carcinoma. Some patients have constitutively elevated AFP levels in the range of 15 to 30 ng/ml. False positive ß-hCG results can be due to cross-reactivity of the assay with luteinizing hormone or from detection of hCG produced by the pituitary gland in hypogonadal men. In men with elevated hCG or LH levels due to hypogonadism, the level should normalize after treatment with supplemental testosterone. Other types of cancer can also cause hCG elevation. LDH is the least specific tumor marker and elevations in LDH can result from almost anything that results in cellular lysis or injury, including myocardial infarction, liver disease and many different cancers.

Germ cell tumors are highly treatable and usually curable cancers when managed appropriately. Serum tumor markers can greatly aide in the medical management of these tumors and it is hoped that the new ASCO guidelines will contribute to more widespread evidence-based use of these important tests.

For references, please email the editor.
Role of Retroperitoneal Lymph Node Dissection in Low-Stage and Advanced Nonseminomatous Germ Cell Testis Cancer

Andrew J. Stephenson, MD, FACS, FRCSC

The development of successful treatment paradigms and excellent survival rates has enabled an assessment of the long-term treatment-related toxicity of successful testis cancer therapy. Chemotherapy and radiation therapy for germ cell tumors (GCT) of the testis are associated with increased risks of secondary malignant neoplasms and cardiovascular disease, similar to that associated with cigarette smoking. Chemotherapy is also associated with risks of peripheral neuropathy, hearing loss, Raynaud’s phenomenon and chronic renal insufficiency. In contrast, retroperitoneal lymph node dissection (RPLND) in the hands of experienced surgeons is associated with a 5% risk of ejaculatory dysfunction (when nerve-sparing techniques are used), small bowel obstruction in approximately 1% of patients and a midline scar.

In the past, investigators tried to limit the need for “double therapy” by recommending the treatment modality associated with the lowest risk of cancer recurrence. However, focus has shifted somewhat to minimize the risks of serious long-term treatment-related sequelae. Given the favorable long-term side-effect profile of RPLND and surveillance relative to cisplatin-based chemotherapy, recent treatment guidelines have placed an emphasis on these treatment modalities in patients with low-stage nonseminomatous (NS) GCT: clinical stage I – no retroperitoneal lymphadenopathy; clinical stages IIA-B – retroperitoneal lymphadenopathy < 5 cm.

For clinical stage I NSGCT, many centers have adopted a non-risk-adapted approach where patients are managed with surveillance, even in the presence of risk factors such as lymphovascular invasion and embryonal carcinoma predominance. Our approach at Cleveland Clinic is to recommend surveillance to clinical stage I patients without these risk factors, and either surveillance or RPLND for those with these risk factors. Two cycles of chemotherapy are not routinely recommended at our institution due to potential for late toxicity. If RPLND is chosen, we recommend that experienced surgeons perform this operation. A recent German randomized trial of RPLND versus one cycle of chemotherapy for clinical stage I NSGCT reported a high rate of local recurrence among those treated by RPLND. Relative inexperience and/or use of limited templates are factors that likely contributed to these poor results. At Cleveland Clinic, a full, bilateral template dissection with a nerve-sparing technique is the preferred approach.

For patients with clinical stage IIA and IIB NSGCT, three to four cycles of good-risk chemotherapy is recommended for those with increasing post-orchiectomy serum alphafetoprotein (AFP) or human chorionicgonadotropin (HCG) levels and/or high-volume retroperitoneal disease (lymph nodes 3-5 cm in size), as the risk of systemic disease is high. In those with normal post-orchiectomy AFP and HCG levels, we recommend RPLND as 50% of patients avoid any chemotherapy and long-term survival approaches 100%. Adjuvant chemotherapy is routinely recommended only to patients with extensive lymph node involvement (> 5 lymph nodes and/or size > 2 cm) with malignant GCT (embryonal carcinoma, seminoma, yolk sac tumor or choriocarcinoma). We recommend surveillance in patients with retroperitoneal teratoma or microscopic involvement with malignant GCT, as cure rates with RPLND alone are 90% or greater.

In advanced NSGCT, resection of residual masses after induction chemotherapy remains an essential component to a long-term cure. The majority of patients with residual masses will have evidence of malignant GCT (8-20%) or teratoma (20-66%). No clinical or pathological criteria (including the percentage reduction in the mass, the size of the residual mass, or the absence of teratoma in the testis) can reliably predict the histology of retroperitoneal lymph nodes after chemotherapy. Even a residual mass size cutoff of 1 cm is insufficient to exclude patients from RPLND.

Key Point:
Retroperitoneal lymph node dissection (RPLND) for low-stage nonseminomatous germ cell testis cancer (NSGCT) in the hands of experienced surgeons is a successful treatment approach that avoids long-term treatment toxicity associated with chemotherapy. At Cleveland Clinic, we recommend surveillance for clinical stage I patients without additional risk factors such as lymphovascular invasion and embryonal carcinoma predominance, and either observation or RPLND for those with increased risk factors. By using a full, bilateral template dissection with a nerve-sparing technique, patients with retroperitoneal teratoma or microscopic involvement with malignant GCT treated primarily with RPLND show a 90 percent or greater cure rate. In advanced NSGCT, post-chemotherapy RPLND to control the retroperitoneum after resolution of serum tumor markers with chemotherapy is essential to the long-term cure of patients as 50% or more have residual teratoma or malignant GCT. In the post-chemotherapy setting, our approach involves a full, bilateral template dissection and select patients are candidates for the nerve-sparing technique. Approximately two-thirds of patients with residual malignant GCT and over 90% with residual teratoma are cured following post-chemotherapy RPLND.
Thus, we advocate a full-bilateral RPLND (with nerve-sparing technique when feasible) to patients with any residual mass after chemotherapy for NSGCT.

Two recent studies have shown favorable outcomes with observation in patients with residual masses < 1 cm after chemotherapy, challenging the need for RPLND in all NSGCT patients with small residual masses following treatment. However, it should be emphasized that these select patients represent only about 25% of the overall cohort of patients who receive chemotherapy for advanced NSGCT. The drawbacks of an observational approach for small residual masses are the need for frequent CT imaging (and the risks associated with radiation exposure) and the risk of early or late relapse with potentially compromised curability. As such, we routinely recommend observation after chemotherapy only to those patients with a normal post-treatment CT scan without teratoma in the primary tumor and who had good-risk features at the start of chemotherapy (AFP < 1000, HCG < 5000, LDH < 1.5x normal, no non-pulmonary visceral metastases). All others are recommended to undergo post-chemotherapy RPLND.
Robotic Partial Nephrectomy: Cumulative Single Center Experience with 175 Consecutive Cases

Riccardo Autorino, MD, PhD, Sylvian Forest, MD, Georges-Pascal Haber, MD, Shahab Hillyer, MD, Michael A. White, DO, Rakesh Khanna, MD, Greg Spana, MD, Robert J. Stein, MD, and Jihad H. Kaouk, MD

Throughout the last two decades, nephron-sparing surgery has been increasingly adopted for the management of small renal tumors. Even as open partial nephrectomy remains regarded in major guidelines as the gold standard treatment, minimally invasive approaches have been developed to overcome the morbidity associated with open surgery. Among them, laparoscopic partial nephrectomy allows smaller incisions, shorter convalescence and recovery time, with similar oncologic and functional outcomes as compared to the open technique. At Cleveland Clinic, the largest experience with laparoscopic partial nephrectomy has been accumulated over a 10-year period with more than 1,000 cases performed.

Robotic technology is being increasingly applied in urological surgery. It provides additional advantages to the surgeon performing laparoscopic partial nephrectomy, such as 3-D vision, articulating instruments, scaling of movement and tremor filtration, and the TilePro™ technology, a live intraoperative ultrasound platform.

Indications for robotic partial nephrectomy have significantly expanded in the last five years with the feasibility and safety of the procedures largely demonstrated. At our institution, a robotic partial nephrectomy program was started in 2006. Since then, it has been consistently implemented so that we now have the largest single institutional experience worldwide with more than 250 cases completed by surgeons in the Center for Robotics & Image Guided Surgery directed by Jihad Kaouk, MD.

Figure 1. (a) Tumor excision after hilar clamping using cold scissors (b) Hemostasis and closure of the collecting system using running absorbable sutures and non-absorbable clips (c) Renal parenchymal defect approximation (after “early” hilar unclamping) using horizontal mattress sutures with non-absorbable anchoring clips

Key Point:
A growing body of evidence from recently published literature shows robotic partial nephrectomy to be an effective and safe technique in patients where a nephron-sparing approach is desirable. Our experience with 175 consecutive procedures using this technique supports established studies and the future of its use.
The indications for robotic partial nephrectomy have been expanded since our initial experience along with a refinement of the surgical technique. We moved from selected cases, such as small peripheral masses, to more challenging ones, such as hilar tumors, larger size tumors and tumors in obese patients.

The surgical technique for robotic partial nephrectomy basically duplicates the steps of a standard laparoscopic partial nephrectomy regarding the transperitoneal approach to the kidney and identification/dissection of the renal vessels. A remarkable difference between the two techniques resides in the two core steps of the procedure, i.e., tumor excision and renal reconstruction. Due to the unique features of robotic technology and instruments that allow the surgeon a better vision of the intraoperative field together with more precise movements, these can be performed in a more safe and effective way.

Specifically, we have developed our own technique of renal reconstruction, which allows us to minimize warm ischemia time, a surrogate parameter to assessing the “impact” of the procedure on the renal function of the patient, and, at the same time, achieve a reliable reconstruction of the kidney. By using a running absorbable suture and special non-absorbable clips, we are able to achieve adequate hemostasis and closure of the collecting system. The hilum is then unclamped (“early unclamp”) and the renal parenchyma defect is finally approximated using another absorbable suture and covered with a hemostatic agent (Figure 1).

A recent analysis of our outcomes after 175 consecutive procedures (130 for renal cell carcinoma, according to the final pathology report) showed a mean OR time of 182 minutes, a warm ischemia of 17.5 minutes and minimal blood loss. Only four intraoperative complications have occurred. Regarding the postoperative course, the mean hospitalization time averages four days, with mean time to ambulation being only 1.4 days. Fourteen cases (8%) required a transfusion focally. Positive margins have been detected in two cases. The assessment of postoperative renal function has shown no significant decline as based on the estimated glomerular filtration rates. The short-term oncological follow-up (mean 11 months) has been encouraging, with no local recurrence (Table 1).

In conclusion, a growing body of evidence from recently published literature and our own experience show that robotic partial nephrectomy represents an effective and safe alternative to other partial nephrectomy techniques in patients where a nephron-sparing approach is desirable.

This article is written for educational purposes only and as a convenience. Cleveland Clinic has no financial interests in nor is it endorsing any product or device described in this article.

For references, please email the editor.

Table 1. Analysis of 175 consecutive robotic partial nephrectomies at Cleveland Clinic.

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A Novel Robotic Platform (VeSPA) Specific for Robotic Single-Site Surgery

Jihad Kaouk, MD, Shahab Hillyer, MD, Riccardo Autorino, MD, Michael White, DO, Rakesh Khana, MD, Greg Spana, MD, and Georges-Pascal Haber, MD

Since its introduction, laparoendoscopic single-site surgery (LESS) has gained momentum in the field of urology. Initial comparison studies have demonstrated improved cosmesis and decreased convalescence postoperative pain as compared to similarly matched conventional laparoscopic approaches. LESS is technically challenging due to the inability to triangulate instrumentation resulting in internal and external clashing, lack of robust retraction and overall surgeon ergonomic discomfort. To minimize the limitations of LESS, we use the current da Vinci® Surgical System (Intuitive Surgical, Sunnyvale, Ca.) and termed the procedure robotic laparoendoscopic single site surgery (R-LESS). Recently, VeSPA, a novel robotic platform, has been developed to facilitate LESS. The system is based on instrument and software modifications of the current da Vinci Si™ system. The initial laboratory experience with VeSPA robotic platform assessed its feasibility and efficiency for urological application at Cleveland Clinic.

The configuration of the current IS3000 da Vinci Si system was modified with the intent to perform R-LESS surgery. The console and slave remain the same. Only arm one and arm two are used, with arm three placed aside. The software has been upgraded to accommodate the use of the specific VeSPA semi-rigid instruments and accessories. A newly designed multi-channel port allows the placement of an 8.5 mm scope, two crossing curved cannulae for the robotic instruments and a 12 mm cannulae for the assistant.

VeSPA instruments

The VeSPA instruments and accessories maintain the same core clinical capabilities of the currently marketed system. They are of similar construction to existing da Vinci Si EndoWrist™ instruments except for the shaft that is semi-rigid, allowing them to be inserted through curved cannulae and distal end of the instrument is without a wrist. The VeSPA instruments and accessories include: needle driver, Cadiere grasper, right-angle Maryland retractor, curved scissors, hook, clip applier and suction irrigator (Figure 1).

Key Point:

In a recently completed lab study, we performed robotic laparoendoscopic single site surgery (R-LESS) procedures using a novel robotic platform (VeSPA). A total of 16 procedures were done including pyeloplasty (n=4), partial nephrectomy (n=4) and nephrectomy (n=8). All cases were completed successfully. Development of robotic systems and instruments dedicated to single site surgery will further improve efficacy of single site surgery and minimize technical challenges and learning curve.

Figure 1: Scope and robotic curved instruments all introduced through a multichannel port.
Access and Robotic Docking

After general endotracheal anesthesia, the animals were placed in the lateral flank position. A 3.5-cm umbilical incision was made. The multichannel single port was inserted through the incision and the curved cannulae were placed through the port, with the curves of the cannulae crossing over each other at the distal end. This allowed alignment of the remote center and effectively re-created triangulation of the instruments.

The robot was brought into the field behind the back of the animal and docked to the cannula in the multichannel single port (Figure 2).

An 8.5 mm robotic 0° lens scope and the VeSPA instruments were attached to the da Vinci Si system and introduced into the abdomen. The instruments were automatically reassigned such that the right hand of the surgeon’s control would control the left instrument, and vice versa. The surgeon controlled the movement and position of each individual instrument’s arm as necessary to perform the surgical procedure, just as with the existing standard robotic instruments. An additional 12 mm cannula was inserted through the same multi channel port to allow the assistant to retract, suction, and pass sutures and clips.

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Table 1. Perioperative outcomes

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of Procedures</th>
<th>Operative Time (minutes)*</th>
<th>Estimated blood loss (ml)*</th>
<th>Warm ischemia time (minutes)*</th>
<th>Conversion</th>
<th>Intraoperative Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyeloplasty</td>
<td>4</td>
<td>55 (40-65)</td>
<td>&lt;20</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial Nephrectomy</td>
<td>4</td>
<td>37.5 (34-40)</td>
<td>30 (30-60)</td>
<td>14.8 (12-20)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Radical Nephrectomy</td>
<td>4</td>
<td>16.8 (8-27)</td>
<td>50 (50-100)</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>110.6 (82-127)</td>
<td>30 (&lt;20-100)</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Values expressed as means (range)

We completed the initial lab study using this novel instrumentation. A total of 16 procedures were done including pyeloplasty (n=4), partial nephrectomy (n=4) and nephrectomy (n=8). All cases were completed successfully. Development of robotic systems and instruments dedicated to single site surgery will further improve efficacy of single-site surgery and minimize technical challenges and learning curve.
Robotic Laparoendoscopic Single-Site Surgery: Single Center’s Cumulative Experience

Michael A. White, DO, Greg Spana, MD, Riccardo Autorino, MD, PhD, Rakesh Khanna, MD, Shahab Hillyer, MD Georges-Pascal Haber, MD, Robert J. Stein, MD, and Jihad H. Kaouk, MD

Since the introduction of the laparoscopic nephrectomy in 1991, laparoscopy has been applied to nearly every urologic procedure and has improved postoperative pain, reduced hospital stays and decreased convalescence. To further decrease the invasiveness of minimally invasive therapy, newer techniques such as laparoendoscopic single-site surgery (LESS) are currently being investigated.

Early clinical experiences with LESS have pointed out several limitations related to technical constraints including lack of triangulation, clashing of instruments and limited operating space. To help overcome these limitations, the da Vinci® Surgical System (Intuitive Surgical, Sunnyvale, Ca.) has been applied to LESS and termed robotic-laparoendoscopic single-site surgery (R-LESS). We report on our cumulative experience with R-LESS.

Data were prospectively entered in Cleveland Clinic’s Review Board-approved LESS database and retrospectively reviewed. Accrued demographic data included patient age, body mass index (BMI), preoperative prostate specific antigen (PSA) level, Gleason score, biopsy characteristics, D’Amico risk classification, tumor size, procedure performed, and sexual health inventory for men (SHIM) score.

After comprehensive discussion, informed consent was obtained and patients were counseled regarding the possibility of additional incisions as warranted during the surgical procedure. Perioperative data including estimated blood loss (EBL), operative time, additional ports or conversion to standard robotic assisted laparoscopy, intraoperative complications, length of stay (LOS), and visual analog pain score (VAPS) scores were recorded. All surgical complications were classified as according to the Clavien Classification.

Between May 2008 and May 2010, a total of 48 (19 upper tract and 29 pelvic) R-LESS procedures were scheduled at our institution (Table). Mean patient age was 59 (21-88) and 62 years (49-89). Mean BMI was 27 (19-35) and 25 kg/m2 (20-30). Mean operative time was 210 (90-360) and 214 minutes (150-420), while mean EBL was 133 (25-600) and 181 ml (50-1000). Length of stay was 2.6 days for upper tract procedures and 3.6 days for pelvic surgeries. Four procedures had to be converted to standard robotic or pure laparoscopy due to instrument clashing, instrument length and gas leakage from the single port. A rectal injury during a radical cystectomy was repaired primarily and healed without incidence.

We have demonstrated that a wide range of surgical procedures are possible through a single incision with the aid of the da Vinci® surgical system. R-LESS offers several potential benefits including a smaller scar, minimally invasive access, and less pain during early and long term follow-up.

To date, we lack a robotic system dedicated to LESS. The available robotic technology is too broad and must be refined to achieve the potential full benefit of this technique. It is not clear if the ideal system will be a flexible robot, miniaturized robotic platforms or a yet to be developed technology. Advances in the field of robotics will hopefully overcome current limitations for LESS and improve outcomes for the patient and surgeon alike.

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Table. Preoperative and Perioperative Data

<table>
<thead>
<tr>
<th></th>
<th>Age (Years)</th>
<th>BMI (Kg/m2)</th>
<th>Operative Time (minutes)</th>
<th>EBL (ml)</th>
<th>LOS (days)</th>
<th>Adverse Events</th>
<th>Conversion to lap or robotic</th>
<th>Visual Analog Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Tract (n=19)</td>
<td>59 (21-88)</td>
<td>27 (19-35)</td>
<td>210 (90-360)</td>
<td>133 (25-600)</td>
<td>2.6 (1-4)</td>
<td>0</td>
<td>3</td>
<td>1.7 (0-5)</td>
</tr>
<tr>
<td>Pelvic Surgery (n=29)</td>
<td>62 (49-89)</td>
<td>25 (20-30)</td>
<td>214 (150-420)</td>
<td>181 (50-1000)</td>
<td>3.6 (1-18)</td>
<td>2</td>
<td>1</td>
<td>1.5 (0-9)</td>
</tr>
</tbody>
</table>
There is an urgent need for better performance of biopsies for detection of prostate cancer, due to an unacceptable false negative rate and imprecise re-biopsies of suspicious phenotypes by handheld transrectal ultrasound (TRUS)-guided prostate biopsy. We designed a TRUS robot, consisting of a motorized endoscope manipulator (ViKY® System, Endocontrol Inc., Dover, Del.) with a TRUS probe attached in place of the endoscope, in an effort to improve the accuracy and reproducibility of prostate biopsies and focal therapies. The compact, easy-to-use ViKY® System has three motors, controlled by a foot pedal, that provide three-degrees-of-freedom motion to the TRUS probe (up-down, right-left and forward-backward). The motors are equipped with Hall sensor-based encoders that integrate with the calibration process to provide precise information on the location of the TRUS probe in real time. The software allows the robot to save 3-D coordinates of up to 24 points.

In our initial assessment of the TRUS robot, we showed that we could direct the robot to return the TRUS probe to a pre-recorded fiducial point on a prostate phantom with minimal registration error, and accurately target a small tumor mimic in the phantom by needle biopsy. Testing on a cadaver was straightforward; the robot moved successfully in its full range of motion with no unexpected movements or rectal injury, enabling visualization of the entire prostate in 2-D images and successful automated acquisition of the 3-D image. Prostatic calcifications in the cadaver were accurately targeted by the TRUS probe.

Our robotic TRUS device may improve the performance of prostate biopsies on several levels. First, even the most refined protocols for handheld TRUS-guided prostate biopsies fail to detect a considerable number of potentially aggressive tumors, compelling a second biopsy, or possibly delaying diagnosis until the cancer is at an advanced, less curable stage. Our device may reduce the false-negative rate and thereby lessen the need for a repeat biopsy. Second, when an atypical histological phenotype, such as high-grade prostatic intraepithelial neoplasia (PIN), is found in a...
Robotic Transrectal Ultrasound  

Continued

given biopsy core, knowledge of the precise location of that core provided by our device should allow better targeted re-biopsy to determine if a coexistent cancer is in that region. Third, data suggests that systematic prostate biopsies enable better predictions of tumor grade and volume than random biopsies. Increasing the precision of systematic biopsies will likely further improve such predictions and may lead to better treatment decisions by physicians. Finally, more precise localization of prostate tumors may be necessary for successful development of targeted focal therapy for men with low-risk, unifocal prostate cancer lesions, many of whom may be currently overtreated. The necessary postoperative biopsy to assess the efficacy of focal ablation of a prostate tumor would be facilitated by knowledge of the precise coordinates of the preoperative biopsy core that detected the tumor. We believe the TRUS robot can improve the performance of prostate biopsies on each of these levels.

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Robotic vs. Laparoscopic Partial Nephrectomy: A Single Surgeon Matched Comparison of 100 Cases

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

Our institution retrospectively reviewed 100 cases from a single surgeon comparing 50 patients treated with robotic partial nephrectomy (RPN) to 50 laparoscopic partial nephrectomy (LPN) cases. The patients were matched for demographics, co-morbidities, tumor specifications and clamping technique. Preoperative, intraoperative and postoperative data were measured and compared (Table 1). After accumulating experience with more than 1,000 laparoscopic partial nephrectomy cases, we adapted our technique to the robotic approach and have now completed more than 250 robotic partial nephrectomies.

The data were comparable between the robotics versus laparoscopic patients. Age (mean RPN 52 vs. LPN 48), body mass index (BMI) (mean RPN 29 kg/m2 vs. LPN 28kg/m2), American Society of Anesthesiologist (ASA) score (mean RPN 2.4 vs. LPN 2.4), Charleston Comorbidity Index (CCI) (mean RPN 0.74 vs. LPN 0.68), tumor size (mean RPN 2.3cm vs. LPN 2.6cm), and preoperative glomerular filtration rate (GFR, mean RPN 83 vs. LPN 78) had no significant difference between the two groups. Intra-operative evaluation had similar outcomes when evaluating for estimated blood loss (mean RPN 334ml vs. LPN 218ml), warm ischemia time (mean RPN 16.5 minutes vs. LPN 19.1 minutes), intraoperative complications (RPN 0 vs. LPN 0), and total operative time (mean RPN 202 minutes vs. LPN 184 minutes). Final pathology was equal among the two groups and there were no positive surgical margins (Table 2).

Based on our experience, RPN offers comparable outcomes to LPN with a faster learning curve for the robotic approach. With improved technique and burgeoning robotic experience, we expect RPN to assume a prominent role in the management of small renal masses.

Table 1.

<table>
<thead>
<tr>
<th>Preoperative Data</th>
<th>LPN (n=50)</th>
<th>RPN (n=50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/ Female</td>
<td>26/24</td>
<td>28/22</td>
<td>0.84</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>48</td>
<td>52</td>
<td>0.57</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
<td>28</td>
<td>29</td>
<td>0.64</td>
</tr>
<tr>
<td>ASA</td>
<td>2.4</td>
<td>2.4</td>
<td>0.89</td>
</tr>
<tr>
<td>CCI</td>
<td>0.68</td>
<td>0.74</td>
<td>0.7</td>
</tr>
<tr>
<td>Side R/L</td>
<td>30/20</td>
<td>23/27</td>
<td>0.16</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>2.3</td>
<td>2.6</td>
<td>0.24</td>
</tr>
<tr>
<td>Inter/Lower/Upper Pole (n)</td>
<td>10/18/22</td>
<td>13/20/17</td>
<td>0.56</td>
</tr>
<tr>
<td>Preoperative eGFR (ml/mn)</td>
<td>78</td>
<td>83</td>
<td>0.33</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Intraoperative Data</th>
<th>LPN (n=50)</th>
<th>RPN (n=50)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>OR time (mn)</td>
<td>184</td>
<td>202</td>
<td>0.04</td>
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<tr>
<td>EBL (cc)</td>
<td>218</td>
<td>334</td>
<td>0.09</td>
</tr>
<tr>
<td>WI time (mn)</td>
<td>19.1</td>
<td>16.5</td>
<td>0.25</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>4.3</td>
<td>4</td>
<td>0.54</td>
</tr>
<tr>
<td>Intraoperative Complications (n)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Conversion to laparoscopy (n)</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Conversion to open</td>
<td>1</td>
<td>0</td>
<td>0.31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postoperative Data</th>
<th>LPN (n=50)</th>
<th>RPN (n=50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>% eGFR Change</td>
<td>-8.51%</td>
<td>-8.91%</td>
<td>0.98</td>
</tr>
<tr>
<td>Postoperative Complications (n)</td>
<td>6</td>
<td>8</td>
<td>0.56</td>
</tr>
<tr>
<td>RCC (n)</td>
<td>43</td>
<td>46</td>
<td>0.34</td>
</tr>
<tr>
<td>Positive Surgical Margin (n)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2.

<table>
<thead>
<tr>
<th>Final Pathology</th>
<th>Laparoscopic Partial Nephrectomy</th>
<th>Robotic Partial Nephrectomy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiomyolipoma</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Benign</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Clear Cell</td>
<td>20</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>Neuroendocrine Carcinoma (Carcinoid Tumor)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Papillary</td>
<td>13</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Unclassified</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Positive Frozen section</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Positive Surgical Margin</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>
Floating kidney (nephroptosis) is often defined as descent of the kidney position for more than two vertebral bodies (or two inches) when the patient’s posture is changed from a supine to an erect position (Figure 1). Although usually asymptomatic, it occasionally presents with pain, soreness of the flank or back during an erect position or after a long walk, episodic hematuria, or upper urinary tract infection resulting in a significant impact on quality of life. Moreover, in severe cases it might result in hydronephrosis and deterioration of renal function. A clinical suspicion is usually raised by typical symptoms induced by posture change and the diagnosis is confirmed by findings of intravenous urography (IVU) to compare placement of the kidneys both in supine and standing positions.

Open nephropexy (fixation of the kidney) for nephroptosis created significant morbidity in the past, and put both the doctor and patient in a dilemma regarding whether treatment was justified. With modern trend of minimally invasive surgery, the author described a modified technique for retroperitoneoscopic nephropexy, which achieved good therapeutic efficacy.

The patient was placed in a standard flank position after general anesthesia. After the retroperitoneoscopic working space was created, 3 laparoscopic ports (12-5-5 mm) were installed (Figure 2). Retroperitoneoscopic nephropexy was performed by suturing the posterior renal capsules and transfixing them to the back muscles (Figure 3). More than 50 patients with symptomatic nephroptosis have been treated with this maneuver with the median operation time of 100 minutes and minimal blood loss. Over 80% of patients treated had complete resolution of symptoms, and an additional 10% had at least partial improvement. All pre-operative hydronephrosis disappeared and follow-up IVU showed definite image improvements in 95% of the patients (Figure 4).

**Key Point:**
Symptomatic floating kidney (nephroptosis) can occasionally cause significant impact on quality of life, hydronephrosis and impaired renal function. A minimally invasive technique of 3-port retroperitoneoscopic nephropexy is a feasible, safe and highly successful option for treating patients with symptomatic nephroptosis. Recent advances with laparoscopic single-site surgery further decrease the number and length of wounds, resulting in the possibility of less postoperative pain and complications.

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**Figure 1.** Patient position and port locations during a left retroperitoneoscopic nephropexy.

**Figure 2.** Standing IVU revealing significant bilateral floating kidneys with mild bilateral hydronephrosis.
The specific merits of this technique include no interference to intraperitoneal organs (due to the retroperitoneal approach), with only the posterior capsular surface needing dissection. By using a special technique to transfix the kidney to the back muscle without a direct suture, intraoperative pulling of the kidney capsule was required due to the possibility of the renal capsule being torn while pulled under retroperitoneoscopic insufflations. Recent advances with laparoendoscopic single-site (LESS) surgery further decrease the number and length of the wounds. All telescopes and working instruments can be delivered through a single 2-2.5 cm incision, leading to less postoperative pain and complications.
Robotic radical cystectomy is gaining popularity as a treatment option for muscle invasive bladder cancer. Most centers offer robotic cystectomy and diversion through a mini laparotomy used for specimen extraction. This incision at times can negate the benefit of laparoscopic surgery, thus we describe a unique approach to the robotic radical cystectomy with complete intracorporeal ileal conduit diversion using the da Vinci® S Surgical System (Intuitive Surgical, Sunnyvale, Ca.).

By using a 6-port approach for cystectomy and extended lymph node dissection, ports are placed more superior to the traditional port placement described for robotic prostatectomy. After the cystectomy and pelvic lymph node dissection the specimen is placed in a 15 mm specimen bag, which is positioned in the pelvis for later retrieval. The left ureter is then transposed to the right side through a mesocolon window made at the level of sacral promontory.

We perform intracorporeal ileal conduit through the Maro- nette technique described by Guru, et al, with modifications based on time-tested principles of open reconstruction. These include a Wallace anastomosis for the ureters, which we feel is more conducive to robotic surgery and isolation of the ileal segment with mesenteric trans illumination.

Isolation of the ileocecal junction (IC) is completed using Prograsp™ in both robotic arms. A suture is then passed through the ileum at a point about 15 cm proximal to IC to mark the distal end of the bowel loop for conduit. The su- ture is then passed again through the abdominal wall to the assistant. This suture is manipulated from outside as Mari- onette to control the distal end of the isolated bowel seg- ment. A 15 cm segment of ileum is then identified proximal to the marionette stitch. By using a laparoscope light, the mesentery of the ileum is trans-illuminated from a right as- sistant port and the mesentery is incised using robotic hook cautery, carefully avoiding blood supply to the bowel. The small bleeders are controlled by fine bipolar coagulation.

The bowel is freed from mesentery at the proposed points of resection for the isolation of the conduit. Two laparo- scopic Endo-GIA 60mm 3.5mm are then used to isolate the bowel segment. The proximal and distal cut ends of ileum are then tied to gather with loose suture of 3-0 silk for easy retrieval later to reestablish bowel continuity. A small hole is then made at the distal end of isolated ileal loop and a 20 French foley catheter is placed in from right assistant port and the loop is irrigated using diluted betadine solution and saline until the returns from the segment are clear.

A Wallace ureteroileal anastomosis is then performed to maximize mobility of the ileal segment until the conduit has been completed. Distal end of both the ureters are placed side by side, and both ureters are spatulated. The spatulated ends of both the ureters are now stitched to each other using continuous 4-0 monocryl suture. The staple line on the proximal end is cut and removed and anastomosed to the ureters in Wallace fashion. Before finishing the an- terior layer, 6 French single J ureteric catheters are passed through the ileal loop and placed across both of ureteroileal anastomoses and brought out of the stoma end of the conduit.

To reestablish the continuity of the ileum, the corners of the

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**Key Point:**

We are currently one of the few centers applying principles of open reconstruction to complete robot-assisted intracorporeal ileal conduit urinary diversion. Our experience has shown that this approach offers early recovery of bowel function by manipulation of the bowel and eliminating traction on the ureters and bowel mesentery.
stapled ends of the bowel are cut. A 12mm port is placed in suprapubic region and using this port a 60mm 3.5mm Endo GIA stapler is then placed within the lumen of the bowel and aligned such that the antimesenteric borders of both the proximal and distal segments of the bowel are facing each other, with the stapler attaching the two lumens together. Another 60mm 3.5mm Endo GIA stapler is passed from the right 15mm assistant port and is used to close the open segment of the side-to-side anastomosis. The anastomosis is thoroughly examined for any possible leaks. A 19 French Jackson-Pratt (JP) drain is placed from the left 8mm robotic port site and positioned near ureterolical anastomosis.

We complete the procedure by cutting and removing the Marionette suture and retrieving the distal end of the ileal conduit through a quarter-shaped incision made at the proposed stoma site with the stoma fashioned in a usual manner. The specimen within the retrieval bag was removed after enlarging the umbilical port incision by 5cm and the incision and port sites are closed.

We believe that the total intracorporeal conduit reconstruction offers an early recovery of bowel function by minimizing the manipulation of the bowel and eliminating traction on the ureters and bowel mesentery, which is applied in extracorporeal reconstruction. This may translate into less postoperative complications, with patients being discharged at 72 hours post-op after removal of the JP drain. The smaller incision also reduces the amount of postoperative pain and need for narcotics and allowing for earlier discharge and faster recovery to normal function.

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As a result of Cleveland Clinic’s pioneering work that began in the late 1980s, the majority of stage T1 renal tumors can now be treated with nephron-sparing surgery. Most often this is performed in an open fashion utilizing partial nephrectomy to remove the tumor and a small amount of surrounding normal renal tissue. Although surgeons have widely adopted laparoscopy for radical nephrectomy of tumors deemed not suitable for nephron-sparing surgery, partial nephrectomy performed by laparoscopy has been underutilized. This is primarily due to the need for intracorporeal suturing after tumor excision. As a result, the use of the daVinci® Surgical System (Intuitive Surgical, Sunnyvale, Ca.) has been increasingly employed to assist in laparoscopic partial nephrectomy. Although robotic technology enables surgeons to sew more easily, this technology comes at an increased cost compared to traditional laparoscopy and is often not advantageous for small renal tumor excision, especially those lesions that are primarily exophytic.

Deeper, endophytic renal tumors require complex suture repair of the collecting system and vessels and often need mattress suture bolstering to compress the parenchymal defect. Smaller exophytic tumors are excised leaving a shallow defect that does not always require nor lend itself to suture bolstering. Additionally, the vessels exposed are usually small and the collecting system is usually intact or has only a small opening. We have found that a single running suture will adequately control the exposed vessels in this circumstance, as well as close any small collecting system defect.

Laparoscopic partial nephrectomy utilizing a single suture repair is well within the capability of most urologists who have basic laparoscopic skills. It requires only one knot to tie and can be replaced with a laparatie if necessary. However, a few points are worth elaborating:

- Initial port placement should be completed based on three components of the operation. The first is dissection of the kidney and preparation of the renal hilum in anticipation of hilar clamping. The second is the partial nephrectomy itself, followed by the final step of placing the single running suture. Most often the first two parts of the operation can be accomplished with appropriate initial port placement. However, an additional 5 mm port is often needed to triangulate the laparoscopic needle holders to sew efficiently. The addition of a 5 mm port does not add morbidity as these port sites do not herniate. By adding an additional 5 mm port a case that would be challenging to repair can be sutured much more readily.

**Figure 1.** Many small renal tumors are primarily exophytic and do not require deep dissection into the normal renal parenchyma. These tumors lend themselves well to laparoscopic partial nephrectomy. The tumor is excised with laparoscopic scissors after the hilum is clamped.
• The sutures required to repair the parenchymal defect should be prepared in advance, prior to clamping of the hilum, with preparation of a backup suture recommended. The length is determined after assessing anticipated size of the defect. A 4 mm by 8 mm Teflon pledget is used to allow tension to be placed on the running suture without tearing the parenchyma. The tail is left several centimeters long and is used to tie to after running the suture back to its initial placement, in a criss-crossing fashion. The suture most often used is 3-0 polyglycolic acid on an SH needle. Smaller diameter needles are difficult to manipulate with laparoscopic needle holders.

• Although only one knot is required with this technique, a laparotie or two locking Weck clips can be used in place of the knot. When using the Weck clip technique, it is important to place the second clip adjacent to the first to prevent slipping.

• After removal of the renal hilum clamp, oozing may occur from the tumor bed. Any small arterial bleeding will need to be sutured with a figure eight stitch, but this is uncommon. The ooze at the tumor bed is easily controlled in the vast majority of patients with the addition of Surgiflo® or Floseal®.

This technique has yielded satisfactory results from both an oncologic standpoint, as well as renal preservation consideration. To date we have had no positive margins and the warm ischemia time has averaged 22 minutes with no patient exceeding 30 minutes. Our approach described is easily transferred and is well within the capability of urologists comfortable with laparoscopic nephrectomy and interested in advancing their skills to performing laparoscopic partial nephrectomy.

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Patients with a small renal mass in a solitary kidney represent a challenging population in which tumor control with maximal nephron preservation is essential. Until recently, partial nephrectomy in an anatomical or functionally solitary kidney was managed by open surgery. Minimally invasive nephron-sparing surgery, such as laparoscopic partial nephrectomy (LPN) and energy-based probe ablation including renal cryoablation have gained interest at select centers worldwide. LPN, by duplicating open partial nephrectomy principles, has emerged as a viable alternative to open surgery. Laparoscopic cryoablation (LCA) offers the advantages of minimally invasive surgery and due to its in situ ablative nature, does not impose surgical ischemia on the solitary kidney. Our study compared peri-operative, functional and oncological outcomes of LPN versus LCA for small renal tumor in patients with a solitary kidney.

Over a 10-year period (2/1998-9/2008), 78 patients with small tumors in a functionally solitary kidney underwent LPN (n=48) or LCA (n=30). Baseline, perioperative and follow-up data were collected prospectively and analyzed retrospectively.

Demographic data were similar between the LPN and LCA groups. Tumors were somewhat larger (3.2 vs. 2.6 cm) in the LPN group. LPN was associated with greater blood loss (391 vs. 162 ml; p=0.003) and trended toward more postoperative complications (22.9% vs. 6.7%; p=0.07). By 3 months postoperative, eGFR decreased by 14.5% and 7.3% after LPN and LCA, respectively (p=0.02). Postoperative temporary dialysis was required after 3 LPN (6.2% vs. 0%, p = 0.16). Median follow-up time for LPN and LCA was 42.7 and 60.2 months respectively. Local recurrence was detected in 4 (13.3%) LCA patients (p=0.02). Overall survival was comparable between LPN and LCA at 3 and 5 years, respectively (p=0.74). Disease specific survival was significantly different between LPN and LCA at 100% and 88% respectively at 5-years (p=0.027). Furthermore, disease free survival at 5-years was significantly worse in the LCA group (64% vs. 96%, p=0.0003). While patients undergoing LCA had a significantly higher preoperative serum creatinine than those that underwent LPN, the increase in sCr postoperatively was significantly higher in LPN (35.1% vs. 14.4%, p=0.013). Furthermore, this is reflected in the significant decrease in eGFR (21.4% vs. 11.0%, p=0.018), suggesting that LCA has superior functional outcomes. In the absence of a study adequately powered to detect a small difference in overall survival in patients with tumor in a solitary kidney, we must balance advantages and drawbacks with respect to renal function and recurrence rate. Here we propose an algorithm based mainly on baseline renal function and life-expectancy to aid the urologist in treatment selection (Figure).

The presence of tumors in a solitary functioning kidney represents an absolute indication for nephron sparing surgery whenever technically feasible. As such, partial nephrectomy has been promoted as the standard of care in all patients with a solitary kidney tumor. Cryoablation destroys the tumor by rapid freeze-thaw cycles at temperatures below minus 20° C. In contrast to LPN, which is excisional, LCA destroys tissue in situ. LPN is technically challenging, requiring time-sensitive intra-corporeal suturing under ischemia. Longer warm ischemia time has been independently associated with decreased postoperative GFR. LCA offers the potential of preservation of renal function and decreased morbidity.
Figure. Proposed treatment algorithm for tumor in solitary kidney based on level of preoperative renal function. This algorithm assumes availability of adequate laparoscopic expertise and infrastructure. Important additional considerations include tumor location, tumor size and individual surgeon's experience level.
Laparoscopic and Robotic Radical Cystectomy for Cancer: Oncological Outcomes up to 10 Years

Devon C. Snow, MD, Georges-Pascal Haber, MD, Amr F. Fergany, MD, Jihad H. Kaouk, MD, and Steven C. Campbell, MD, PhD

While open radical cystectomy (ORC) with pelvic lymph node dissection (PLND) is the gold standard for organ confined muscle invasive or recurrent high-grade superficial bladder cancer, interest has burgeoned for minimally invasive techniques. Reports have shown that laparoscopic radical cystectomy (LRC) and laparoscopic robotic-assisted radical cystectomy (RRC) are associated with lower surgical blood losses, decreased need for blood transfusion, earlier return of bowel function, and decreased hospital stays, as well as improved post operative recovery. Since the first laparoscopic cystectomy there has been increasing evidence of the safety of this procedure, however there has been continuing debate about the long-term oncological outcomes. The previous longest follow-up was from our institution and looked at oncological outcomes at up to five years. Because of our clinical volume and early adoption of these techniques, our institution was in a favorable position to help answer remaining questions regarding the safety and efficacy of LRC for treatment of urothelial bladder cancer. Therefore, we report here the up to 10-year oncological outcomes and patient survival after laparoscopic and robotic-assisted laparoscopic radical cystectomy (L/RRC).

After reviewing our prospective database, we identified 121 patients who underwent LRC (105, 87%) or RRC (16, 13%) between December 1999 and September 2008 for either muscle invasive or BCG refractory bladder cancer. Most tumors were urothelial carcinomas (102, 84%) and high-stage (> pT2, 81, 67%). Extended lymph node dissection was performed in 72 patients (60%) with a median of 14 (range 0-43) lymph nodes removed (Table 1). Follow-up data were available in 108 patients. By calculating follow-up from last contact or from time of death we had a mean follow up of 20 months with a range of 10 months to 10 years. Sixty-five

Table 1. Pathologic features

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients (%)</th>
<th>Positive soft tissue margins</th>
<th>Lymph node range (ave) N0,N1,N2</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT0</td>
<td>12 (10%)</td>
<td>0</td>
<td>0-20 (8) 12,0,0</td>
</tr>
<tr>
<td>pTa</td>
<td>3 (2%)</td>
<td>0</td>
<td>8-28 (13) 3,0,0</td>
</tr>
<tr>
<td>pTis</td>
<td>7 (6%)</td>
<td>0</td>
<td>2-26 (13) 7,0,0</td>
</tr>
<tr>
<td>pT1</td>
<td>18 (15%)</td>
<td>1</td>
<td>2-31 (16) 18,0,0</td>
</tr>
<tr>
<td>pT2</td>
<td>33 (17%)</td>
<td>1</td>
<td>4-26 (14) 31,1,1</td>
</tr>
<tr>
<td>pT3</td>
<td>44 (36%)</td>
<td>6</td>
<td>2-43 (14) 26,9,10</td>
</tr>
<tr>
<td>pT4</td>
<td>4 (3%)</td>
<td>1</td>
<td>2-20 (7) 1,0,3</td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>8</td>
<td>median 14 N1=10 N2=14</td>
</tr>
</tbody>
</table>

Table 2. Comparison of LRC oncological outcomes with previously reported lymph node counts and survival rates.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Overall Survival at (years)</th>
<th>Recurrence Free Survival at (years)</th>
<th>Cancer Specific Survival at (years)</th>
<th>Average lymph node count</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORC 1,2,3,4</td>
<td>59-66% (5)</td>
<td>62-68% (5)</td>
<td>75-77% (2-3)</td>
<td>11-43</td>
</tr>
<tr>
<td>LRC 1, 5,6,7,8</td>
<td>50-87% (2-3)</td>
<td>56-83% (2-3)</td>
<td>75-77% (2-3)</td>
<td>10-18</td>
</tr>
<tr>
<td>RRC 9,10,11</td>
<td>90-96% (1-2)</td>
<td>86-92% (1-2)</td>
<td>73% (5)</td>
<td>16-19</td>
</tr>
<tr>
<td>Current study</td>
<td>45% (5)</td>
<td>73% (5)</td>
<td>73% (10)</td>
<td>14</td>
</tr>
</tbody>
</table>
patients (54%) had no evidence of disease, three patients (2%) were living with recurrence, 52 patients (43%) were dead, and one patient’s status was unknown. Twenty-six (50%) patients died from cancer specific causes, 16 (31%) died from unrelated causes and 10 (19%) died of unknown causes. Importantly, to our knowledge no patient developed port-site recurrence. The 10-year actuarial overall and cancer-specific survival was calculated at 38% and 74% respectively (Figure).

Upon literature analysis the length of follow up for LRC series varied from 18 - 38 months and that for RRC 13-23 months. Here we report the longest follow-up currently available and respond to previous concerns about the efficacy of laparoscopic lymph node dissection, possible higher positive surgical margins rates because of the lack of tactile feedback, concerns about port site metastasis and the effect of pneumoperitoneum on bladder cancer cells. It has become increasingly clear that an extended PLND provides a survival advantage presumably because it identifies patients who require adjuvant chemotherapy, provides tumor debulking and removes micrometastasis. Herr, et al showed that patients in whom more than 14 lymph nodes were removed had a statistically significant survival advantage at 10 years. A median of 14 lymph nodes were removed in our series, which was within the previously reported ranges for both open and laparoscopic radical cystectomy (Table 2).

Our data suggest that LRC/RRC with extended PLND provides oncological outcomes comparable to those from contemporary series of ORC. Ideally a randomized trial would be performed, however given patient demands and the difficulty in performing that study, analysis of outcomes like this are necessary to show efficacy of innovative treatments such as LRC or RRC. From our analysis LRC/RRC shows promise in minimizing the morbidity of radical cystectomy while providing oncological outcomes similar to the current gold standard, ORC.

For references, please email the editor.

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Figure. Kaplan-Meier curves for: A, overall survival 58%, 43% and 38% for 3, 5, and 10 years respectively; B, cancer-specific survival 74%, 74% and 74% for 3, 5, and 10 years respectively;
Robot-assisted radical prostatectomy has rapidly become the most popular modality to treat localized prostate cancer (PCa). By applying the latest technical development in minimally invasive techniques to this effective procedure, laparoendoscopic single-site surgery (LESS) holds the promise of further reducing the morbidity associated with standard laparoscopy. The surgeon can perform a broad range of major urological procedures, both extirpative/ablative and reconstructive, by accessing the abdominal cavity through a single incision at the level of the umbilicus. Introduced only three years ago, this technique has rapidly gained the interest of urologists worldwide and more than 500 cases have been reported so far.

Investigators at Cleveland Clinic have pioneered the development and the application of LESS in the field of urological surgery and we currently hold the largest worldwide clinical experience with this technique, completing almost 200 cases to date. Yet, early clinical experiences with LESS have also identified some technical limitations that may preclude a diffusion of the technique on a large scale aside from major referral centers. The authors acknowledged the limitation of embarking on this procedure due to challenges related to ergonomics and intracorporeal suturing, claiming a potential application of robotics.

To overcome these limitations, the da Vinci® Surgical System (Intuitive Surgical, Sunnyvale, Ca.) has been applied to LESS and the term robotic LESS (R-LESS) is used to define this further step. Some of the benefits of the da Vinci robot-assisted laparoscopic techniques over conventional laparoscopy include superior ergonomics, larger optical magnification of the operative field, enhanced surgeon dexterity within the field of view, and greater precision of surgical manipulation. Kaouk et al. reported the initial human series on R-LESS, including radical prostatectomy, dismembered pyeloplasty and radical nephrectomy.

More recently, in a study appearing in the October 2010 issue of European Urology, the same group reported their initial experience of R-LESS RP with the aim of demonstrating the feasibility of the procedure, describing the technique and analyzing early outcomes.

After positioning the patient in steep Trendelenburg, the procedure starts with a 3 - 4.5 cm. skin incision at the level of the umbilicus, allowing the placement of a SILS port (Covidien) through a 2 cm fascial incision. A robotic port (8 mm) is placed at the most caudal portion of the incision on the right side, then repeated on the opposite side with another 5-mm or 8-mm robotic port. The robotic 12-mm scope is introduced through the SILS port, and a 5-mm channel remains free in case the suction needs repositioned or sutures need to be passed (Figure 1). The da Vinci S® or Sisystem® are then docked and the procedure started.

The following surgical steps duplicate the standard robotic RP technique: bladder mobilization, defatting of the prostate and incision of the endopelvic fascia, ligation of the dorsal venous complex, bladder neck dissection, seminal vesicle dissection, prostatic dissection and division, and urethrovesical anastomosis (Figure 2).
When indicated, an interfascial nerve-sparing approach can be accomplished with a combination of sharp dissection and robotically applied Hem-o-lok clips.

Overall, 20 patients have been included in this analysis. The perioperative outcomes have been encouraging: mean blood loss 129 ml, mean operative time 187.6 min, and no intraoperative complications with need for conversion to standard robotic RP in only one case. Mean length of hospital stay has been 2.5 days. Seventy-one percent of patients had their catheters removed one week postoperatively and 29% after two weeks. Early oncologic outcomes have also been encouraging with postoperative PSA values <0.03 ng/ml. The 23.5% positive margin rate is consistent with prior published robotic series and likely a result of the learning curve. A trend toward improved urinary continence has been observed over the follow-up period. Sexual function has been preserved in the three patients who underwent a nerve-sparing technique. Cosmesis, as evaluated by the surgical team was excellent, with a skin incision mostly concealed within the umbilicus (Figure 3). Only one high-grade complication occurred (i.e., intensive care admission due to urosepsis), with the patient recovering uneventfully.

In conclusion, in this study we were able to demonstrate that R-LESS RP can be safely performed. By reducing some of the difficulties encountered with conventional LESS RP, it allows the duplication of a standard robotic RP. Comparative investigation to traditional robot-assisted RP are warranted and awaited to further define the role of this surgical procedure in the armamentarium of prostate cancer treatment.

For references, please email the editor.

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Laparoendoscopic Single-Site Radical Cystectomy and Pelvic Lymph Node Dissection: Initial Experience and Two-Year Follow-Up

Jihad Kaouk, MD, Raj Goel, MD, Michael A. White, DO, Wesley M. White, MD, Riccardo Autorino, MD, PhD, Georges-Pascal Haber, MD, and Steven C. Campbell, MD, PhD

Radical cystectomy with bilateral lymph node dissection is considered the standard of care for patients with muscle invasive urothelial carcinoma of the urinary bladder, and is also viable for patients with non-muscle-invasive cancer who have failed conservative treatment. Yet, this approach is reportedly associated with significant morbidity.

Minimally invasive approaches have been developed and found to provide comparable disease-specific outcomes with less morbidity regarding pain control and rapid recovery when using both laparoscopic and robotic techniques.

Laparoendoscopic single site surgery (LESS) is a development in minimally invasive surgery that eliminates the need for additional lateral ports and may further reduce patient morbidity. Herein, we describe our technique and initial experience with use of LESS for performing radical cystectomy with lymph node dissection. Patients described had a muscle-invasive tumor or a high-grade refractory urothelial tumor that failed intravesical therapy. Perioperative and pathologic outcomes together and pain assessment at the time of discharge was reported using the visual analog pain scale.

Key Point:
Laparoscopic single site surgery (LESS) radical cystectomy and pelvic lymph node dissection is feasible in both male and female patients. Negative node margins and adequate nodal sampling can be obtained during radical cystectomy for urothelial carcinoma without the need for additional ports. While the initial series of patients from our experience proved the procedure’s feasibility, long-term evaluation is pending.

Technical aspects:

Patient is placed in the lithotomy position with steep Trendelenburg. Single-port abdominal incision was established using 1.8 cm incision via Hasson’s technique. A multi-channel port with a triluminal valve system, which can accommodate three 5 mm laparoscopic instruments were used. These specific laparoscopic instruments provide flexibility and steerability to minimize external clashing by placing the power supply cords and the digital imaging cords behind the scope. Manual controls of the scope provide the needed visibility while minimizing external movements.

Extraction of bladder incision after extending the incision to \( \leq 5 \) cm. Wound protector added before extraction to prevent contact between the specimen and the incision.

Final incision, after extraction.
and clashing.

In males, the procedure begins with identification of the ureter at the crossing of the vessels at the pelvic brim, with dissection of the ureter as distally close to the ureteral entry to the urinary bladder. The distal ureter is clipped with Hem-o-lok clips and sent for frozen section. The posterior dissection of the bladder and prostate is developed by creating a plane between the bladder and the rectum, which helps develop the lateral pedicles for the bladder and prostate. Pedicle control is established using a 5 mm harmonic scalpel or LigaSure®. The prevesical space and space of Retizus are developed and by using articulating needle drivers intracorporeal ligation of the dorsal plexus is accomplished. Followed by mobilization of the urethra, which is occluded using Hem-o-lok and complete mobilization of the prostate and bladder the specimen is mobilized from the pelvis.

In female patients, a similar pattern is used in addition to prepping the vaginal vault. A narrow strip of the anterior vaginal wall is resected along with the posterior wall of the urinary bladder.

The lymph node dissection template was maintained within the boundaries of the genitourinary nerve laterally, the node of cloquet distally, and up to the aortic bifurcation proximally. Nodes were sent separately based on their anatomic location.

The ileal conduit was constructed extracorporeally.

A total of three patients underwent the procedure, two males and one female, using a single port with no additional ports needed at the time of the surgery. Surgery was performed in 2007 and patients were followed for more than two years (mean 25 months). No immediate operative or postoperative complications were encountered. One patient needed one unit of packed red blood cells due to preoperative anemia (HgB of 8.4g/dl).

With experience, operative times showed improvement. The first patient operative time was 360 minutes, and the third required 285 minutes. Operative time included the cystectomy and pelvic lymph node procedures, but did not include the diversion. Negative surgical margins were obtained in all three patients. Lymph node yield (mean 16+/- 3 lymph nodes) was similar to published laparoscopic series. Prostate cancer was identified in one patient, with a Gleason score of 7 with focal extraprostatic extension. Final pathology revealed negative margins for both the prostatic and urothelial carcinoma. Frozen section of ureteral and urethral margins were negative. Postoperative evaluation of the patients included history and physical examination, comprehensive metabolic panel, chest X-ray, stomal cytology, computed tomography (CT) scan at six- month intervals. Follow-up for two years did not reveal any evidence of recurrent or metastatic disease or development of biochemical failure for prostate cancer.

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Bioartificial Kidney Update: Implant Marking New Milestones

William Fissell, MD

A milestone implantation of an artificial kidney membrane was presented in an abstract at the American Society of Nephrology’s annual meeting in November 2010. A multidisciplinary team from Cleveland Clinic; University of California, San Francisco (UCSF); University of Michigan; and six other centers has been developing an implantable artificial kidney as an alternative to dialysis and transplant in a project funded by the National Institutes of Health (NIH).

The implantable artificial kidney is based on two new technologies that overcome fundamental barriers to miniaturization of existing dialysis systems. First, a highly efficient hemofiltration membrane developed by Shuvo Roy and Aaron Fleischman at Cleveland Clinic and UCSF allows waste products through the membrane, but retains albumin and other plasma proteins in the blood. The elongated pores of the membranes reduce resistance to liquid flow, membrane area and the pressure needed for filtration. This innovation allows the artificial kidney to be reduced to an implantable size while using the patient’s own blood pressure to drive filtration.

Second, H. David Humes at University of Michigan pioneered a technique to harvest cells from donor kidneys and expand them in cell culture. These cells formed a living metabolically active bioreactor in a large scale bioartificial kidney tested at University of Michigan, Cleveland Clinic, and other centers. Living cells in the implantable artificial kidney accept ultrafiltrate from the silicon membrane and transport salt and water back into the blood, reducing needs for dialysate and replacement fluid.

The exact identity of the toxins that accumulate in renal failure remains elusive. However, the renal tubule can reabsorb salt, glucose, and amino acids while rejecting toxins and waste products.

Our work has been organized around a fundamental principle of building components that cannot be grown and growing those that cannot be built.

Our bioartificial kidney research continues to proliferate solutions to scientific dilemmas to support the implantation. We have developed a novel set of polymers that can coat the membrane and make it compatible with blood, solving a major issue for a new membrane material. It seems to perform at least as long as conventional filters with no degradation in performance. At first, it was unclear that cultured cells would transport salt and water like cells in a kidney, but the team tailored the environment of the cells in a specialized bioreactor to coax performance from the cells. Finally, in May 2010, the team assembled the key pieces of the project in a feasibility demonstration.

The blood compatibility and the ability of the novel membranes to withstand the rigors of packaging and surgical handling were confirmed when Matthew Simmons, MD, pioneered the surgery, connecting the cartridge in place of a pig’s kidney. Blood flowed and millimeter by millimeter the ultrafiltrate flowed down the drain tube. Hours later, the fluid continued to flow, confirming that the new membrane’s ability to function.

The team plans to scale up the hemofilter to allow long-term evaluation of the membranes’ performance over weeks to months of blood exposure, and integrate the cell bioreactor into the cartridge. Our research has pieced together a small-scale example of what may eliminate the need for dialysis in the future.
Hemodialysis Patient Preference for Type of Vascular Access

Rachel B. Fissell, MD, MS

Strong associations have been reported between central venous catheter (CVC) use in hemodialysis (HD) patients and lower survival and higher morbidity. Much of the 30-40% higher case-mix adjusted mortality rate for HD patients in the United States compared to those in several European countries appears to be explained by differences in vascular access (VA) use between these two regions. The substantial body of literature supporting a central role of VA in the morbidity and mortality of HD patients has motivated efforts to increase use of fistulas and decrease use of catheters and grafts in HD patients, particularly by nephrologists in those countries with the lowest fistula and the highest catheter rates.

The type of VA used for HD treatment is related to several factors. One factor that is both influential and potentially modifiable is the patient’s own preference. It is likely that a patient’s preference for type of VA is influenced by his own individual patient characteristics and medical conditions, as well as the country in which he lives. The urgent need to increase fistula use while decreasing catheter and arteriovenous graft use in HD patients makes it imperative to have a better understanding of any potentially modifiable factors, such as patient preference for a catheter, a fistula or graft.

There are several potential influences on a patient’s preference for a particular type of vascular access. Some of these potential influences may make a particular patient reluctant to follow the recommendation of a nephrologist to have a fistula created or a graft placed. For example, a patient may prefer a catheter because placement of a graft or fistula involves surgery, or because use of a fistula or graft necessitates six, often-painful large bore needle sticks a week. Patients with catheters also are often able to leave the dialysis unit more quickly than patients with fistulae or grafts who may need 10 to 45 minutes of pressure on their VA to achieve hemostasis. A patient may know another patient whose access required surgical revision and may be reluctant to commit to even the possibility of multiple surgeries. Thus, there are several reasons why patients may have difficulty trading the short-term benefits of the catheter for the longer-term, less immediate and potentially more abstract survival benefit of a fistula or a graft.

In a recent study of patient preference, the Dialysis Outcomes and Practice Patterns Study (DOPPS III), using a sample from 2005-2008, found that patient preference for VA type varied greatly across countries. Preference for a catheter was indicated by 1% of HD patients in Japan versus 58% in Belgium and 55% in Canada. Among patients currently using a catheter, patient preference for a catheter ranged from 39% in Italy to 72-92% in Sweden, Germany, Canada and Belgium. Among all patients, preference for a catheter versus arteriovenous (AV) access, regardless of type of access, was associated with older age, less time on dialysis, female gender, lower albumin, congestive heart failure and presence of recurrent cellulitis or gangrene.

In this study, widespread and remarkable variation was seen in patient VA preference across countries. The strong associations with patient factors raise the possibility that these may influence preference for a catheter. Country variation in catheter use and patient VA preference suggests opportunities to influence patient choice to improve VA outcomes.

This article is based on an ASN 2009 abstract: Fissell RB, Fuller DS, Morgenstern H, Gillespie BW, Mendelssohn DC, Rayner HC, Robinson BM, Schatell D, Kawanishi H, Pisoni RL: Hemodialysis Patient Preference for Type of Vascular Access: Variation Across Countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS).

Rachel B. Fissell, MD, MS, a Cleveland Clinic nephrologist, is part of the team working on this analysis.
Renal Artery Stenosis: Is Stenting the Answer?

James F. Simon, MD

Renal artery stenosis (RAS) has always been an intriguing problem because, as classically taught, its diagnosis and treatment can lead to improvement and possibly cure of high blood pressure and kidney dysfunction. In reality, however, RAS is not nearly so straightforward and the most recent literature suggests that in most patients, correcting the stenosis provides no benefit.

In general, the procedure of choice to correct RAS is stenting, which has become relatively easy to perform. There has been a surge in the number of renal interventions in the last decade, with an estimated 261% increase in renal interventions from 1996 to 2005. The conclusions of these first two paragraphs present a troubling dichotomy between practice patterns and proven clinical benefit.

Early non-randomized trials showed improvement in blood pressure control and renal function after renal revascularization. However, neither of the two published randomized control trials (RCTs) comparing stenting to medical therapy alone were able to reproduce these results. The STAR study, a notably underpowered trial, showed no difference in rates of renal function decline at two years in 140 patients with RAS and hypertension. The Angioplasty and Stenting for Renal Artery Lesions ASTRAL trial showed no difference in the rate of blood pressure control or decline in kidney function in 806 patients at one year. Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), the other major RCT, is currently enrolling patients with RAS and uncontrolled hypertension.

The American College of Cardiology/American Heart Association guidelines recommend stenting be considered in patients with declining renal function, resistant hypertension or recurrent flash pulmonary edema. Unfortunately, each of these indications is quite subjective. The problems that plague the RCT’s are the same problems that plague the world of renal intervention in general. Interpretation of the degree of stenosis can be quite subjective, and ASTRAL left this up to the individual interventionalists. In addition, since there was no set minimum stenosis for enrollment, ASTRAL enrolled a significant number of patients with clinically insignificant RAS (<70%), possibly diluting the effect of the interventions. Additionally, the interpretation of the terms “resistant” hypertension and “declining” renal function can be quite variable. These analyses lead to interventions in patients that, when looked at more critically, could be predicted to not benefit. But because the diagnostic tests for RAS are so easy to obtain, primary care providers often refer patients directly to interventionalists without solid indications for stenting. This bypasses the nephrologist who may better determine the clinical indications for intervention and also establish a relationship with the patient for long-term follow-up to determine whether stenting should be performed or not.

Unfortunately, because of the design flaws, the current RCT’s do not definitively lay to rest the problems that persist in the field of renal artery stenosis. Nay-sayers, mostly interventionalists, point to poor study design and power analyses as reasons to ignore the results altogether. Additionally, neither study was able to identify the subgroup of high-risk patients who would benefit from stenting, a subgroup that is much smaller than previously thought. As a result, many renal stents are placed without meaningful benefit, and adequate follow-up of renal function and stent restenosis is often not performed.

Unless CORAL yields results different from the currently published RCT’s, the future of RAS research should involve identifying the subgroup of patients who will most benefit from stenting. Only in this way can some consistency be brought to the field of RAS and the ultimate goal, to better serve our patients’ medical needs, be achieved.

**Key Point:**

Interpretation of the degree of renal artery stenosis and its possible result in high blood pressure and kidney dysfunction can be relatively subjective, with recent randomized controlled studies leaving room for interpretation as to the need for stenting. We recommend a multidisciplinary approach to RAS with the involvement of a nephrologist familiar with the disease to better optimize the chances of a beneficial outcome by more stringently selecting patients for interventions.
Protein Catabolism in Critically Ill Patients on Continuous Renal Replacement Therapy

George Thomas, MD, and William Fissell, MD

Acute kidney injury (AKI) is a common complication of acute illness, and renal replacement therapy is the mainstay of supportive treatment for these patients. Continuous renal replacement therapy (CRRT) is utilized in critically ill and hemodynamically unstable patients. Recently reported randomized studies (The VA/NIH Acute Renal Failure Trail Network [ATN] Study and Randomized Evaluation of Normal versus Augmented Level [RENA] Replacement Therapy Study) did not show any significant improvement in mortality or improvement of kidney function when the delivered dose of CRRT was increased. The reasons for this are unclear, and it is possible that the potential benefit of increased uremic toxin removal using high dose CRRT may be obscured by competing morbidities.

One possible competing morbidity is dialysis-induced malnutrition. Dialysis-associated protein catabolism has been well described in the literature, and an altered amino acid profile in these critically ill patients could indicate altered protein metabolism that is further contributing to their morbidity. Amino acid repletion during CRRT in these patients could potentially increase muscle protein synthesis and improve nutritional variables, and possibly better outcomes.

Cleveland Clinic has a large ICU AKI program, averaging 250 new inpatient ICU CRRT starts per year and approximately 2,500 days of CRRT treatment annually. Currently, the systems we most commonly use for CRRT are the Gambro Prismaflex and the NxStage Express, which have larger membrane surface areas than those reported in prior studies. We are conducting a pilot study to examine amino acid profiles in patients undergoing CRRT using high performance liquid chromatography (HPLC) assays, specifically focusing on the modality of continuous venous hemodialysis (CVVHD) to establish the magnitude of change in amino acids before and during CRRT, and the loss of amino acids in the spent dialysate (effluent). Our preliminary data shows a significant alteration in amino acid profiles in these patients. We propose to build on data from this pilot study to design a trial that will help to define optimal amino acid dosing regimens in critically ill patients managed with CRRT, as well as its effects on patient morbidity and survival.

For references, please email the editor.
Acute kidney injury (AKI) requiring renal replacement therapy (RRT) following heart transplantation is reportedly uncommon, as its occurrence predicts significant morbidity and mortality. Emerging data from non-transplant patients highlights the striking frequency and relative prognostic importance of less severe AKI not requiring RRT, including a rise in creatinine as little as 0.3mg/dl above baseline compared to those without AKI. In those patients, one observes a higher incidence of subsequent chronic kidney disease (CKD), as well as a higher in-hospital and long-term mortality rate. Based on this, a new schema have been proposed by the Acute Kidney Injury Network (AKIN) to standardize the diagnosis and classification of AKI severity in order to better investigate and manage these patients (Table). Though much work in heart transplant patients has been done to describe chronic kidney disease, there is limited information in the literature regarding AKI, and virtually none regarding the incidence and clinical consequences of less severe AKI not requiring RRT. The heart transplant program at Cleveland Clinic is one of the busiest in the nation, and thus provides a unique opportunity for clinical inquiry.

**Key Point:**

The heart transplant program at Cleveland Clinic is one of the busiest in the nation, allowing us a unique opportunity for clinical inquiry into acute kidney injury (AKI) following heart transplantation requiring renal replacement therapy. Our cohort analysis found a significant number of heart transplant recipients suffered AKI, with the majority of subjects having stage 1. These findings of what is often deemed as "clinically inconsequential" rises in creatinine merit attention by the specialist.

We performed a cohort analysis of prospectively collected data on 368 heart allograft recipients. AKI immediately post-heart transplant was defined and the severity classified by the AKIN criteria. Impaired kidney function upon discharge was defined as an estimated glomerular filtration rate (eGFR) < 60ml/min/1.73m2, based on the revised MDRD equation. We found 182 (68.2%) subjects with and 75 (74.3%) without a pre-operative baseline eGFR greater than 60ml/min/1.73m2 suffered AKI post-transplant, the majority (i.e., 78%) being stage 1 (Figure). This finding highlights the previously unrecognized commonality of less severe
Table: Acute Kidney Injury Network Schema for the Diagnosis and Classification of Acute Kidney Injury

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 μmol/l) or increase to more than or equal to 200% (1.5- to 2-fold) from baseline</td>
<td>Less than 0.5 ml/kg per hour for more than 6 hours</td>
</tr>
<tr>
<td>2</td>
<td>Increase in serum creatinine to more than 200% to 300% (&gt; 2- to 3-fold) from baseline</td>
<td>Less than 0.5 ml/kg per hour for more than 12 hours</td>
</tr>
<tr>
<td>3α</td>
<td>Increase in serum creatinine to more than 300% (&gt; 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl [≥ 354 μmol/l] with an acute increase of at least 0.5 mg/dl [44 μmol/l])</td>
<td>Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours</td>
</tr>
</tbody>
</table>

*α Given wide variation in indications and timing of initiation of renal replacement therapy (RRT), individuals who receive RRT are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of RRT*

AKI in heart transplant recipients. There was a significantly higher incidence of stage 1 AKI in those with baseline eGFR < vs. > 60ml/min/1.73m2 (52.5% vs. 33.3%, p=0.02) and a trend to a higher incidence of more severe stage 2 or 3 AKI in those with baseline eGFR > vs. < 60ml/min/1.73m2 (34.8% vs. 21.8%, p=0.43). More importantly, in those who suffered any stage of (n=257), there was a higher risk of having impaired kidney function upon discharge (HR 2.2, p<0.01).

In the general population, it is debated whether the patients with less severe AKI is of clinical consequence in the long-term. Indeed, the majority of our patients with AKI were in the stage 1 stratum, requiring only a rise from baseline of 0.3mg/dl to qualify. However, epidemiologic analyses of large numbers of non-transplant patients would imply that even patients with stage 1 AKI do experience inferior outcomes with regard to renal function and mortality, both in the short and long-term. As such, our findings of higher rates of impaired kidney function upon discharge are in line with these findings and imply that indeed even previously thought “clinically inconsequential” rises in creatinine merits nephrological attention as well. We are currently extending our analysis to gather long-term follow up data on our cohort and further extend our knowledge of what ultimately may happen to heart transplant recipients who suffer postoperative AKI, whether dialysis is needed or not.
Accuracy of Morning Urine Protein-to-Creatinine Ratio in Acute Kidney Injury

Jonathan J. Taliercio, DO, and James F. Simon, MD

Acute kidney injury (AKI) is the single-most common reason for a nephrology consultation in hospitalized patients. The most common cause of AKI is acute tubular necrosis from variable causes such as ischemic nephropathy, medication-induced nephrotoxicity, sepsis and contrast-induced nephropathy. One of the initial diagnostic tests is a urinalysis (UA) to assess for the presence of proteinuria and hematuria. Its presence would suggest a possible alternate process, such as glomerulonephritis. Under normal circumstances, proteinuria greater than +1 on a UA should be quantified using either a morning spot protein-to-creatinine ratio or a 24-hour protein collection. The aggressiveness of the diagnostic algorithm may be directly affected by the degree of proteinuria. If heavy proteinuria is found and the etiology is unknown, a percutaneous kidney biopsy is often performed, which entails potentially significant complications. Therefore, accuracy of quantifying proteinuria is paramount.

The 24-hour urine collection is the gold standard of quantifying protein excretion. Disadvantages include inconvenience of collection and storage, and potential for improper collection techniques. Approximately 15% of all 24-hour urine collections are omitted even in the confines of a structured study protocol because of collection errors leading to invalid results and repeat testing. Therefore, the urine spot protein-to-creatinine ratio has emerged as a surrogate for 24-hour urine protein excretion. When collected as a first-morning void sample, the protein-to-creatinine ratio has been shown to correlate in a linear fashion to 24-hour urine protein excretion.

The advantage of spot urine testing is that it is quick and easy to obtain. However, there are several limitations to its use. There is a circadian rhythm of urine protein excretion, which yields higher excretion rates during the late afternoon, suggesting the timing of collection may alter test results. Additionally, the protein-to-creatinine ratio presumes a predefined range of creatinine excretion but factors such as variable body mass, especially at extremes, may not reflect accurate results from the protein-to-creatinine ratio. Despite these controversies, it is generally accepted in practice that the spot urine protein-to-creatinine ratio can be used as an easy, convenient tool to estimate 24-hour urine protein excretion. All of the published studies and the recommendations that are based upon them involve patients with stable renal function. However, practice patterns have tended to drift away from the restriction to patients with stable renal function and been routinely implemented in clinical practice in patients with AKI. The accuracy of urine spot tests in patients with AKI has never been validated in a clinical study.

The results of our prospective study of patients with non-oliguric AKI who have dipstick positive proteinuria to compare the results of the morning protein-to-creatinine ratio to the 24-hour urine collection were presented at the American Society of Nephrology meeting in November 2010.

For references, please email the editor.

Key Point:

Our analysis of the urine spot protein-to-creatinine ratio as a comparable surrogate for 24-hour urine protein excretion addresses limitations and the advantages of its use for patients with acute kidney injury (AKI). Our prospective study of patients with non-oliguric AKI and dipstick positive proteinuria is comparing results of the morning protein-to-creatinine ratio to the 24-hour urine collection.
Vitamin D Deficiency’s Impact on CKD Patients: Determining the Best Formulation and Regimen for Replacement

James F. Simon, MD

In the past decade, 25OH (inactivated) vitamin D deficiency has been recognized as a widespread problem. Low vitamin D levels have been associated not only with bone health, but with cancer development, immune function, joint pain and cardiovascular health. Thus, in recent years, the medical community has seen the number of patients diagnosed and treated for vitamin D deficiency skyrocket.

Replacement regimens have not been studied rigorously, so practitioners are left to their own reference guidelines and clinical experience when choosing a treatment. Practice patterns range from aggressive replacement with prescription-strength vitamin D2 (50,000 units weekly) to moderate doses of over-the-counter vitamin D3 (1000-2000 units daily), with D3 shown to be more potent than D2 in replacing vitamin D. Duration of therapy is not standardized, nor is the question of what to do when the D level is normalized. Many practitioners simply stop therapy, often resulting in recurrent Vitamin D deficiency.

Vitamin D deficiency in chronic kidney disease (CKD) is quite common. It is known that use of vitamin D analogs, which resemble the active (1,25OH2) vitamin D produced by the kidneys from inactivated vitamin D, to treat secondary hyperparathyroidism is associated with decreased cardiovascular events and death in patients with end stage renal disease (ESRD). Since the need to use these medicines is much less common in non-dialysis dependent CKD patients, this benefit has not been rigorously studied.

The National Kidney Foundation, via the K/DOQI guidelines, established practice patterns for treating 25OH vitamin D deficiency using vitamin D2. These guidelines were opinion based, were published before high dose D3 was available and have never been studied in patients with CKD. It has been the experience of this author that the K/DOQI guidelines does not provide adequate vitamin D supplementation to replenish most patients and that levels quickly decline after the regimen is completed.

Key Point:

Vitamin D deficiency is common and increasingly seen as important to overall health. Its treatment is not standardized in the general population. Guidelines exist to replace vitamin D in CKD patients, but these guidelines are felt to be inadequate. The UPGRADE trial will study the effectiveness of the K/DOQI guidelines using different vitamin D formulations to treat Vitamin D deficiency in CKD patients.

Hyperparathyroidism, presumed to be secondary to decreased vitamin D activation by the kidney, has been established as the earliest CKD-related comorbidity to develop. Furthermore, one study in Europe showed that parathyroid hormone (PTH) levels could be brought into target ranges in a majority of CKD stage 3 and 4 patients with inactivated vitamin D supplementation alone without relying on the more expensive vitamin D analogs. This suggests that a majority of secondary hyperparathyroidism in early stages of CKD has less to do with renal dysfunction and more to do with vitamin D deficiency.

The UPGRADE trial, which is currently enrolling at Cleveland Clinic (clinicaltrials.gov/ct2/show/NCT01173848), will investigate several of these issues. It is a randomized, double-blinded trial comparing the efficacy of ergocalciferol (D2) versus cholecalciferol (D3) in treating vitamin D deficiency in patients with stages 3 or 4 CKD, vitamin D deficiency and secondary hyperparathyroidism when given at the doses recommended in the K/DOQI guidelines. This study will examine the comparable efficacy of the different vitamin D formulations and assess the adequacy of the K/DOQI dosing guidelines in replacing vitamin D in CKD patients. Lastly, as a secondary outcome, it will investigate how often PTH levels are brought into goal ranges when vitamin D deficiency is treated.
The electronic medical record (EMR) has enabled creation of a chronic kidney disease (CKD) registry, a database that contains demographic information, critical parameters and outcome measurements of more than 57,000 CKD patients who have received medical care within the Cleveland Clinic Health System since January 2005. Using a system EMR, patients were identified using the following criteria: 1) estimated glomerular filtration rate (eGFR) below 60mL/min/1.73 m² (measured in outpatients at least twice in an interval greater than three months), or 2) ICD-9 Diagnostic Code for kidney disease such as diabetic nephropathy, polycystic kidney disease, glomerulonephritis, or hypertensive nephrosclerosis. This database will be used to identify and enroll patients in clinical research projects.

Data elements within the CKD registry include:

- Patient demographics
- Blood pressure (BP), height, weight, Body Mass Index (BMI)
- Comprehensive laboratory testing, including glomerular filtration rate (GFR), anemia management, calcium, phosphorus, phosphate parathyroid hormone (PTH), vitamin D, lipids, and other measures
- Medications
- Co-morbid diseases, especially cardiovascular disease and its risk factors.

The registry, which will interface with the U.S. Renal Data System (USRDS) and the Social Security network, is uniquely designed to track the management of CKD over the entire care spectrum, ranging from the primary care environment, traditional nephrologic care, CKD clinic and renal replacement therapy with either dialysis or transplantation.

The registry will address the following in the scope of CKD management:

- Prevalence of CKD by stage within the Cleveland Clinic Health System.
- CKD recognition by physician and the healthcare team
- CKD progression with loss of GFR over time. The goal will be to produce a “CKD progression tool” for use by physicians, healthcare teams and patients in preparing for future CKD needs such as education, vascular access or renal replacement therapy including dialysis or renal transplantation.

We are now embarking on a more ambitious project to explore the role of EMRs in identifying and managing CKD patients throughout our health system. Development of a CKD registry was the initial objective of this comprehensive program. Additional objectives include implementation of clinical decision tools (“Physician Alerts”) within the EMR based on clinical guidelines in CKD management; measuring the utility and impact of Physician Alerts on quality of care and cost; and determining potential barriers to physician acceptance of Physician Alerts.

Details of the rapid development of the CKD registry using EMRs, as well as preliminary registry findings, were presented this fall at the American Society of Nephrology’s Renal Week 2009 in San Diego.

The initial success of this project reflects a collaborative effort of the Department of Nephrology, Quantitative Health Sciences team, and the eResearch team in the Information Technology Division. More recently, the team has manuscripts accepted for publication in prestigious Nephrology journals that describe these efforts. Additional abstracts have been submitted to the American Society of Nephrology’s 2010 Renal Week in Denver on topics such as the use of the CKD-EPI equation for GFR, vitamin D deficiency in obese CKD patients and progression of CKD in the elderly.

An article describing the development and validation of this registry was recently published. Cleveland Clinic will be participating in the CDC Chronic Kidney Disease surveillance program. This will provide an opportunity to assess the prevalence and impact of CKD on our healthcare system and assess the quality of care delivered to those with this condition nationwide. Apart from several ongoing research projects with this registry, we are also initiating collaborative research projects with other leading universities across the nation.
Optimizing BP Control by Extending the Office into the Home

Mohammad A. Rafey, MD, MS

Telemedicine innovations and mobile health (mhealth) applications will play an increasingly important role in managing healthcare by providing those tools that are critically important to managing a patient’s health in the home through remote patient monitoring. Disease management with real time feedback will extend the office not only into the home but link offices and hospitals with nursing homes, assisted living facilities and sub acute facilities. Remote patient monitoring has the potential to decrease hospitalizations and readmission rates, and increase a patient’s compliance to a plan of care.

National surveys over the past two decades reveal that only one third (33%) of patients receiving treatment for hypertension have their blood pressure controlled to the recommended goal. And yet results from major clinical trials in hypertension published in the past decade, such as the African American Study of Kidney Disease and Hypertension (AASK) and the Action to Control Cardiovascular Risk in Diabetics (ACCORD) Trial have shown that achievement of goal blood pressure and maintaining blood pressure level within a pre-specified range is a possible and realistic goal. It is likely that the patient and healthcare provider relationship and connectivity resulting from a more intense patient-nurse/physician interaction in research trials is lacking in general clinical practice and is likely the ‘missing link’ for ideal blood pressure control. With recent technological advances, we are now closer to alternative, less expensive options in patient care that would require fewer office visits and yet offer the opportunity for close monitoring of patients to achieve their goal blood pressure. In essence these advances would provide the “missing connectivity” critical for optimal BP control, which is achieved in clinical research studies.

The Center for Blood Pressure Disorders in the Department of Nephrology and Hypertension has set up collaborations with industry during the past two years to evaluate wireless blood pressure devices as the basis for establishing a Virtual Hypertension Program. This program allows healthcare providers to monitor a patient’s blood pressure, with patient feedback provided in real time to include adjustments and changes in antihypertensive medications communicated to the patient’s designated pharmacy. Feedback is provided on a biweekly basis until an individual patient’s blood pressure goal is achieved and then on a monthly basis to maintain blood pressure at goal.

Key Point:
Innovative methods utilizing newer technology and devices to improve patient-physician connectivity, communication and interventions in a proactive manner have shown to achieve goals in hypertension control both at an individual and at the population level.

A recent collaboration with the Department of Health Information Technology at Cleveland Clinic and Microsoft HealthVault evaluated the transmission of data from a home BP device to a personal computer to a Web-based data repository and then to the electronic medical record at Cleveland Clinic. Patients and physicians could then access the data in MyChart, an individualized interactive health record component in a patient’s electronic chart. Preliminary findings from these observational data are promising and demonstrate a 26% reduction in physician office visits for hypertension.

We are also evaluating a wireless blood pressure device that transmits a patient’s readings directly to healthcare providers without the need for a cell phone or Internet connectivity. This Virtual Hypertension Clinic study is a randomized prospective study, which examines changes in mean systolic and diastolic blood pressures during a four-month time period vs. a usual care group. Patients will send at least six readings (3 a.m. - 3 p.m.) a week during the study period. Biweekly communication with the participant and medication adjustments will be made as needed.

In addition to a streamlined technology that provides physicians with uninterrupted data on an individual patient’s blood pressure, and the cooperation of an educated patient who understands the importance of blood pressure control, it is essential that healthcare providers are universally aware of the importance of guidelines for home blood pressure monitoring.

Recently, our survey of 162 physicians providing healthcare in the community showed that most physicians identified hypertension control as an integral part of their practice. Surprisingly, 68% of physicians stated they were unaware of the key aspects of recent national guidelines on home blood pressure monitoring, an important barrier to achieving hypertension control in the community. Improved dissemination of national guidelines for management of hypertension among community physicians will be an essential first step in an endeavor to improve blood pressure control.
Corin: Its Effect on Hypertension and Kidney Disease

Qingyu Wu, MD, PhD

In 1949, Dr. Irvine H. Page, the founding Director of Research at Cleveland Clinic, proposed the “Mosaic Theory of Hypertension,” which specifies that a steady state exists in the circulation in which the important regulatory factors are in equilibrium to maintain blood pressure -- conditions that disturb the regulatory balance are expected to cause hypertension. Today, it is well known that a variety of environmental, behavioral and genetic factors interact and influence blood pressure.

Natriuretic peptides, mainly atrial and brain natriuretic peptides (ANP and BNP), are cardiac hormones that prevent hypertension by lowering vasotension and blood volume (Figure). These peptides are activated by a membrane protease, corin, we discovered in the heart. The human CORIN gene is located on chromosomes 4p12-13. In population genetic studies, including the Dallas Heart Study and the Chicago Genetics of Hypertension Study, a corin variant allele (T555I/Q568P) was found in African-Americans with hypertension and cardiac hypertrophy. By analyzing samples from the African American Study of Kidney Disease and Hypertension (AASK) study, we found a similar allelic frequency of the corin variants in this cohort of African Americans with hypertension and kidney disease. We also found that the corin variants had reduced enzyme activities, indicating that genetic changes alter corin protein structure and impair its function. In a recent clinical study, patients with heart failure who carry this corin variant allele were found to have worse clinical outcomes such as high rates of hospitalization and death.

As a membrane protein, corin is anchored on the surface of cardiomyocytes. More recently, we and others detected soluble corin in human plasma, indicating that corin is cleaved from the cell surface. We found that plasma corin levels were significantly lower in patients with heart failure and that the reduction correlated with the disease severity. These data indicate that corin defects may represent an important mechanism underlying hypertension and heart disease.

Key Point:

By analyzing samples from the African American Study of Kidney Disease and Hypertension (AASK), our data indicates that the human corin gene defects may represent an important mechanism underlying hypertension and heart disease. Our findings also suggest that impaired corin expression and/or function may contribute to sodium retention in patients with kidney disease.

In addition to the heart, lower levels of corin expression have been detected in other tissues including the kidney. A recent microarray analysis has found that renal corin mRNA expression was reduced in rat models of proteinuric kidney disease. In these animal models of kidney disease, the reduction of corin mRNA was associated with increased expression of epithelial sodium channel (ENaC) proteins. As ENaC promotes sodium reabsorption in the kidney, these new findings suggest that impaired corin expression and/or function may contribute to sodium retention in patients with kidney disease.
Mohammad A. Rafey, MD, MS

The diagnosis and management of “resistant hypertension” has been a legacy identity in the Department of Nephrology and Hypertension for decades. Throughout this time, our department has made major contributions in the field of hypertension, with a major focus on defining pathophysiologic mechanisms in the individual patient and matching the most appropriate pharmacologic regimen for control.

Typically, resistant hypertension is defined as “blood pressure that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes.” A significant percentage of patients diagnosed with resistant hypertension may in fact have identifiable underlying factors that contribute to incorrect diagnosis or pseudo-resistance. Such factors include incorrect technique of blood pressure measurement, non-adherence of patients to prescribed antihypertensive therapy, suboptimal dosing of antihypertensive medications, and the white coat hypertension effect.

Under the directive of Emmanuel A. Bravo, MD, of the Resistant Hypertension Program in our Center for Blood Pressure Disorders, the objective is to determine whether drug resistance is due to non-adherence and/or omission of directions, or true secondary causes. The neuroendocrine and hemodynamic profile obtained as part of evaluation provides an insight into the mechanism of elevation in blood pressure, which helps tailor antihypertensive therapy and achieve optimal blood pressure control. This outpatient program should obviate the need to hospitalize such patients with resistant hypertension in order to make a definitive diagnosis. In addition, neurohumoral markers provide clues for existence of secondary hypertension.

Patients present for evaluation after overnight fasting, and are asked to hold all antihypertensive medications when presenting to the hypertension lab on the morning of evaluation. Blood pressure is then measured with an automated office blood pressure measuring device and noninvasive hemodynamic testing is performed to measure body volume and vascular resistance. Blood is drawn for electrolytes, renal function, renin and aldosterone levels, plasma catecholamines and metanephrines.

Each patient’s medications are reviewed, including evaluation for adequate dosing and appropriate combinations of their antihypertensive regimen; also, adherence to recommended antihypertensive therapy is confirmed. Patients then receive oral antihypertensive medications and blood pressure is recorded at ultra short one-minute intervals of 10 to 15 minutes. The blood pressures are recorded and analyzed after the test period. If the patient remains hypertensive, a dose of intravenous furosemide is given. The objective is to determine whether drug resistance is due to non-adherence or omission of specific medication classes, such as diuretics. At the point at which the blood pressure response to anti-hypertensive medications reaches a maximum level, repeat hemodynamic testing is performed to evaluate the change in volume and vascular resistance.

A comprehensive report including the results of biochemical, neuroendocrine and hemodynamic tests provide the basis for formulating an individualized and rational management plan for each patient. These patients are followed closely until the antihypertensive regimen is optimized and blood pressure is better controlled. The majority of patient types referred to the Resistant Hypertension Program include: the elderly with isolated systolic hypertension and, those with multiple drug therapy resistant hypertension, supine hypertension and orthostatic hypotension, and primary hyperaldosteronism.

Patients with autonomic insufficiency and supine hypertension represent a growing population of individuals with resistant hypertension who are evaluated in the program. These individuals are evaluated as to whether increased systemic vascular resistance explains the propensity to supine hypertension. Patients are kept in the supine position for a designated period of time during which the BP recording is taken. A vasodilator is administered and subsequent BP’s examined.

With the initiation of Resistant Hypertension Program, we have taken a step forward understanding this problem at an individual basis and customize therapy that helps to improve blood pressure control. Data generated from this population seen in the program will be a valuable resource which should expand our understanding of specific patient types and BP control into the future.
The use of care pathways is becoming increasingly more common in many disciplines of medicine and surgery to optimize patient management and throughput, while assuring that a patient has a good experience with no added morbidity. Vaginal sling surgery with use of a mid-urethral tension-free synthetic tape is the most commonly performed anti-incontinence surgery in the United States. Despite its popularity, no good consensus exists for postoperative management of these patients especially as it relates to outpatient care and catheterization interval. Furthermore, a previous study of U.S. urologists who perform slings showed that omore than 25% routinely send patients home or keep them in the hospital for extended periods of time to facilitate voiding trials. This adds unnecessary expense and time in most cases. To this end, we have developed a postoperative care pathway for patients undergoing outpatient solitary mid urethral synthetic sling surgery.

Women who underwent mid urethral sling (MUS) surgery without concomitant pelvic surgery were prospectively enrolled. The postoperative protocol consists of retrograde filling of the bladder with 300mL of fluid within one hour after surgery. Subjects then rate their force of stream (FOS) compared to baseline force of stream on a visual analog scale. Those with a FOS ≥50% are immediately discharged regardless of post-void residual (PVR). Only those unable to void, or those rating their FOS <50% and having a PVR>500mL are discharged with a catheter. Subjects were then telephoned within one week of surgery and followed up at 4-6 weeks postoperatively. The primary outcome was unexpected visits to the emergency room or office for voiding dysfunction or urinary retention. Further analysis for urinary tract infection and other markers of voiding function were also measured. Over a six-month period, 114 women were prospectively enrolled and completed follow-up. Of these, 105 (92.1%) passed the protocol and were discharged home without a catheter. Fourteen subjects were discharged home with elevated PVRs (range 152-427mL), representing those who would have been discharged home with catheters by many traditional voiding protocols. No subject presented to the emergency room or office for retention or voiding dysfunction prior to their scheduled visit. The average time patients were present was 139.2±58.0 minutes from arrival to recovery room. Thus, subjects reporting a FOS ≥50% can be safely and rapidly discharged after uncomplicated MUS regardless of PVR. Scanned PVRs do not add much value in those able to void. Following this postoperative care protocol, patients can be discharged home in under three hours after mid urethral sling surgery.

For references, please email the editor.
We recently prospectively evaluated the incidence of UTI in those undergoing sling surgery when only a single dose of perioperative antibiotics was given. A total of 101 consecutive women undergoing isolated synthetic sling surgery were enrolled. Fourteen percent went home with a Foley catheter. Telephone follow-up was completed at one week postoperatively with questioning of symptoms of UTI. Office follow-up with examination and urinalysis was performed one month postoperatively.

Overall, 6% of women developed a UTI postoperatively. This is similar to previously published results when longer courses of antibiotics were utilized. No patient developed a wound infection or infection related to the sling. The only preoperative variable associated with the development of a UTI was post-void residual (PVR). The average preoperative PVR for those with a UTI was 62 ml, while the amount for those without a UTI was 27 ml.

Our study supports the recent AUA Best Practice Guideline that recommends limiting antibiotic usage for slings to less than or equal to 24 hours. In fact, it indicates that one perioperative dose is sufficient. Future practice guidelines should consider limiting antibiotic use to a single dose so complications from antibiotics themselves may be further reduced.

## Stem Cells Home to Urethra and Facilitate SUI Recovery Via Local Secretion of Paracrine Factors

Charuspong Dissaranan, MD, Michelle Cruz, Howard B. Goldman, MD, and Margot S. Damaser, PhD

The etiology of stress urinary incontinence (SUI) is multifactorial and includes: damage to pelvic floor muscles, tissues and nerves during delivery; insufficient nerve regeneration; and biochemical changes with age. Vaginal delivery can injure the nerves, muscles and connective tissues responsible for maintaining continence and is an important risk factor for development of SUI.

Stem cell therapy marks a new paradigm in the treatment of SUI. Adult, or innate, stem cells are tissue-specific cells that exist within the organs of origin and have the capacity to differentiate into multiple cell lineages. Within the genitourinary system, adult stem cells have been demonstrated to regenerate the kidney, bladder and urethra.

We have previously demonstrated that MCP-3, a stem cell homing cytokine, and its receptors are upregulated after childbirth injury in rats. Recent studies suggest that systemically injected stem cells can facilitate repair after injury by secreting paracrine-acting proteins such as growth factors.

In this study, we hypothesize that stem cells will facilitate functional recovery after a simulated childbirth injury via the paracrine effect of secreted proteins.

To visualize where the stem cells go after injection, we injected bone marrow-derived stem cells labeled with a luciferase reporter gene into rats immediately after a simulated childbirth injury. Bioluminescence imaging in vivo 12 hours later showed well-defined clusters of stem cells with a high intensity signal in the rat that received a simulated childbirth injury. In contrast, only scattered cells with low intensity were observed in the sham injury rat (Figure). This data indicates that stem cells home to injured organs after childbirth injury and have the potential to restore function of those organs after injury.

**Key Point:**

By determining that stem cells home to injured organs after childbirth injury and potentially restore function of those organs, we will be able to determine the therapeutic potential of mesenchymal stem cells and their secreted proteins to treat stress urinary incontinence.

![Figure: Bioluminescence imaging of rats that received bone marrow-derived stem cells labeled with a luciferase reporter gene after simulated childbirth injury [A] or sham injury [B].](image)

Functional recovery determined by leak point pressure testing, external urethral sphincter electromyography and pudendal nerve electroneurography are presently under way. These functional outcomes will be compared between rats receiving bone marrow-derived stem cell and rats receiving conditioned media to demonstrate if improvements in functional recovery are from a paracrine effect of the cells. If our hypothesis is correct, it may be possible to utilize the secreted proteins themselves instead of the cells.

The results of this study will enable us to determine the therapeutic potential of mesenchymal stem cells and their secreted proteins to treat stress urinary incontinence.
Transvaginal Excision of Mesh Erosion Involving the Bladder after Mesh Placement Using a Prolapse Kit

Howard B. Goldman, MD

Approximately 11% of women will require surgery for pelvic organ prolapse or incontinence by the time they reach age 80. Recently, because of concerns of the durability of prolapse repairs, many have started using transvaginally placed mesh in the hopes of reducing long-term recurrence rates. Some of the potential complications of this procedure include mesh extruding into the vagina or eroding into the bladder. Extrusion of mesh into the vagina is typically removed via a transvaginal approach. However, most reports of removal of intravesical mesh to date have included an abdominal approach. We present our experience with a novel technique for pure transvaginal excision of mesh erosion involving the bladder due to mesh placement using a prolapse kit.

Under general anesthesia, the patient is placed in the dorsal lithotomy position and the vagina and abdomen are prepped and draped in standard fashion. Cystoscopy is performed to evaluate the extent of mesh erosion (Figure 1). Retrograde pyelograms are performed to rule out ureteral involvement. Temporary bilateral open-ended ureteral stents are inserted. A 1% lidocaine with 1:200,000 epinephrine mixture is infiltrated under the vaginal skin and a U-shaped incision is made. The vaginal wall is dissected to create a U-flap, which serves as the final layer of closure for the repair (Figure 2). Dissection of the vaginal skin is performed laterally from the U-flap toward the pelvic sidewall. When only a small area of mesh has eroded into the bladder, the remainder may be found relatively superficially under the vaginal wall. If a substantial volume of mesh has eroded into the bladder, it may not be immediately identified and the detrusor muscle must be incised vertically in the area of the mesh (which is determined with cystoscopic guidance) until it is detected. A right angle clamp can be used to mobilize the mesh off the bladder in the midline. An incision is made in the midline of the mesh (Figure 3), after which the lumen of the bladder is visible. Any remaining overlying tissues (superficial to the mesh) are bluntly and sharply dissected off. By grasping on the midline (incised edge) of the mesh and pulling laterally, the bladder wall underneath the mesh is carefully peeled off the mesh using both sharp and blunt dissection (Figure 4). The ureteral catheters are palpated or visualized through the cystotomy to ensure one is clear of the distal ureters during this portion of the dissection. After all tissue has been cleared off the mesh (superficial and deep), the mesh is incised as far laterally as feasible and removed. At this point, one is left with a relatively straightforward cystotomy.

Closure is then performed in three layers. The mucosal layer is reaproximated carefully using 3-0 Vicryl suture to stay medial to the ureteral catheters. The next two layers involve the detrusor muscle and are closed using 2-0 Vicryl suture (Figure 5). If for some reason the closure is tenuous, a Martius flap could be placed at this point. The anterior vaginal wall is closed with 2-0 Vicryl suture, with care taken to not overlap suture lines. The open-ended ureteral stents are removed and replaced with double-J ureteral stents, which are placed to prevent any potential ureteral obstruction from inflammation and edema involving the bladder base and trigone. A vaginal packing is placed and an indwelling catheter is left at the completion of the operation.

We have utilized this approach for a number of cases with excellent results. By avoiding an abdominal incision, the morbidity is minimized and patients are able to resume normal activities sooner.
Decreasing Radiation Exposure During Fluoroscopic Studies: A Quality Improvement Project

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

Radiation exposure from diagnostic medical imaging has become an important public health issue. There has been a dramatic increase in diagnostic imaging procedures over the last decade resulting in elevated medical exposures to ionizing radiation. Over time repeat exposures to ionizing radiation can result in high cumulative effective doses of radiation to both the patient and staff involved in imaging procedures. This is of particular interest to urologists who perform fluoroscopy-guided procedures on a routine basis. The As Low As Reasonably Allowed (ALARA) principle aims to reduce exposure to ionizing radiation for both the patient and operator to the lowest levels reasonably possible without compromising diagnostic or therapeutic efficacy.

Fluorourodynamics (FUDS) is a diagnostic procedure in urology, which uses fluoroscopic imaging to visualize the anatomy of the lower urinary tract during bladder filling and voiding. While reading FUDS, we noted that many of the images obtained did not contribute to the diagnostic value of the study. Thus, patient’s radiation exposure was higher than clinically necessary.

In order to obtain accurate diagnosis during FUDS while limiting the amount of radiation to the minimum necessary for high-quality interpretation, we instituted a Quality Assurance (QA) protocol to optimize the amount of radiation during FUDS.

During the QA protocol, fluoroscopy was limited to 4-5 static images: a scout image, one image during the filling phase, one image during valsalva, one image during voiding, and a repeat voiding image without a catheter if the patient was unable to void with a catheter. The physician was permitted to obtain additional images if clinically warranted.

We evaluated whether the decrease in the number of fluoroscopic images translates into a significant reduction in radiation. The number of spot films, fluoroscopy time, AK, and dose area product (DAP) from FUDS performed by our division during the three months prior to the conceptualization of the QA protocol were compared to FUDS performed by our division three months after the initiation of the protocol.

Fifty-four FUDS performed in three months prior to the conceptualization of the protocol were compared to 43 FUDS performed after the initiation of the protocol. The mean number of spot films recorded before and after the QA protocol was 11.2 and 5.6 respectively (p<0.001). The mean fluoroscopy time decreased from 40.9 seconds to 11.7 seconds per procedure (p<0.001). The mean AK decreased from 15.48 mGy to 4.25 mGy, and the mean DAP decreased from 518.90 mGycm² to 150.28 mGycm² (p<0.001 and p<0.001 respectively).

We then evaluated whether decreasing fluoroscopic images per the QA protocol affects the interpretation of FUDS. Four fellowship-trained female urologists reviewed 10 FUDS with 5 or more images performed prior to the initiation of the protocol. A questionnaire was completed after reviewing the patient’s history, physical and FUDS containing images that correlate with the new protocol. A second questionnaire was completed after reviewing all fluoroscopic images. There was no difference in treatment or diagnosis in 100% of 40 FUDS evaluations.

In accordance with the ALARA principle, our QA protocol significantly decreased the amount of radiation during each FUDS without changing diagnosis or treatment recommendations. As more projects like this are completed, we will be better able to control radiation dosage to patient and physician alike especially as more techniques seem to require fluoroscopic guidance, and as minimally invasive technologies continue to emerge.

For references, please email the editor.
Initial Experience with the Conceal™ Low Profile Inflatable Reservoir

Lawrence S. Hakim, MD, FACS

Implantation of a three-piece multicomponent inflatable penile prosthesis (IPP) remains the gold standard device for many prosthetic surgeons. For patients with a history of prior abdominal-pelvic surgery, including robotic prostatectomy, radical cystectomy or colorectal surgery, the standard transcutaneous or infrapubic placement of the fluid reservoir component into the perivesical space can be challenging and potentially result in an inadvertent vesical, vascular or bowel injury during the surgical procedure.

To avoid these complications in this high-risk patient population, prosthetic surgeons have occasionally opted to use either a malleable, self-contained or two-piece prosthetic device. In cases where a three-piece IPP device is utilized and prior scarring precludes safe placement of the reservoir into the space of Retzius, an alternative has been the surgical placement of a ‘standard’ round or cylindrical shaped 100 cc fluid reservoir into an ectopic location, through either the same opening or a counter incision. These standard-shaped reservoirs have been placed intra-abdominally, superficially or in a location below Scarpa’s fascia. While certainly a feasible alternative, ectopic placement of the standard shaped reservoir typically results in an easily visible and palpable reservoir and a less than desirable cosmetic result, especially in men who have minimal or no abdominal obesity.

The Conceal Low Profile Inflatable Reservoir (American Medical Systems [AMS], Minn.) was specifically designed to minimize the risks associated with the standard placement of an IPP fluid reservoir after pelvic surgery, while addressing the issues of visibility and poor cosmesis associated with ectopic placement of the standard fluid reservoir. The Conceal reservoir is a flat, pancake-shaped, one-size fluid reservoir that is designed to accommodate up to 100 cc of saline (see illustration below). The reservoir is compatible with all AMS 700 IPP cylinder and pump configurations and the inner shell surface is lined with a Parylene coating to improve durability. Due to its unique shape and contour, this reservoir device can be filled maximally and still maintain its unobtrusive and impalpable low profile. Recently, urologic surgeons at Cleveland Clinic Florida were the first in the world to implant this innovative device into a patient upon its initial limited release.

To date, we have implanted 15 men with the Conceal™ Low Profile Inflatable Reservoir with Inhibizone™ (IZ) antibiotic coating via a minimally invasive transcutaneous approach. After placement of the corporal cylinders through a single small (4 cm) scrotal incision, the external inguinal ring is identified. A space is then created through the ring, either through or above the transversalis fascia, toward the ipsilateral shoulder in either the right or the left lower abdomen. Patient ages range from 54 to 75 years, with nine of the patients having a prior history of robotic prostatectomy, three of the patients having a history of multiple prior pelvic surgeries and the remaining three patients with pure vasculogenic erectile dysfunction. Surgical times ranged from 35 to 55 minutes. Reservoir fluid volumes ranged from 65 to 100cc and there have been no intraoperative complications from penile prosthesis implantation in any of these patients. During postoperative evaluation, the reservoirs were not visible and there were no complaints of discomfort at the reservoir area or reported auto-inflation.

Our initial experience has demonstrated that the Conceal Low Profile Reservoir is an effective and unobtrusive implantable prosthetic device that can safely be implanted without difficulty and without increase in complication rate, blood loss or surgical time. The Conceal Low Profile Reservoir allows for facile placement of a standard three-piece IPP while minimizing any risk of vascular, bowel or vesical injury, especially in high-risk patients following prior pelvic surgery and can be a vital element in the urologic prosthetic surgeon’s armamentarium. Further long-term follow-up with the Conceal Low Profile Reservoir continues at Cleveland Clinic Florida.

This article is written for educational purposes only and as a convenience. Cleveland Clinic has no financial interest in nor is it endorsing any product or device described in this article.
Understanding the Hypospadias Patient’s Problems Extending into Adulthood: Results from Two Studies

Hadley M. Wood MD, Christina Ching MD, and Kenneth W. Angermeier, MD

Little is known about the natural history of hypospadias. To better characterize this population, we reviewed our experience with adult hypospadias patients with respect to how these patients present, what symptoms they experience and the extent of their surgical history.

Fifty-five adult hypospadias patients were divided into three categories: 1) patients who have undergone >2 urethral reconstructions with resulting penile deformity, tissue loss and significant scarring with persistent problems; 2) patients experiencing late failure in adulthood after an initially successful childhood repair; and 3) hypospadias patients who had never been repaired. An anonymous, mail-based survey of a subset of these men was completed to further characterize long-term functional, sexual, and psychosexual outcomes in these men and compare them with a group of age-matched men who underwent urethral reconstruction for acquired urethral stricture disease.

Patients completed three questionnaires: 1) the Brief Male Sexual Inventory (BMSI); 2) a urinary function (UF), genital perception (GP), psychological impact (PI), and sexual function (SF) questionnaire; and 3) a demographic and historical questionnaire.

With a median patient age of 37 years (range: 18 - 72), the most common presenting complaints (incidence 50.9%) were obstructive or irritative voiding symptoms. Urethrocutaneous fistula (UCF) was the second most common (14.5%), while recurrent urinary tract infections (UTIs) was third (12.7%). Penile curvature was present in 23.6% of patients and penoscrotal webbing or transposition was present in 5.4%. Upon examination, balanitis xerotica obliterans (BXO) was present in 12.7% of patients. The majority of our patients presenting for repair were so-called hypospadias “cripples” (category I) (58.2%), while 29.1% represented late failures (category II). Seven patients (12.7%) had never been repaired. An anonymous, mail-based survey of a subset of these men was completed to further characterize long-term functional, sexual, and psychosexual outcomes in these men and compare them with a group of age-matched men who underwent urethral reconstruction for acquired urethral stricture disease.

Patients who had undergone similar operations for acquired urethral stricture disease of the same age were used as controls (N=24). There were no differences seen in the two groups regarding highest educational level achieved or annual income, or validated sexual function and hypospadias-specific questionnaires. Self-reported type or number of urinary complications, infertility and erectile problems (prior to urethral reconstruction) were also similar. While a large number of patients in both groups reported curved erections, the majority reported the extent of the curve 5 - 15 degrees. More patients in the hypospadias group reported infertility. Among the six patients treated for infertility in the hypospadias group, etiology was reported as male (N=3), mixed (N=2), and unknown (N=1).

The majority of adult patients with hypospadias presenting to our practice and who ultimately need repair are those already having had multiple previous repairs with continuing complications, primarily related to stricture disease and development of late urethrocutaneous fistulae. The patients composing category III serve as a model for patients with uncorrected hypospadias as they become adults. In our series, no patient reported psychological sequelae of the cosmetics of their uncorrected hypospadias. Voiding symptoms were the main complaint, followed by a higher risk of chordee (57.1%) and BXO (42.9%) in this subgroup in comparison to the other categories. Likely as a result of BXO, these patients were also at risk for more severe stricture disease. We feel these risk factors, as well as the association of BXO with squamous cell carcinoma (2-50%) should be included in counseling parents. The overrepresentation of BXO in this subgroup also contradicts the popularly held belief that BXO in the adult hypospadias patient is a phenomenon related to prior use of skin-containing donor materials used in reconstruction.

Key Point:

Adults with a history of hypospadias present with a variety of problems related to their condition or prior corrective surgeries, including voiding complaints, fistulae, curvature of erection and de-novo strictures due to balanitis xerotica obliterans (BXO). We have found that over half of men who present in adulthood with urethral problems have undergone multiple prior operations, yet nearly 30% of these men reported only a single operation in childhood and 13% of these men have never undergone corrective surgery. Finally, adult men with hypospadias report similar urinary, sexual and psychological outcomes compared with age-matched men who undergo urethral reconstructive procedures for acquired urethral stricture disease.

Twenty-six hypospadias patients completed questionnaires. Patients who had undergone similar operations for acquired urethral stricture disease of the same age were used as controls (N=24). There were no differences seen in the two groups regarding highest educational level achieved or annual income, or validated sexual function and hypospadias-specific questionnaires. Self-reported type or number of urinary complications, infertility and erectile problems (prior to urethral reconstruction) were also similar. While a large number of patients in both groups reported curved erections, the majority reported the extent of the curve 5 - 15 degrees. More patients in the hypospadias group reported infertility. Among the six patients treated for infertility in the hypospadias group, etiology was reported as male (N=3), mixed (N=2), and unknown (N=1).

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Our survey results present an encouraging assessment of adult hypospadias patients; in particular, they do not demonstrate any differences when compared with age-matched controls with respect to sexual function or satisfaction, genital appearance and urinary function.

These findings can also help dispel some commonly-held myths about genital reconstruction, particularly on children. Finally, possibly because our cohort was relatively older (42 years) than previously published series (13-25 years), we found a lower level of reported ejaculatory dysfunction, adaptive behaviors related to anxiety about penile deformity and overall sexual dissatisfaction.
Evaluation and Treatment of Men with Chronic Prostatitis/Chronic Pelvic Pain Syndrome Using the UPOINT System

Daniel A. Shoskes, MD

To better classify men suffering from chronic pelvic pain syndrome (CPPS) and guide multimodal treatment, we developed a clinical phenotyping system, UPOINT. A cohort of 100 men with CPPS were prospectively classified in each UPOINT domain (urinary, psychosocial, organ-specific, infection, neurologic/systemic, and tenderness) and treatment was guided by this classification.

The findings show that 84% of patients had significant improvement in their symptoms with a minimum follow up of 6 months. While not a placebo/sham study, these results compare favorably with published trials of monotherapy for this condition. All domains of the NIH Chronic Prostatitis Symptom Index significantly improved, including quality of life.

As a result, we have created an online resource that allows urologists to enter patient data to determine the UPOINT phenotype and suggested therapies.

Category III prostatitis, also known as chronic pelvic pain syndrome (CPPS) is a common condition with significant impact on quality of life. There is little consensus on appropriate therapy, resulting in a high level of frustration from both the patient and urologist. Part of the problem is the heterogeneous nature of CPPS, which is by definition a syndrome rather than a disease that can be targeted by one specific therapy. Large multicenter trials of promising treatments (e.g., antibiotics, alpha blockers, neuroleptic agents) have often shown minimal or no benefit when compared with placebo; however the heterogeneous nature of patients in these studies may have prevented a positive result. This would be analogous to testing an effective migraine drug in patients only defined as having a headache, which could include patients with a brain tumor, infected tooth or neck spasm. Currently we do not have validated biomarkers to classify patients in a way that could guide therapy. A scheme of our current best understanding of the pathophysiology of CPPS is seen in Figure 1.

In response to this situation, we have proposed a six-point clinical phenotyping system to classify patients with chronic pelvic pain (CPPS and interstitial cystitis) and direct appropriate therapy. The clinical domains are Urinary symptoms, Psychosocial dysfunction, Organ specific findings, Infection, Neurologic/Systemic, and Tenderness of muscles. This produces the mnemonic UPOINT. Each domain is clinically defined, is linked to specific mechanisms of symptom production or propagation and is associated with specific therapy. Symptom severity is measured using the National Institutes of Health Chronic Prostatitis Symptom Index (CPSI) [Figure 2]. We have shown that the number of positive UPOINT domains correlate with symptom severity and duration. These findings have been confirmed by researchers in Sweden, Italy and Germany.

Our ultimate goal was to use UPOINT to improve patient outcomes. In a recent prospective study published in Urology, 100 CPPS patients at Cleveland Clinic were treated with multimodal therapy, offering specific therapy for each positive domain (e.g., Urinary: alpha blocker or antimuscarinic; Psychosocial: stress reduction/psychologic support; Organ Specific: quercetin; Infection: antibiotic; Neurologic/Systemic: amitriptyline or pregabalin; Tenderness: pelvic floor physical therapy). With a minimum follow up of 6 months (average 50 weeks), 84 patients (=84%) reached the primary endpoint of a 6 point or greater improvement in total CPSI. The chance of reaching the primary endpoint was not significantly different regardless of number of positive domains. Fifty-one patients had a 50% or greater improvement in total CPSI, while 84 patients had at least a 25% or greater improvement. The improvement seen in all groups was not simply due to regression to the mean of more symptomatic patients, since number of UPOINT domains did not correlate with drop in CPSI. In addition, drop in CPSI did not correlate with symptom duration or number of therapies. While this was not a placebo-controlled study, the incidence and magnitude of improvement was significantly higher than reported in prior large or multicenter studies of comparable duration.

We have created an online resource that will allow urologists to enter patient data to determine UPOINT phenotype and suggested therapies. This can be found at upointmd.com and clevelandclinic.org/upoint. It is our hope that such a simple algorithmic approach can simplify the care and improve the outcomes for men who suffer with CPPS.
Figure 1: Proposed Pathophysiology of Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Figure 2: UPOINT Domains and Associated Therapies
Kidney Transplant Team Using New Drug to Treat Antibody-Mediated Rejection

Richard Fatica, MD, and Stuart Flechner, MD

Improvements in anti-rejection drug treatments following kidney transplantation have reduced the rates of acute cellular rejection, but another form of rejection, humoral or antibody-mediated rejection (AMR), can still occur. Recipient antibodies directed against mismatched human leukocyte antigen (HLA) proteins expressed by the kidney donor organ can cause allograft injury. This type of rejection shortens the kidney transplant lifespan and has historically been treated with a non-selective regimen of antibody removal with plasmapheresis and suppression with intravenous gammaglobulin (IVIG) with limited success. One of the difficulties in treating this problem has been the lack of agents that target the source of antibody, the plasma cell.

The drug Velcade (bortezomib) has been approved by the FDA to treat the blood cell cancer multiple myeloma. Bortezomib is a proteasome inhibitor and effective against plasma cells, which produce antibody. Several laboratories have demonstrated in vitro that Bortezomib causes apoptosis of plasma cells, diminishing antibody production. This led groups in the United States and Europe to suggest that bortezomib might have a role in decreasing the production of post-transplant donor specific antibody (DSA), directed against the kidney. In a combined effort, a treatment plan was adopted and members of the Departments of Urology, Nephrology, Pathology, and Hematology, in conjunction with Allogen, have just reported the largest single center series to date on the use of bortezomib in the treatment of AMR in kidney transplantation. There were 16 recipients of a kidney-only and four recipients of a kidney-combined organ transplant (pancreas or liver) in the study.

The protocol consists of four sessions of plasmapheresis and bortezomib 1.3mg/m2 intravenously over two weeks. This is then followed by an IVIG infusion. When measuring the immunodominant HLA antibody, all patients have some fall from peak titers, with an average fall of over 60% (Figure 1). These are durable in about half the patients, while 10% became completely free of measured DSA. The maximum fall in antibody titers is usually seen in the first four weeks. One year after treatment, 85% of treated patients have retained their kidney transplant, and three have returned to dialysis in a population where early graft loss is common.

Key Point:
We have reported the largest single center series to date on the use of bortezomib in the treatment of antibody-mediated rejection (AMR) in kidney transplantation. One year after treatment, 85% of treated patients have retained their kidney transplant, and three have returned to dialysis in a population where early graft loss is common.

Change in levels of anti-HLA DSA before and after treatment for antibody mediated rejection using bortezomib. DSA reported as MESF using flow beads or MFI using Luminex bead assay.

A) Results reported in 16 kidney only recipients with AMR.
B) Results reported in 4 kidney-combined organ transplant recipients with AMR.
One of the treated patients illustrates the course of AMR after bortezomib treatment with stabilization of his renal transplant histology 13 months after treatment (Figure 2).

Bortezomib appears to be well tolerated with transient side effects including nausea, vomiting, diarrhea, edema, and thrombocytopenia in about 30% of treated patients. The combination of bortezomib, a proteosome inhibitor with plasmapheresis and IVIG, appears to be safe and effective at reducing the antibody in acute humoral rejection in kidney transplant patients. Future trials should be controlled, and evaluate different Bortezomib dosing strategies that include longer courses or retreatment schedules, directed by a combination of DSA titers and graft histology.

Figure 2: Upper-left: implant biopsy day 0 from 45yo deceased donor with essentially normal architecture (H&E stain 200x); Upper-right: 3.5 mo post transplant showing mild interstitial inflammation (H&E stain 200x); Lower-left: immunofluorescence staining C4d 100% of peritubular capillaries; Lower-right: 13 months after treatment of AMR with bortezomib, showing no residual inflammation.
What Drives the Association Between Longer Waiting Times on Dialysis with Diminished Kidney Transplant Outcomes?

J. D. Schold, PhD, and Sankar D. Navaneethan, MD, MPH

There is long-standing literature indicating patients that are on dialysis for longer periods prior to transplantation have diminished post-transplant outcomes. These results, derived from both single centers and national registries, suggest a substantial benefit for end stage renal disease (ESRD) patients to receive a transplant rapidly. Research indicates that patients may have a doubling of life expectancy associated with transplantation, and for those who receive a transplant while minimizing time on dialysis this benefit may be even more substantial.

However, there are several potential explanations for the association with longer waiting times on dialysis with diminished outcomes following transplantation. One is the direct morbidity associated with dialysis that may manifest after the transplant procedure. These are primarily considered to be associated with increased cardiovascular risks that may accumulate over time while undergoing maintenance dialysis. In addition, there are many factors that are not only physiological in nature but also characteristic of cultural or socioeconomic factors, which have been associated with delays in listing for transplantation and longer waiting times. These include socioeconomic status, gender, race/ethnicity, education and pre-existing morbidities. An important underlying question, to inform both policies and patient interventions, is whether longer diminished survival following transplantation is more indicative of morbidity associated with extended periods of maintenance dialysis or conversely a proxy for patients with poorer access to care and preexisting comorbidities, which can delay placement on the waiting list.

In a recent collaborative study with faculty from Cleveland Clinic, Case Western Reserve University and the University of Arizona, we evaluated the impact of waiting time on dialysis on transplant outcomes using data from a national transplant registry. By examining the relative impact of waiting time prior to placement on a waiting list and waiting time following placement on the waiting list, we found that pre- and post-listing ESRD durations are distinct phases with different associated factors with highly variable impact on transplant outcomes. Results from the study suggest that greater focus on factors associated with pre-listing duration among potential kidney transplant recipients is needed.

Cumulatively, the study suggests that pre- and post-listing ESRD durations are distinct phases with different associated factors and highly variable impact on transplant outcomes. Results suggest that greater focus on factors associated with pre-listing duration among potential kidney transplant recipients is needed. These findings further refine our understanding of the previously documented relationship of dialysis time and transplant outcomes, which may also have important implications for organ allocation policy and interventions to improve outcomes among patients with traditionally poor access to care.

For references, please email the editor.
Figure. Association of Overall Graft Survival with Pre- and Post-Listing ESRD Duration

Abbreviations: ESRD = End Stage Renal Disease; DD = Deceased Donor; LD = Living Donor
Renal failure is an unfortunate and frequent accompaniment or complication of transplantation of the liver, heart, lung and small intestine. The occurrence of renal insufficiency after transplantation of a non-renal organ in the immediate postoperative period is multifactorial and includes, but is not limited to, many reversible factors such as calcineurin inhibitor nephrotoxicity, volume depletion, hypotension and pre-existing renal insufficiency antedating the non-renal transplant. Some of these risk factors would be expected to resolve with optimal perioperative medical and surgical management. The persistence and progression of post-transplant renal failure in the non-renal organ transplant (NRTx) recipient would then prompt either listing for a kidney transplant (KTx) or the start of dialysis, depending on the magnitude of decline in renal function and the expected prognosis in the recipient.

Using data from the national Scientific Registry of Transplant Recipients (SRTR) for all KTx candidates with NRTx (1995-2008), incidence rates of NRTx candidate listing were compared to trends in KTx without NRTx. The efficacy of kidney transplantation relative to dialysis was measured in time-dependent Cox models incorporating candidates with the applicable prior organ transplant as a reference group. Overall, 4,904 NRTx candidates were listed over the study period, growing from <1% of candidates prior to 1995 to 3.3% in 2008 (Figure 1). Thirty-eight percent of NRTx candidates were listed preemptively as compared to 21% of other candidates (p<0.001) (Figure 2). NRTx transplant candidates had dramatically shorter half-lives (lung=2.8 years, liver=4.0 years, heart=3.8 years) following listing compared to prior kidney transplant recipients (9.2 years) (Figure 3). KTx demonstrated a survival advantage for each type of NRTx candidate relative to kidney transplantation candidates listed after NRTx comprise a significant and more rapidly growing cohort compared to the general candidate population. NRTx candidates are frequently listed preemptively, but have rapid decline once on the waiting list. The more frequent preemptive listing of NRTx for KTx may reflect greater access to specialized transplant care. These candidates may be prime candidates for extended criteria donor (ECD) transplants if associated with shorter waiting time durations due to high waitlist mortality.

The clinical relevance of our findings to the transplant community and practicing nephrologists lies in the fact that NRTx kidney candidates are an emerging and growing segment of the kidney candidate pool and that appropriate transplant decision-making in this group of patients presents many complexities in the clinical and ethical domains. The fact that kidney transplant listings are increasing in the NRTx population is perhaps an indication of both the growing burden of chronic kidney disease in this population and the growing numbers of NRTx. This further suggests that definition of risk factors for development of ESRD and relevant preventive strategies in the NRTx population need to be studied systematically. Listing these NRTx candidates for ECD kidneys may be a viable strategy to decrease waiting time and offset increasing waitlist mortality.

The medical care of such patients may demand the structured involvement of physicians skilled in the organ-specific care of NRTx, as well as immunosuppression, care of chronic kidney disease and ESRD planning through all phases of transplantation.
Figure 2. Preemptive Placement on the Kidney Transplant Waiting List by Presence and Type of Prior Organ Transplant

- p-value < 0.001 comparing NRTX with other candidate groups

Figure 3. Patient Survival after Placement on the Waiting List by Presence and Type of Prior Transplant

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The Glickman Urological & Kidney Institute, one of 26 institutes at Cleveland Clinic, is a world leader in treating complex urologic and kidney conditions in adults and children. Our physicians have pioneered medical advances including dialysis, partial nephrectomy, laparoscopic and robotic urologic surgery, and the bioartificial kidney, while serving tens of thousands of patients annually. Cleveland Clinic is a nonprofit, multispecialty academic medical center, consistently ranked among the top hospitals in America by U.S. News & World Report. Founded in 1921, it is dedicated to providing quality specialized care and includes an outpatient clinic, a hospital with more than 1,300 staffed beds, an education institute and a research institute.

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