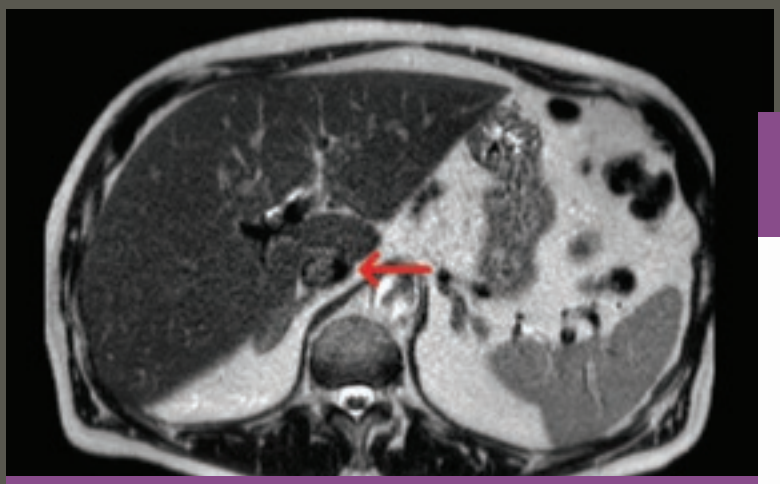
Cleveland Clinic

Glickman Urological & Kidney Institute

A Physician Journal of Developments in Urology and Nephrology

Vol. 25 | Winter 2016

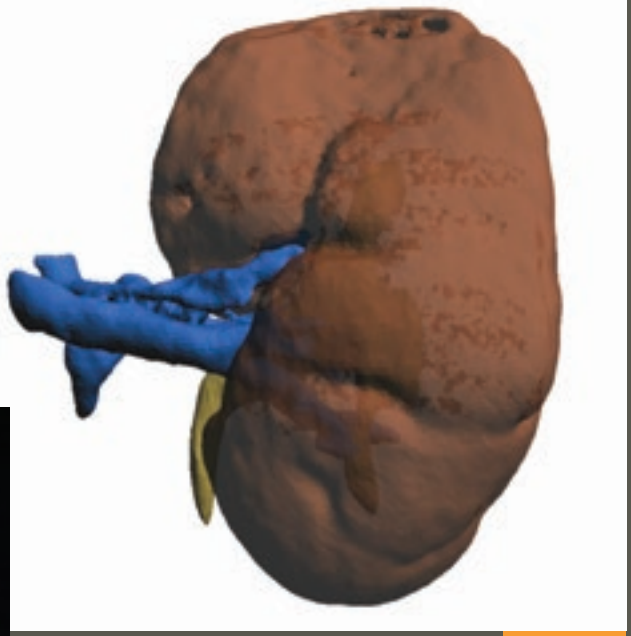
# Urology & Kidney Disease News



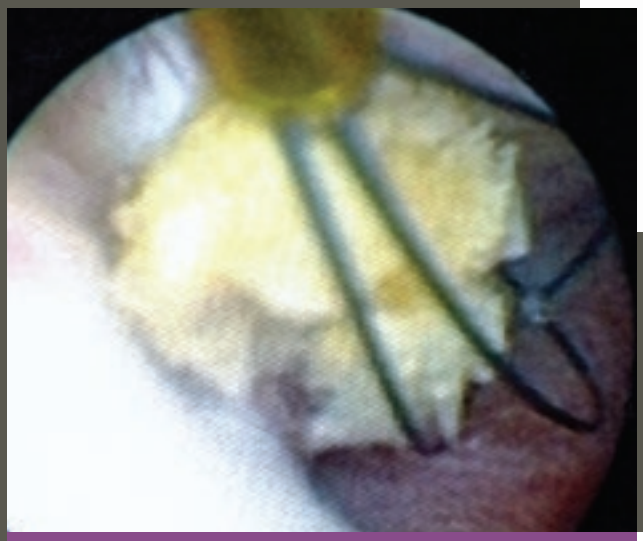
Robotic Surgery a Viable Option to Manage Renal Tumor-Associated Thrombi

p.16

Exploring 3-D Printing's Potential in Renal Surgery



p.14

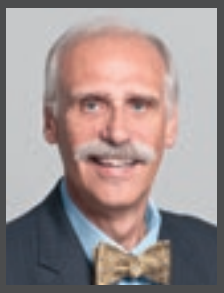


Kidney Stone Removal to Thwart Recurrent Urinary Tract Infections: A 50-50 Proposition

p.45

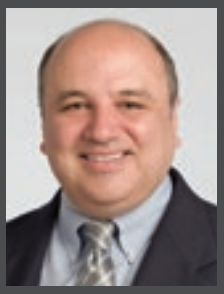
## Department Chairs

**Edmund Sabanegh Jr., MD**
Associate Chief of Staff,
Cleveland Clinic
Chairman, Department
of Urology
Director, Center for Male Fertility
Glickman Urological
& Kidney Institute



**Robert J. Heyka, MD**
Chairman, Department
of Nephrology and
Hypertension
Glickman Urological
& Kidney Institute

## Medical Editor



**Daniel Shoskes, MD, MSc, FRCS(C)**
Glickman Urological
& Kidney Institute

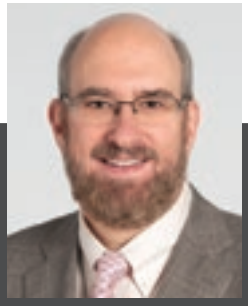
# Urology & Kidney Disease News

*More News Articles Available Online*

**Consult QD** — Urology and Nephrology

A blog featuring insights and perspectives from Cleveland Clinic experts. Visit today and join the conversation.

**ConsultQD.clevelandclinic.org/urology-nephrology**



# Chairman's Report

**Eric A. Klein, MD**

*Chairman, Cleveland Clinic Glickman Urological & Kidney Institute*

Dear Colleagues,

Welcome to the Winter 2016 edition of the Glickman Urological & Kidney Institute's *Urology & Kidney Disease News*.

We've had another remarkable year, highlighted by the experience of caring for a pregnant 35-year-old woman who recently sought treatment from us. While she should have been experiencing the joys of impending motherhood, a routine prenatal ultrasound had revealed a large mass in her right kidney suggestive of renal cell carcinoma. She suddenly faced the agonizing dilemma of how to aggressively treat the cancer while minimizing harm to her unborn baby.

After seeking opinions at a few other centers, she came to Cleveland Clinic and we did what we do best: We kick-started a multidisciplinary collaboration including our urologic oncology and minimally invasive surgery teams in the Urological & Kidney Institute, our high-risk obstetric team in the Ob/Gyn & Women's Health Institute, our maternal anesthesia team from the Anesthesiology Institute, and a team of bioethicists. The result was the successful and uncomplicated performance of the world's first-known robot-assisted partial nephrectomy in a pregnant patient.

As **Georges-Pascal Haber, MD, PhD**, and **Daniel Ramirez, MD**, explain on P. 19, the procedure, though not without risk, offered a number of potential benefits for mother and child, including reduced respiratory depression, reduced wound complications and shortened recovery time. It also took advantage of our wealth of experience in minimally invasive urological surgery, and the multidisciplinary teamwork that is part of the Urological & Kidney Institute's and Cleveland Clinic's DNA.

I'm happy to report that the patient's tumor was successfully excised and she subsequently gave birth to a healthy child. While renal cell carcinoma in pregnancy fortunately is rare, the robotic partial nephrectomy demonstrates our ability to take on the most complex cases, to work cooperatively, and to harness leading-edge science, technology and research to help our patients.

Those principles have helped us earn No. 1 or No. 2 national rankings in urology and nephrology each of the last four years from *U.S. News & World Report*. I believe you'll see our commitment to excellence in the accounts in these pages, and in our institute's diverse activities in 2015:

- **Audrey Rhee, MD**, and **Jihad H. Kaouk, MD**, write about two other Cleveland Clinic minimally invasive urological surgery "firsts" — robot-assisted partial nephrectomy in a pediatric patient (P. 51), and a robot-assisted perineal approach for radical prostatectomy (P. 12). Dr. Kaouk, with **Peter Caputo, MD**, also recounts (P. 14) the growing role for 3-D printing in renal surgery training and planning.

- **George Thomas, MD, MPH, FACP**, describes (P. 33) our researchers' and patients' participation in the landmark Systolic Blood Pressure Intervention Trial (SPRINT), which showed the benefits of aggressive blood pressure management in older hypertensive adults to curb cardiovascular disease rates and mortality risk.

- In an effort to help the many women suffering from stress urinary incontinence, Cleveland Clinic is part of a phase 3 trial to test autologous muscle-derived stem cells to repair the urinary sphincter. On P. 47, **Courtenay Moore, MD**, details the study.

- **Stuart Flechner, MD**, and **David Goldfarb, MD** (P. 48-49), document the latest achievements of our kidney transplant program, which in 2015 took part in a record-setting multiple paired-donor transplant chain, and had the nation's best adult three-year living-donor graft survival for transplants performed between 2009 and 2011.

- **Nima Sharifi, MD**, **Hannelore Heemers, PhD**, **Steven C. Campbell, MD**, PhD, and **Brian I. Rini, MD**, bring promising news from the urologic oncology front. Drs. Sharifi (P. 22) and Heemers (P. 26) are doing notable work on prostate cancer, exploring (respectively) a potent new anti-tumor compound that's more effective than its parent drug, and efforts to selectively target androgen receptor actions involved in cancer progression. Drs. Campbell and Rini and their colleagues are pooling their multidisciplinary skills to preserve kidney function in renal cell carcinoma by shrinking tumors enough to enable partial nephrectomy.

- Multidisciplinary cooperation is the cornerstone of our new **Prostate Cancer Center of Excellence**, which was established with a competitive grant from our Lerner Research Institute to form lasting connections among cancer research partners across Cleveland Clinic's

many institutes and departments. The center's core goals are to develop more clinically relevant prostate cancer models, gain insights on resistance mechanisms and identify predictive features of indolent disease or progression.

- For the second straight year, our **Urology Residency Program** has been ranked No. 1 nationally by the online physician network Doximity. Training the next generation of urologists and nephrologists has internal and external benefits. It's an opportunity for us to shape medicine's future. And the shared motivation to help our residents and fellows succeed is yet another tie that binds our faculty.
- An indicator of our institute's global reach is the consulting agreement we reached with Hospital Israelita Albert Einstein in Sao Paulo, Brazil, in 2015. The arrangement is intended to help the medical center improve its urologic services through observation and training.

We're excited by the opportunities that await in 2016 and appreciate the chance to update you on our progress. As always, if we can help with a patient, a clinical issue or a research project, please let us know.

**Eric A. Klein, MD**
Chairman, Glickman Urological & Kidney Institute
Professor of Surgery, Cleveland Clinic
Lerner College of Medicine
kleine@ccf.org; 216.444.5591
On Twitter: @EricKleinMD

## New Prostate Cancer Scientist

**Hannelore V. Heemers, PhD,** joined Cleveland Clinic's Lerner Research Institute as an associate staff member in the Department of Cancer Biology. Dr. Heemers' research focuses on understanding specific molecular mechanisms that lead the androgen receptor to drive prostate cancer progression. Her group's long-term goals are to develop novel prostate cancer-selective forms of androgen deprivation therapy and to optimize and personalize the administration of available forms of androgen deprivation therapy.

## 2015 Glickman Urological & Kidney Institute Appointments

**Steven C. Campbell, MD, PhD**, a member of the Section of Urologic Oncology, has been appointed Associate Director of Cleveland Clinic's Graduate Medical Education program. The program is one of the largest in the country, with approximately 1,400 residents and fellows in 70 accredited training programs. Dr. Campbell is also Director of Cleveland Clinic's Urology Residency Program, ranked No. 1 in the United States for the second straight year. In addition, he is the 2016 President of the Society of Pelvic Surgeons.

**Manoj Monga, MD**, Director of Cleveland Clinic's Stevan B. Streem Center for Endourology and Stone Disease, has been named Secretary of the American Urological Association.

**Mark Stovsky, MD, MBA**, a member of the Department of Urology and Science and Technology Innovations Officer at Cleveland Clinic Innovations, has been named President of the American Association of Clinical Urologists.

**James Ulchaker, MD**, a staff member of the Department of Urology, is President-Elect of the American Urological Association's North Central Section.

**Hadley Wood, MD**, a staff member of the Center for Genitourinary Reconstruction, has been named President of Cleveland Clinic's Women's Professional Staff Association.

## Honors and Awards

**Phillip M. Hall, MD**, a Clinical Professor at Cleveland Clinic Lerner College of Medicine and a staff consultant for the Department of Nephrology and Hypertension, is the 2015 recipient of the Master Teacher Award, presented by Cleveland Clinic's Board of Governors.

**Charles Modlin, MD, MBA**, Cleveland Clinic's Executive Director of Minority Health and the founder and Director of the Minority Men's Health Center, has been named the 2015 Black Professional of the Year by the Black Professionals Association Charitable Foundation.

**Eric A. Klein, MD**, Chairman of Glickman Urological & Kidney Institute, received the 2015 Philip S. Hench Distinguished Alumnus Award from the University of Pittsburgh School of Medicine.

## Urology Residency Program Ranked **No. 1 for Second Year**

Cleveland Clinic's Urology Residency Program has been named No. 1 in the nation for 2015–2016 by the online physician network Doximity in collaboration with *U.S. News & World Report*. This is the second year that Doximity has ranked urology residency programs, and the second year that Cleveland Clinic has been listed No. 1 overall.

Our urology program also ranked No. 1 in:

- Reputation for quality of clinical training (based on a nationwide survey of board-certified urologists)
- Research contributions from graduates in the last 10 years (based on collective h-index and research grants)

## Upcoming CME Events — Save the Dates

### April 8, 2016 — Ambulatory Urology Symposium

InterContinental Hotel and Conference Center, Cleveland
Course Co-Directors: Edmund Sabanegh Jr., MD, and Ryan Berglund, MD

### Oct. 20-22, 2016 — Nephrology Update

The Ritz-Carlton, Cleveland
Course Director: Brian Stephany, MD

### Oct. 21-22, 2016 — 8th Annual Symposium on Robotic Urologic Surgery

InterContinental Hotel and Conference Center, Cleveland
Course Director: Jihad H. Kaouk, MD

*Please visit **ccfcme.org** for more details about these events.*

# Education and Outreach Efforts Improve Patient Experience

*by Diana Baker, BSN, RN*

Diana Baker, BSN, RN

Cleveland Clinic's Glickman Urological & Kidney Institute has taken several steps to advance our core mission of improving patient experience, with the launch of live online chats, patient education classes and shared medical appointments.

These programs have proved to be extremely popular with patients. We have found that many people with questions and concerns take advantage of the live chat feature, which we began in 2014. We answer questions on topics ranging from kidney stones to prostate and kidney cancer. We provide guidance and, if needed, referrals to Cleveland Clinic services.

We view live chats as the wave of the future — a way to help people seeking easy access to reliable healthcare information, and a tool to attract new patients to Cleveland Clinic. After a live chat, participants are asked to complete a survey. Their feedback has shown us that patients find the experience convenient and are satisfied that their questions were answered.

## Education Classes Address Prostatectomy Concerns

In 2015 we launched education classes for patients facing prostatectomy due to cancer. We chose prostatectomy as the subject of our first education class because the procedure is very common and raises many questions about erectile dysfunction and incontinence, two potential side effects.

During the one-hour classes, we review the prostatectomy process, including discussion of presurgery, the hospital stay, postoperative recovery and possible side effects. Our goal is to make patients as comfortable as possible. Spouses, significant others and family members are invited to attend. The classes serve not just as information sessions but also as a support group for patients, who are able to share their concerns and help each other.

We hold the classes twice a month at our main campus and monthly at our Hillcrest Hospital, with plans to expand to other locations. We also plan to post videos of the classes on our website for those who can't attend in person, and we are exploring live-streaming classes so that viewers can ask questions in real time. We intend to expand the education classes to address other types of urological surgery.

We hope to eventually publish the results of patient satisfaction surveys related to their experience with the education classes.

## Shared Medical Appointments Provide Support

Finally, Glickman Urological & Kidney Institute offers shared medical appointments (SMAs) in the area of minority men's healthcare. SMAs are an innovative approach that brings together a small group of patients with common needs to meet with physicians and other healthcare professionals. The sessions last about 90 minutes and are especially valuable for patients with chronic diseases.

The minority men's SMAs, led by Charles Modlin, MD, MBA, Cleveland Clinic's Executive Director of Minority Health and the founder and Director of the Minority Men's Health Center, consist of groups of five to 10 patients. They focus on health issues such as diagnosis and treatment options for erectile dysfunction, screening and treatment of prostate cancer, benign conditions of the prostate, hypertension, diabetes, heart disease, kidney disease, organ donation, and healthcare disparities affecting African-Americans.

Cleveland Clinic piloted SMAs more than 10 years ago and now offers them at several of our hospitals and family health centers.

Our patients enjoy the opportunity to relate to other people who are dealing with similar health issues. They share stories and ideas, learn from one another. and truly create a bond.

*Ms. Baker (bakerd4@ccf.org; 216.445.2013) is a Care Coordinator for Glickman Urological & Kidney Institute's Department of Urology.*

# Expansion of Urology Advanced Practice Providers' Responsibilities Benefits Patients and Clinical Staff

*by Dana Longo, MPH, NP, and Hadley Wood, MD*

Dana Longo, MPH, NP

Hadley Wood, MD

In 2015, the Glickman Urological & Kidney Institute's Department of Urology transformed its patient clinics to benefit patients and staff.

Previously, the majority of our advanced practice providers (APPs) — nurse practitioners and physician assistants — were practicing within a physician practice. Their roles included seeing patients before and after surgery as well as assisting with clinics, scheduling, routine patient care and phone calls. In 2014, we began to shift our model to one in which APPs are at the front lines, providing high-quality urological care in our main campus and community facilities independent from physician practices.

The shift in practice not only demonstrates Cleveland Clinic's commitment to utilize APPs to their full capability, but also follows a 2010 Institute of Medicine recommendation that nurses should "practice to the full extent of their education and training." The change has created more appointment slots for patients, increased access to physicians' clinics for more complex or surgical cases and, most importantly, increased APPs' job satisfaction.

## Preparing for New Roles

The transition wasn't simple or quick. The Department of Urology began considering the shift after surveying our APPs in 2013. It was apparent that the members of the urology advanced practice team had a strong desire to see and manage their own patients.

While the advanced practice group represented decades of urology care experience, many APPs had "islands" of excellence from practicing in highly specialized clinics but had a relative lack of experience in more fundamental areas.

To address this, the team created an educational program that included reading, assessment and didactic lectures that covered all aspects of general urology. Each module was delivered at two-week intervals to provide enough time for the group to engage in self-directed learning.

In addition, the team worked closely to identify geographical areas where access needed to be expanded and paired APPs with physician mentors to continue on-the-ground training. These relationships not only fostered ongoing education but promoted acceptance of the new team members in their expanded roles and encouraged further collaboration among physicians and APPs.

We also incorporated a quality review program into our efforts. This program involved external review of randomly selected patient charts for accuracy of clinical decision-making, documentation and billing. The reviews were then shared with the appropriate APP to provide an opportunity for review and reflection.

## Cultural Change

This shift represented a substantial cultural change in our department for physicians, nurses, administrative personnel and the advanced practice team. It has not been without challenges. Ultimately, however, through teamwork and good communication, our care model now integrates physicians and advanced practice providers in a fairly seamless fashion. The American Urological Association has decided to adopt Cleveland Clinic's APP education program as the official online education program for the association's nurse practitioner and physician assistant members.

*Ms. Longo (longod@ccf.org; 216.445.4781) is a nurse practitioner in the Glickman Urological & Kidney Institute's Department of Urology.*

*Dr. Wood (woodh@ccf.org; 216.444.2146) is a staff member of the Urological & Kidney Institute's Center for Genitourinary Reconstruction and an Assistant Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

# Summer Internship Program Invites Students to Engage in Bench Research and Scientific Writing

*by Ashok Agarwal, PhD, HCLD*

Ashok Agarwal, PhD, HCLD

With the number of physicians pursuing research careers declining, medical schools are emphasizing the development of physician-scientists. Preparatory programs have emerged, although very few provide an actual hands-on research experience for students.

In response, Glickman Urological & Kidney Institute's American Center for Reproductive Medicine (ACRM) has developed — and continues to refine — a unique summer internship program that introduces premedical and medical students to the dynamic field of medical research. During this seven-week program, interns:

- Attend lectures by renowned speakers. ACRM faculty and invited scientists/clinicians from around the world speak on topics ranging from male and female infertility to writing a scientific abstract. While the internship focuses on reproductive medicine, interns learn research concepts applicable in any lab.
- Receive training from accomplished mentors. Seasoned Cleveland Clinic scientists and clinicians serve as preceptors. They guide interns through research and writing projects, teaching them the necessary techniques and protocols.
- Conduct original bench research. Projects are carefully planned, tested and approved by Cleveland Clinic's Institutional Review Board. Teams of five or six interns are assigned to each project, where they apply knowledge gained from lectures, mentoring and prior coursework to solve clinical problems.
- Draft a scientific manuscript. Each intern is assigned a topic according to his or her interest. Mentors provide guidance but interns work independently, surveying literature, analyzing findings and clearly communicating their conclusions in writing.
- Present research results. At the end of the program, each bench research team presents its findings. In addition, each intern presents a summary of his or her scientific manuscript. Presentations are judged by faculty and guest physicians/scientists.
- Develop essential "soft" skills. As future professionals, interns learn important attributes such as professionalism, leadership and volunteerism through the program's activities.

Past participants say that the opportunity to conduct bench research and write scientific manuscripts sets our program apart from others. These elements are largely why our program remains highly competitive, accepting only about 15 percent of applicants.

From its inception in 2008 through 2013, our internship program trained 114 students from 23 states and 10 countries. More than 70 percent were undergraduates. Almost none had prior research experience. However, through our program, these students successfully:

- Performed 12 bench research projects on current and emerging topics in reproductive medicine
- Published 98 research articles in peer-reviewed reproductive, fertility, andrology and urology journals

Past interns credit our program with helping them gain acceptance into top medical schools, coveted residency programs and professional positions. Since 2010, Case Western Reserve University School of Medicine has honored our program three times with its Scholarship in Teaching Award, commending impact on medical education and student careers.

By offering this foray into medical research, ACRM is not only helping future physicians recognize and appreciate the value of research and its impact on patient care, but is also inspiring them to pursue research-oriented careers.

*Dr. Agarwal (agarwaa@ccf.org; 216.444.8182) is Director of the Glickman Urological & Kidney Institute's Andrology Center and of the American Center for Reproductive Medicine. He is also a Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

# Urologic Oncology Care Paths Focus on Best Practices, Value-Based Care

*by Andrew Stephenson, MD*

Andrew Stephenson, MD

During the last few years, Cleveland Clinic has broken new ground by developing condition-specific care paths within our various clinical institutes. This effort focuses on operationalizing best practices to guide clinical workflow, with an emphasis on quality and value-based care (see sidebar for additional detail).

Cleveland Clinic's Glickman Urological & Kidney Institute has nearly 20 care paths completed or in development.

Two years ago, the Center for Urologic Oncology implemented two of the Urological & Kidney Institute's first care paths — for bladder cancer and prostate cancer. These care paths have served as excellent models for the care paths that have followed, especially because one (bladder cancer) addresses a condition that is complex to treat, while the other (prostate cancer) is more straightforward. (On the horizon: a care path for localized kidney cancer.)

We took a comprehensive, inclusive approach to creating the care paths. They were developed and vetted in committees of relevant stakeholders, including — but not limited to — urologists, pathologists, radiologists, medical oncologists, radiation oncologists, nutritionists, pharmacists and nurses.

It's important to note that care paths serve as best practices guidance, but they aren't concrete or inflexible — we still encourage clinicians to use their professional judgment and experience to guide treatment plans and recommendations.

## Prostate Cancer Care Path

This was the first care path we implemented. The prostate cancer care path is short and straightforward, since the treatment for prostate cancer is now largely universally standardized. Therefore, this care path focuses on ensuring that clinicians use evidence-based medicine in the context of value-based care. Essentially, it provides guidance on eliminating unnecessary expensive tests in favor of less expensive ones.

## Bladder Cancer Care Path

The management of patients with invasive bladder cancer requires multidisciplinary care, making it complex and possibly leading to variability in treatment. In developing this care path, we identified the best guidance for multidisciplinary care of individual patients, incorporating not only evidence-based medicine and clinical guidelines, but also our institutional expertise.

The bladder cancer care path is a set of standardized steps to assess preoperative risk and to optimize patients prior to surgery, perioperatively and postoperatively, decreasing lengths of stay and reducing complications. For example, it includes discharge planning for cystectomy patients as a way to minimize readmissions and complications.

## How Care Paths Are Working So Far

The Urological & Kidney Institute's overarching goal with care paths is to make it easier for clinicians to consistently deliver cost-effective, evidence-based care. Based on initial observations, we are making progress toward that goal.

Because we have codified best practices, our clinical teams are very clear about what the care paths entail, and we have seen good adherence. The Urological & Kidney Institute reduced its cystectomy costs by 15 percent from 2013 to 2014. Although we did not begin implementing our care paths until 2014, we believe they were a factor in those cost reductions.

Stay tuned. We're hoping that our first two urologic cancer care paths soon will be integrated into our electronic medical record system, along with operational tools that will better allow us to measure the impact of these efforts. We'll be monitoring clinician adherence, patient-reported outcomes and costs in 2016 and beyond.

*Dr. Stephenson (stephea2@ccf.org; 216.445.1062) is Director of the Glickman Urological & Kidney Institute's Center for Urologic Oncology and is a staff member of the Cleveland Clinic Cancer Center. He is also an Associate Professor of Medicine at Cleveland Clinic Lerner College of Medicine.*

## What Is a Care Path?

Cleveland Clinic care paths start with evidence- and consensus-based "guides," which are succinct manuals detailing the appropriate steps in patient management for the condition at hand, with supporting rationales. The guides, developed by multidisciplinary teams of Cleveland Clinic experts, are translated into algorithms and workflows for practical application.

### The care path initiative is focused on three major areas:

- Standardizing clinical management around the care path guide, with a focus on delivering consistent, value-based, patient-centered care.
- Integrating workflows and algorithms into the electronic medical record where appropriate and when possible.
- Tracking patient-reported outcomes to help drive care.

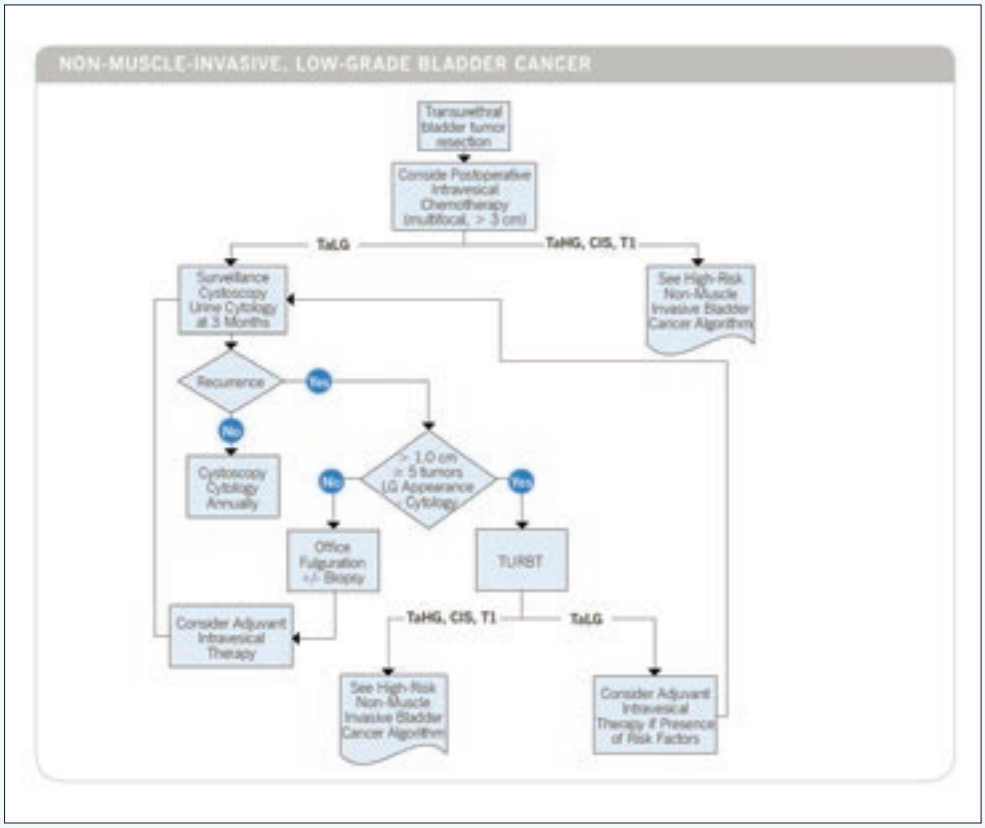
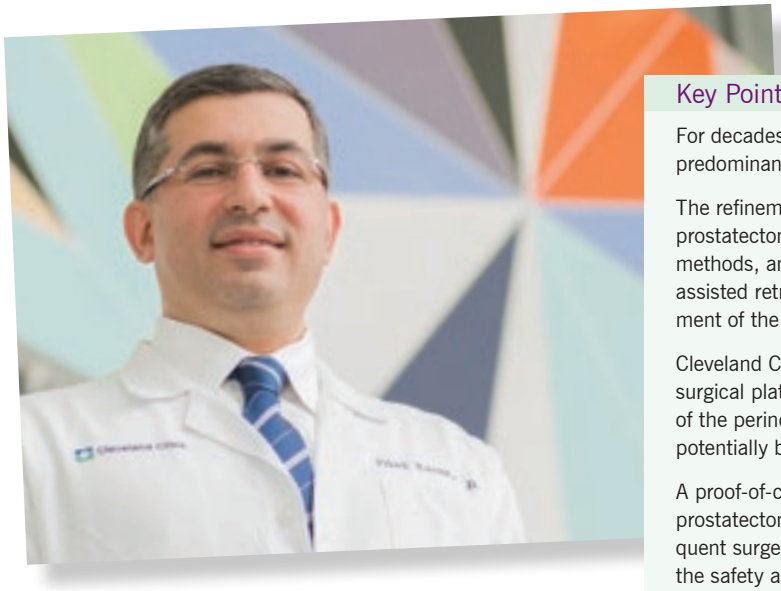



**Figure 1. Care path for non-muscle-invasive low-grade bladder cancer.**

# Robot-Assisted Radical Perineal Prostatectomy: From Laboratory to Clinic

*by Jihad H. Kaouk, MD*



## Key Points

For decades, open radical perineal prostatectomy was the predominant surgical approach for localized prostate cancer.

The refinement of the retropubic approach to radical prostatectomy, the application of cavernous nerve-sparing methods, and the development of laparoscopic and robot-assisted retropubic procedures caused the virtual abandonment of the perineal approach.

Cleveland Clinic researchers hypothesized that the robotic surgical platform could help overcome anatomic challenges of the perineal approach to radical prostatectomy and potentially benefit patients.

A proof-of-concept study of robot-assisted radical perineal prostatectomy using a cadaver model, and several subsequent surgeries involving human patients, have established the safety and reproducibility of the procedure.

The use of a purpose-built robotic system for single-site surgery should further enhance the robot-assisted radical perineal prostatectomy technique.

From its introduction in 1905 until the mid-1970s, open radical perineal prostatectomy (RPP) was the predominant surgical approach for localized prostate cancer. Though RPP provides the most direct access to the prostate, it is a technically and ergonomically challenging procedure due to the deep, narrow confines of the perineal anatomy.

With the refinement of the retropubic approach to radical prostatectomy (RRP) and the application of cavernous nerve-sparing methods in the 1980s, and the later development of laparoscopic and robot-assisted retropubic procedures, the perineal approach has been largely abandoned.

This preference for the retropubic technique seems to be based more on surgeon habits, familiarity and training experience than on evidence-based medicine. While open RRP is less anatomically complex, there are no randomized studies to date that show its definitive superiority over RPP in terms of cancer control and continence rates. Reported advantages of the perineal approach include shorter operative time and hospital stay, lower cost for patients who do not require bilateral pelvic lymph node dissection, and lower blood loss and transfusion rates.

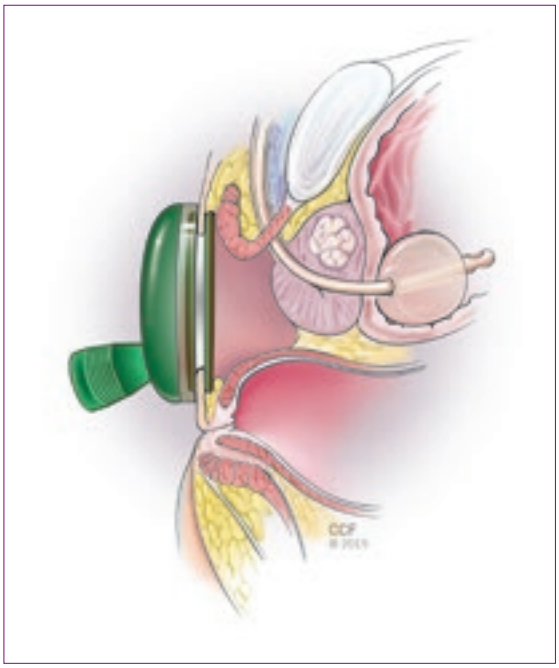
## Developing and Testing the Robotic Approach

The robotic platform has enhanced the ability to perform dissection and reconstruction in confined anatomical spaces. The Center for Robotic and Laparoscopic Surgery in Cleveland Clinic's Glickman Urological & Kidney Institute has considerable expertise in complex robotic procedures and has pioneered the use of single-site robotic urologic surgery. We hypothesized that the robot platform could help overcome the anatomic challenges of the perineal approach to radical prostatectomy and potentially benefit patients. We decided to test our hypothesis with a proof-of-concept study of robot-assisted radical perineal prostatectomy (RRPP) using a cadaver model.

Our previous experience and understanding of the limitations of single-site surgery was instrumental in the development of our RRPP technique, but we still encountered challenges that required many hours of experimentation, troubleshooting and adjustment. Those challenges included patient positioning, robot docking, port selection and placement, incision size, initial dissection steps, and the identification of anatomical landmarks through the robot's viewing scope. We worked through these issues by performing RRPP in five male cadavers. We recently described our initial experience in the *Journal of Endourology*.[1]

We utilized the da Vinci Si™ system in a three-arm configuration. A 12-mm trocar (robotic scope), a 10-mm trocar (assistant) and two 8-mm trocars were inserted through a GelSeal® Cap in a diamond-shape configuration, with the 12-mm trocar at the bottom and the 10-mm trocar at the top. The cadaver was placed in the lithotomy/steep Trendelenburg position.

After initial investigation in the first cadaveric model, we concluded that single-port placement and the $CO_2$ insufflation step should follow central tendon division and external sphincter muscle retraction using the Belt approach. This step minimized the chance of rectal injury, and insufflation assisted in keeping the rectum away from the operative field (Figure 1).



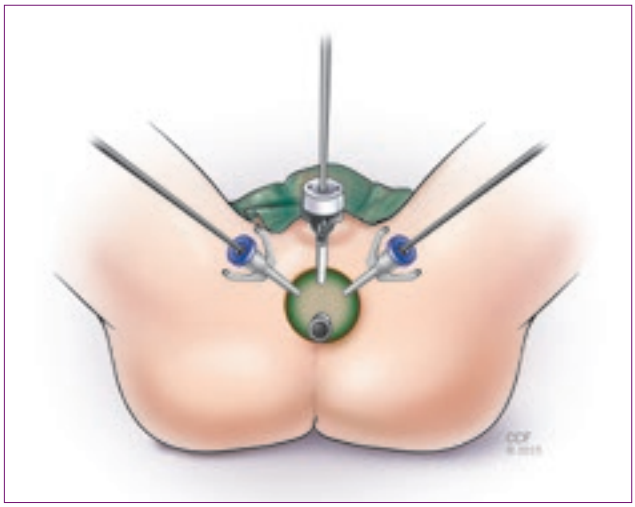


**Figure 1 (left). Schematic drawing illustrating sagittal view of the placement of single-port device after initial dissection.**

**Figure 2 (above). Schematic drawing illustrating instruments' location in the single port.**

## Overcoming Sword Fighting and Other Issues

The limitations of single-site surgery using the existing robotic platform needed to be further addressed. Some technical disadvantages included "sword fighting" among instruments within the operative field and clashes between bulky robotic arms deployed into the single-site port externally.

To overcome these issues, we placed the camera port in a more anterior position with a 30-degree up optic, while the robotic trocars were placed posterolaterally and the assistant port was placed at the six o'clock position. The robot was brought over the cadaver's head and docked. This arrangement allowed for optimal spacing of the ports (Figure 2), minimizing internal and external clashes while allowing space for the assistant to introduce instruments for suction and vascular control.

After docking and division of the rectourethralis muscle, the posterior aspect of the Denonvilliers fascia was incised and the prostate's posterior plane, vas deferens and seminal vesicles were dissected. The prostatic pedicles were controlled, followed by prostatic apical dissection and the transection of the urethra. The anterior and lateral planes of the prostate were dissected, followed by bladder neck junction identification and complete excision of the prostate. After creation of vesicourethral anastomosis, the robot was undocked and the single-port device was removed.

In the first three cadavers reported, we successfully completed nerve-sparing RRPP with no injuries to surrounding structures. Median total operative time was 89 minutes. We were satisfied that we had resolved all procedural and technical issues and that the procedure was feasible.

Potential clinical advantages included the elimination of the three initial steps typically performed in the robot-assisted laparoscopic retropubic approach (bladder mobilization, endopelvic fascia opening and dorsal vein complex control), which theoretically could result in reduced operative time and blood loss. As a completely extraperitoneal approach, RRPP virtually eliminates risks of injury to the small bowel or major vessels during trocar placement, which, although rare, can be catastrophic. It also avoids having to deal with extensive adhesions in patients with previous abdominal surgeries. Although RRPP uses $CO_2$ insufflation to improve visualization, it eliminates the need for pneumoperitoneum and its possible complications, particularly in obese patients.

While the cadaver model provided an optimal evaluation of multiple aspects of RRPP, the absence of bleeding limited our ability to fully assess the procedure. We obtained Institutional Review Board approval to evaluate RRPP in human patients. For these early procedures, we selected patients diagnosed with localized prostate cancer and a risk for lymph node positivity of no more than 4 percent. Because of uncertainty regarding the efficacy of nerve sparing in the cadaver model, we decided out of caution to restrict our initial patients to those who were nonpotent.

## Looking Ahead

To date we have performed six RRPPs in this group — to our knowledge, the first documented use of a robot-assisted perineal approach for radical prostatectomy. All procedures were successfully completed, with no major complications. All patients were discharged within 12 hours of surgery and required minimal pain control measures. Of note, two of these patients previously had undergone extensive intra-abdominal surgeries, which posed significant challenges for a retropubic approach and made RRPP an ideal alternative.

We believe we have established the safety and reproducibility of RRPP in human patients. The use of a purpose-built robotic

system for single-site surgery should further enhance the RRPP technique.

Our future efforts will involve continuing to assess the efficacy and clinical feasibility of RRPP, including evaluating the preservation of nerve function and the ability to perform bilateral pelvic lymph node dissection robotically through the single incision. Postoperative studies also will be needed to compare RRPP results to those of standard techniques.

*Dr. Kaouk (kaoukj@ccf.org; 216.444.2976) is Director of the Glickman Urological & Kidney Institute's Center for Robotic and Laparoscopic Surgery and is the Urological & Kidney Institute's Vice Chair for Surgical Innovations. He holds the Zegarac-Pollock Family Foundation Endowed Chair and is a Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

### *Reference*

1. *Laydner H, Akça O, Autorino R, Eyraud R, Zargar H, Brandao LF, Khalifeh A, Panumatrassamee K, Long JA, Isac W, Stein RJ, Kaouk JH. Perineal robot-assisted laparoscopic radical prostatectomy: feasibility study in the cadaver model.* J Endourol. *2014 Dec;28(12):1479-1486.*

## 3-D Printing: A Training, Educational and Procedural Aid in Renal Surgery *by Jihad H. Kaouk, MD, and Peter Caputo, MD*

Jihad H. Kaouk, MD

Peter Caputo, MD

Three-dimensional (3-D) printing is a new technology that is rapidly being incorporated into the practice of medicine.

The technology involves robotically depositing successive layers of material — plastic, metal or even biological tissue — under computer control to form objects of virtually unlimited shape or geometry. 3-D printing is proving useful in the arena of regenerative medicine, with the manufacture of customized surgical implants, prosthetics and medical devices. In the near future, 3-D bio-printing with living tissue may allow the production of replacement organs and body parts.

At Cleveland Clinic's Glickman Urological & Kidney Institute, we strive to find innovative methods to improve patient care and to introduce new information to physicians-in-training and patients. Currently we are investigating 3-D printing for training and educational purposes.

### Key Points

The combination of medical imaging and three-dimensional printing produces highly accurate models of patients' unique renal anatomy.

Cleveland Clinic is evaluating the technology's use in surgical training and simulation, in patient and physician education, and potentially for automated surgery.

### Imaging-Based Modeling Re-creates Anatomy

Cross-sectional imaging allows for accurate 3-D rendering of individual patient anatomy. From this rendering we are able to print a 3-D structure that precisely replicates the unique renal anatomy.

We have found that by using imaging-based 3-D kidney models as an educational and visualization aid, medical students and resident physicians are better able to characterize a particular patient's renal tumor.

This visualization benefit extends to patients too. Patients with newly discovered renal masses can hold and examine a 3-D rendering of their kidney and tumor, helping us educate them about their condition and further engage them in their care. Studies have shown that by improving patients' health literacy, we improve their ability to participate in important healthcare decisions, which can lead to better outcomes.

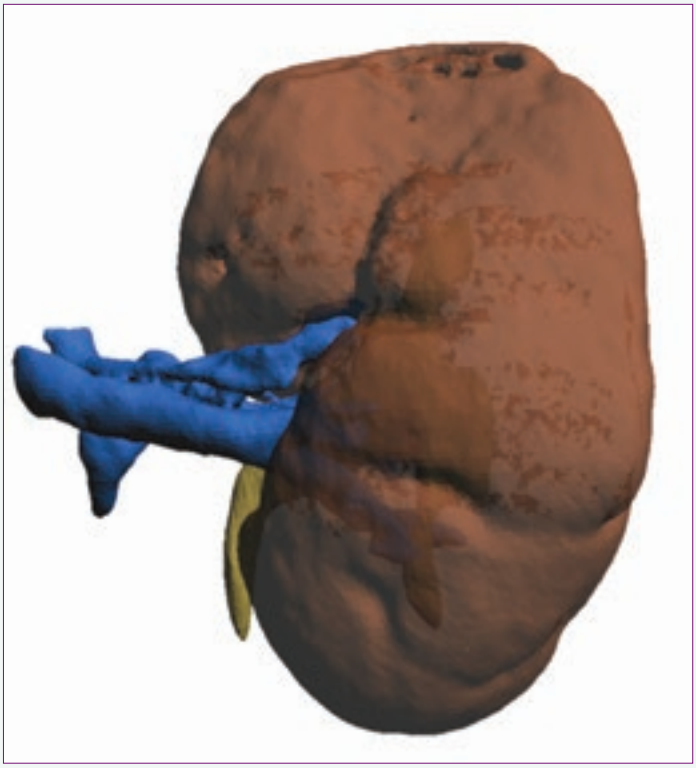


**Figure 1. A high-resolution reconstructed image based on 3-mm crosscuts from a patient's kidney CT scan. The reconstructed image allows for detailed identification of kidney vasculature, collecting system and parenchyma, including tumor characteristics. A high-resolution image is crucial for 3-D printing.**

## Reducing the Surgical Learning Curve

Application of these 3-D kidney models to patient-specific surgical scenarios may also benefit our surgical trainees, with the goal of shortening the learning curve for difficult surgical procedures. Patient-specific 3-D kidney models utilized for preoperative planning and even surgical simulation may enable a trainee to obtain fewer positive margins, shorten ischemic times and preserve more viable kidney parenchyma.

The use of 3-D renal models for surgical simulation may help train the next generation of surgeons. The combination of a 3-D model and a robotic surgical system could provide a surgical simulation that very closely mimics real-life surgical scenarios, allowing surgical residents and novice surgeons the opportunity for hands-on robotic system experience before ever entering the operating room.

## Paving the Way for Automated Surgery

Additionally, 3-D models are being used in the development of automated surgical approaches. In this scenario, a skilled surgeon using a patient-specific 3-D renal model controls the robotic system to remove a tumor from the surrounding normal kidney.

The surgeon repeats this procedure several times on identical 3-D models while the robotic system analyzes and records each of the surgeon's movements. The surgeon and robotic system are then able to select the most successful surgical movements specific to the patient's anatomy and store them for future use.

Applying that stored information after the robotic surgical system has been spatially oriented in a live surgery should allow the completion of a complex surgical procedure in a fraction of the time required for a conventional surgery. Although the implementation of automated surgical technology is perhaps decades away, the aim is to provide high-quality, patient-specific automated surgery that will translate to better outcomes.

*Dr. Kaouk (kaoukj@ccf.org; 216.444.2976) is Director of Cleveland Clinic Glickman Urological & Kidney Institute's Center for Robotic and Laparoscopic Surgery and is the Urological & Kidney Institute's Vice Chair for Surgical Innovations. He holds the Zegarac-Pollock Family Foundation Endowed Chair and is a Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

*Dr. Caputo (caputop@ccf.org) is a fellow in the Urological & Kidney Institute's Department of Urology.*

# Robotic Level III IVC Tumor Thrombectomy: Surgical Technique

*by Daniel Ramirez, MD; Benjamin Cohen, MD; Venkatesh Krishnamurthi, MD; and Georges-Pascal Haber, MD, PhD*

Daniel Ramirez, MD

Benjamin Cohen, MD

Venkatesh Krishnamurthi, MD

Georges-Pascal Haber, MD, PhD

## Key Points

Surgery for a renal neoplasm with associated inferior vena cava (IVC) thrombus is challenging and is typically managed using an open approach.

High-volume centers are gaining experience using robot-assisted surgical techniques to manage renal tumors with associated tumor thrombi, but there are few reports of a robotic approach to treat level III thrombi.

Cleveland Clinic's initial experience with robotic surgery to manage renal cell carcinoma and associated level III IVC thrombi shows the procedure is feasible in select patients and has some potential benefits, although open surgery will remain the standard of care.

Treating renal neoplasm with associated inferior vena cava (IVC) thrombus presents a challenging surgical endeavor. Manifestation of tumor thrombus within the renal vein or IVC occurs in 4 to 10 percent of patients with renal cell carcinoma (RCC), and traditionally these patients have been managed with open surgery due to the complex nature of the procedure.[1,2]

Several staging systems exist to describe the extent of the IVC thrombus.[3,4] Various series have described the management of patients with level I-II tumor thrombi via a laparoscopic approach.[5,6] With surgeons' growing experience using robotic techniques, renal tumors with associated tumor thrombi are increasingly managed with a robot-assisted approach at high-volume centers of excellence.[7-11] Nonetheless, there is a paucity of literature describing robotic techniques for treatment of level III tumor thrombi.

The primary steps for right-sided radical nephrectomy and level III IVC thrombectomy include early ligation of the right renal artery in the intra-aortocaval space, circumferential control of the IVC above and below the tumor thrombus, control of the left renal vein, and use of intraoperative transesophageal and intraperitoneal ultrasound to delineate the extent of the tumor prior to IVC cross-clamping (Figure 1).

## Case Study

The patient is a 75-year-old Caucasian man with a medical history significant for chronic kidney disease stage 3 and prior right hip replacement. He initially presented with abdominal pain and gross hematuria. Cross-sectional imaging for hematuria workup revealed a central 9.8-cm right-sided renal mass with an associated suprarenal IVC tumor thrombus. MRI performed two weeks prior to surgery for staging of the thrombus showed a tumor thrombus extending into the retrohepatic IVC above the level of the short hepatic veins (Figures 2 and 3) and associated with retroperitoneal lymphadenopathy.

The patient's metastatic workup was negative. Preoperative creatinine and hemoglobin levels were 1.53 mg/dL and 11.3 g/dL, respectively. Consultation with medical oncology was obtained prior to surgery for consideration of preoperative neoadjuvant immune-modulation treatment. The consensus was to proceed with robotic radical right nephrectomy, retroperitoneal lymph node dissection and IVC tumor thrombectomy, with close observation of the pulmonary lesions.

It is generally recommended to repeat cross-sectional imaging for reassessment of the tumor thrombus within two weeks prior to surgery to determine if there has been any interval growth. In patients with level III thrombi, the central focus of the operation is meticulous dissection and control of the IVC in order to perform successful cavotomy, tumor thrombus extraction and caval reconstruction while minimizing bleeding. In our case, four short hepatic vessels required division (Figure 4). Total operative time was 353 minutes and estimated blood loss was 150 cc. No intraoperative or postoperative transfusions were required. Extended operative time was expected as this was the first robotic approach for a level III thrombus performed at our institution.

## Uneventful Recovery

Postoperatively, the patient was taken to the post-anesthesia care unit for anesthesia recovery, and was subsequently

admitted to the regular nursing floor. The patient was ultimately found to have pT3bN1 disease, and final histological assessment revealed nuclear grade 3 collecting duct RCC.

The patient advanced to clear liquids several hours after surgery and was given a regular diet on postoperative day two. He was discharged on postoperative day three. The patient's hemoglobin reached a nadir of 9.3 g/dL immediately after surgery and was 9.5 g/dL on the day of discharge. Hemoglobin and creatinine levels at one-week follow-up were 10.6 g/dL and 1.52 mg/dL, respectively. The patient received prophylactic low-molecular-weight heparin for 28 days after surgery.

## Further Experience Needed

Robotic surgery for management of RCC and associated level III IVC thrombi is feasible in select patients. As with any novel technique, further experience with long-term follow-up is necessary. At high-volume institutions, this approach appears to be a viable option, with potential lower EBL and shorter convalescence compared with open surgery. Nevertheless, open surgery should currently remain the standard of care for patients with this complex condition, as the main goals for success remain safety and cancer control.

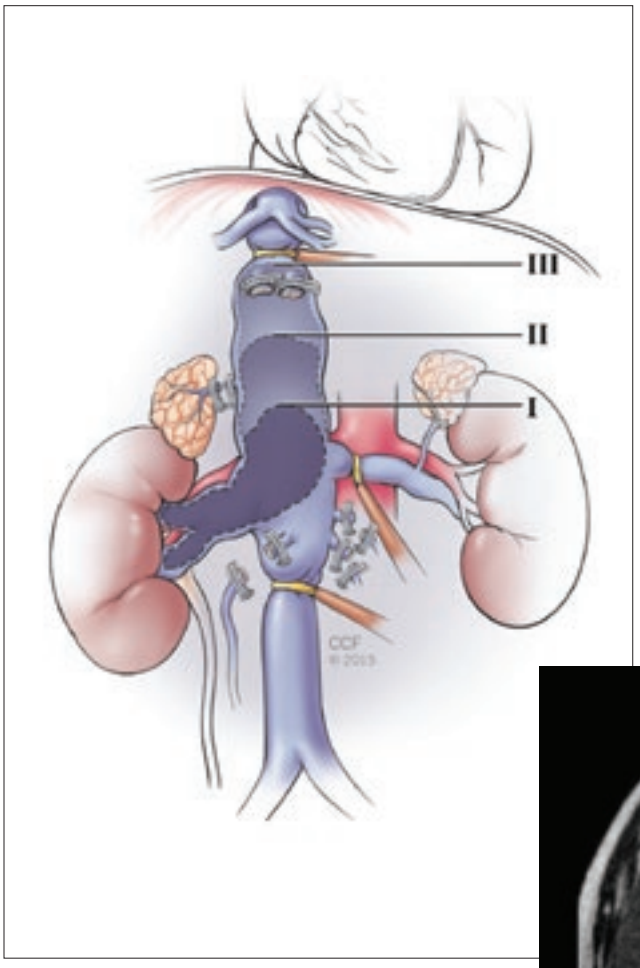
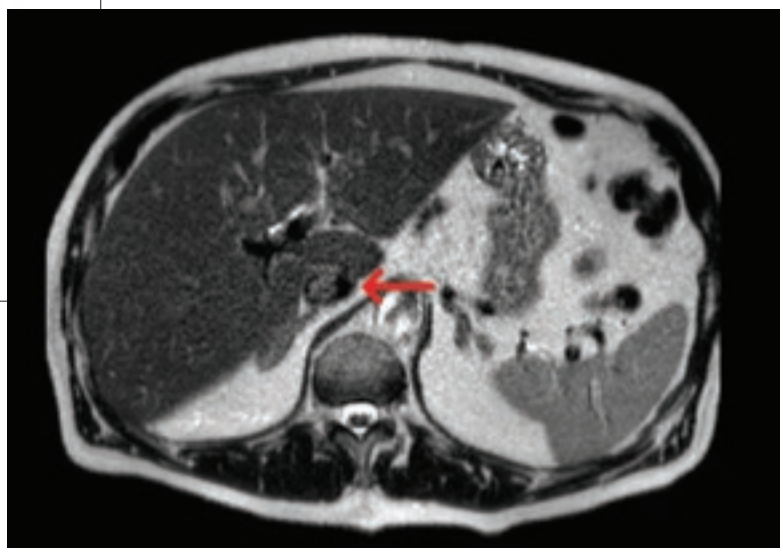



**Figure 1. Intracorporeal control of IVC with Rommel-style tourniquets.**

**Figure 2. Axial MRI demonstrating cranial extent of the tumor thrombus.**



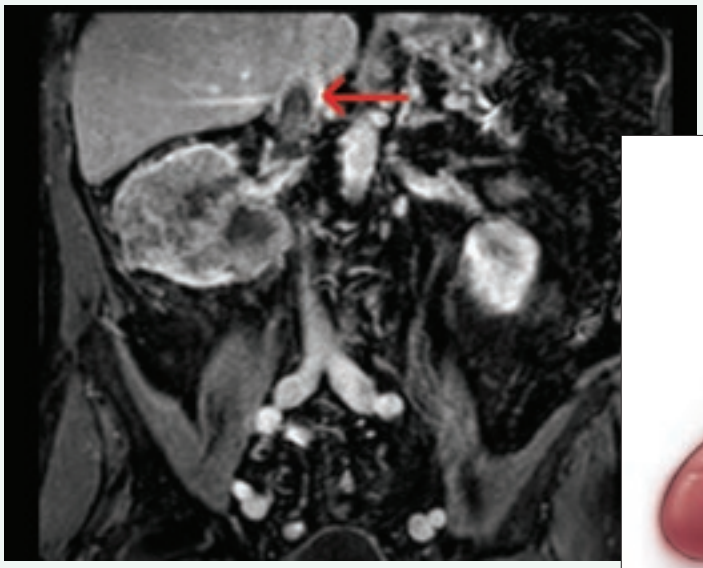


**Figure 3. Coronal MRI demonstrating cranial extension of the tumor thrombus.**

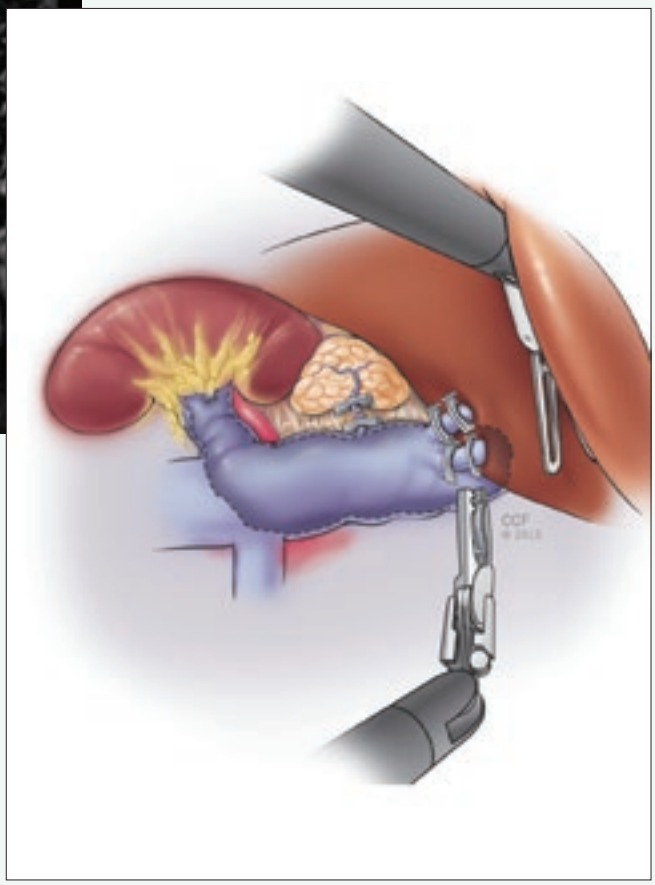


**Figure 4. Control and ligation of short hepatic vessels for intrahepatic IVC control.**

*Dr. Ramirez (ramired3@ccf.org) is a clinical fellow in the Glickman Urological & Kidney Institute's Department of Urology.*

*Dr. Cohen (cohenb4@ccf.org) is chief resident in the Department of Urology.*

*Dr. Krishnamurthi (krishnv@ccf.org; 216.444.0393) is a staff member of the Department of Urology and of the Transplant Center.*

*Dr. Haber (haberg2@ccf.org; 216.445.4781) is a staff member of the Department of Urology.*

## References

1. *Skinner DG, Pritchett TR, Lieskovsky G, et al. Vena caval involvement by renal cell carcinoma. Surgical resection provides meaningful long-term survival.* Ann Surg. *1989; 210:387-392.*
2. *Haferkamp A, Bastian PJ, Jakobi H, et al. Renal cell carcinoma with tumor thrombus extension into the vena cava: prospective long-term followup.* J Urol. *2007;177:1703-1708.*
3. *Mootha RK, Butler R, Laucirica R, et al. Renal cell carcinoma with infrarenal vena caval tumor thrombus.* Urology. *1999;54:561-565.*
4. *Neves RJ, Zincke H. Surgical treatment of renal cancer with vena cava extension.* Br J Urol. *1987;59:390.*
5. *Savage SJ, Gill IS. Laparoscopic radical nephrectomy for renal cell carcinoma in a patient with a level I renal vein tumor thrombus.* J Urol. *2000;163:1243-1244.*
6. *Desai MM, Gill IS, Ramani AP, Matin SF, Kaouk JH, Campero JM. Laparoscopic radical nephrectomy for cancer with level I renal vein involvement.* J Urol. *2003;169:487-491.*
7. *Abaza R. Initial series of robotic radical nephrectomy with vena caval thrombectomy.* Eur Urol. *2011; 59:652-656.*
8. *Gill IS, Metcalf C, Abreu A, et al. Robotic level III inferior vena cava tumor thrombectomy: the initial series.* J Urol. *2015 Oct;194(4):929-938.*
9. *Rogers CG, Linehan WM, Pinto PA. Robotic nephrectomy for kidney cancer in a horseshoe kidney with renal vein tumor thrombus: novel technique for thrombectomy.* J Endourol. *2008;22:1561-1563.*
10. *Lee JY, Mucksavage P. Robotic radical nephrectomy with vena caval tumor thrombectomy: experience of novice robotic surgeons.* Korean J Urol. *2012; 53:879-882.*
11. *Abaza R, Angell J. Robotic partial nephrectomy for renal cell carcinomas with venous tumor thrombus.* Urology. *2013; 81:1362-1367.*

# Robotic Partial Nephrectomy During Pregnancy: First Report and Special Considerations

*by Daniel Ramirez, MD, Georges-Pascal Haber, MD, PhD*

Daniel Ramirez, MD

Georges-Pascal Haber, MD, PhD

## Key Points

Though renal cell carcinoma is rare in women of childbearing age, renal surgery during pregnancy may be performed successfully at high-volume institutions using a multidisciplinary approach.

Laparoscopic partial nephrectomy has advantages over open surgery in these cases, including reduced risk of respiratory and wound complications, expedited recovery, decreased narcotic requirement after surgery, and lower blood loss. Robot-assisted laparoscopic surgery is a further refinement of the procedure.

Cleveland Clinic's recent experience with the first reported robotic partial nephrectomy in a pregnant patient demonstrates that the procedure is safe and feasible but requires multidisciplinary cooperation and careful operative planning.

Renal cell carcinoma (RCC) rarely occurs in women of childbearing age, with an estimated annual incidence of less than five cases per 100,000 women. Nevertheless, renal surgery during pregnancy may be necessary for management of large tumors, lesions at risk for hemorrhage, or active bleeding. Such surgery has previously been shown to be feasible when indicated.[1,2]

Laparoscopic surgery offers many advantages over open surgery for management of renal neoplasms in the pregnant patient, including decreased rates of wound complications, decreased risk of maternal hypoventilation, decreased risk of respiratory depression in the fetus in light of reduced narcotic requirement for postoperative pain control, and shorter hospitalization with faster convalescence.

Only a handful of reports of laparoscopic nephrectomy during pregnancy have been described in the literature.[4-7] Historically, surgical procedures were postponed until the second trimester of pregnancy to avoid the danger of spontaneous abortion during the first trimester or preterm labor during the third trimester, but contemporary studies and guidelines report that surgical procedures may be safely performed at any time during pregnancy. [3, 8-11]

While the literature does not currently address the use of the robotic platform for performing laparoscopic procedures in these circumstances, the same surgical tenets exist for this approach.

## Patient Counseling and Surgical Planning

Our institution recently performed the first reported robotic partial nephrectomy in a 35-year-old healthy pregnant patient at 20 weeks of gestation for treatment of a 7.5-cm renal mass with a RENAL score of 11.

Diagnosis of the mass was made during routine anatomical ultrasonography of the fetus at 18 weeks of gestation. The patient ultimately underwent MRI with gadolinium contrast to better characterize the mass (Figure 1). On MRI she was found to have an enhancing 7.5-cm right-sided upper pole renal mass, consistent with RCC.

Perioperatively, her case was managed using a multidisciplinary approach, with cooperation among specialists in anesthesia, high-risk obstetrics, maternal-fetal medicine, urology and our institutional bioethics committee. After a thorough discussion about the potential risks and benefits of surveillance until after delivery, renal mass biopsy and surgery, the patient and her family decided to proceed with robotic partial nephrectomy. Preoperatively the patient's serum creatinine was 0.54 mg/dL and her hemoglobin was 11.2 g/dL.

## Details of the Surgical Procedure

Fortunately, the patient presented with a right-sided renal neoplasm, allowing for intraoperative left lateral decubitus positioning. In this position, the gravid uterus falls away from the inferior vena cava (IVC), reducing the IVC's compression. Compression of the IVC may considerably reduce venous return to the heart, resulting in diminished cardiac output and potential maternal hypotension, with possible decreased placental and fetal perfusion during surgery.

Intra-abdominal access was obtained with the Veress needle lateral to the lateral border of the rectus muscle at the level of the 11th rib. This access was obtained more lateral to where we usually obtain access to avoid the gravid uterus. Contemporary guidelines suggest that laparoscopic access during

pregnancy may be performed via an open Hasson technique, optical trocar, or use of Veress needle with modification of location depending on prior surgery and fundal height. Insufflation was maintained at or below 12 mm Hg to decrease the risk of IVC or pulmonary compression, since pregnant women experience reduced lung pulmonary volumes and lower functional residual capacity secondary to diaphragmatic displacement from a gravid uterus.

Operative time was 253 minutes, warm ischemia time was 36 minutes and estimated blood loss was 120 mL. The patient had a routine postoperative course and recovered well. Prophylactic heparin was avoided to decrease the risk of bleeding after partial nephrectomy.

## Outcome Shows Procedure's Safety, Feasibility

Maternal fetal medicine and obstetrics assessed the patient and fetus prior to surgery, immediately after surgery in the post-anesthesia care unit, and daily during her hospitalization and found normal fetal movements and heart tones at each evaluation. The patient's creatinine peaked at 0.81 mg/dL and her hemoglobin reached a nadir of 9.6 g/dL. She was discharged on postoperative day six in excellent condition. Final pathology demonstrated a 6.6-cm chromophobe renal cell carcinoma with negative margins. Four months later, the patient vaginally delivered her baby boy at term without complications.

## Cooperation, Planning Are Vital

We found that robotic partial nephrectomy during pregnancy is safe and feasible but requires multidisciplinary cooperation and careful operative planning to ensure optimal safety of mother and fetus. Early involvement of high-risk maternal-fetal medicine, obstetrics, anesthesiology and pharmacy are imperative to ensure optimal outcomes.

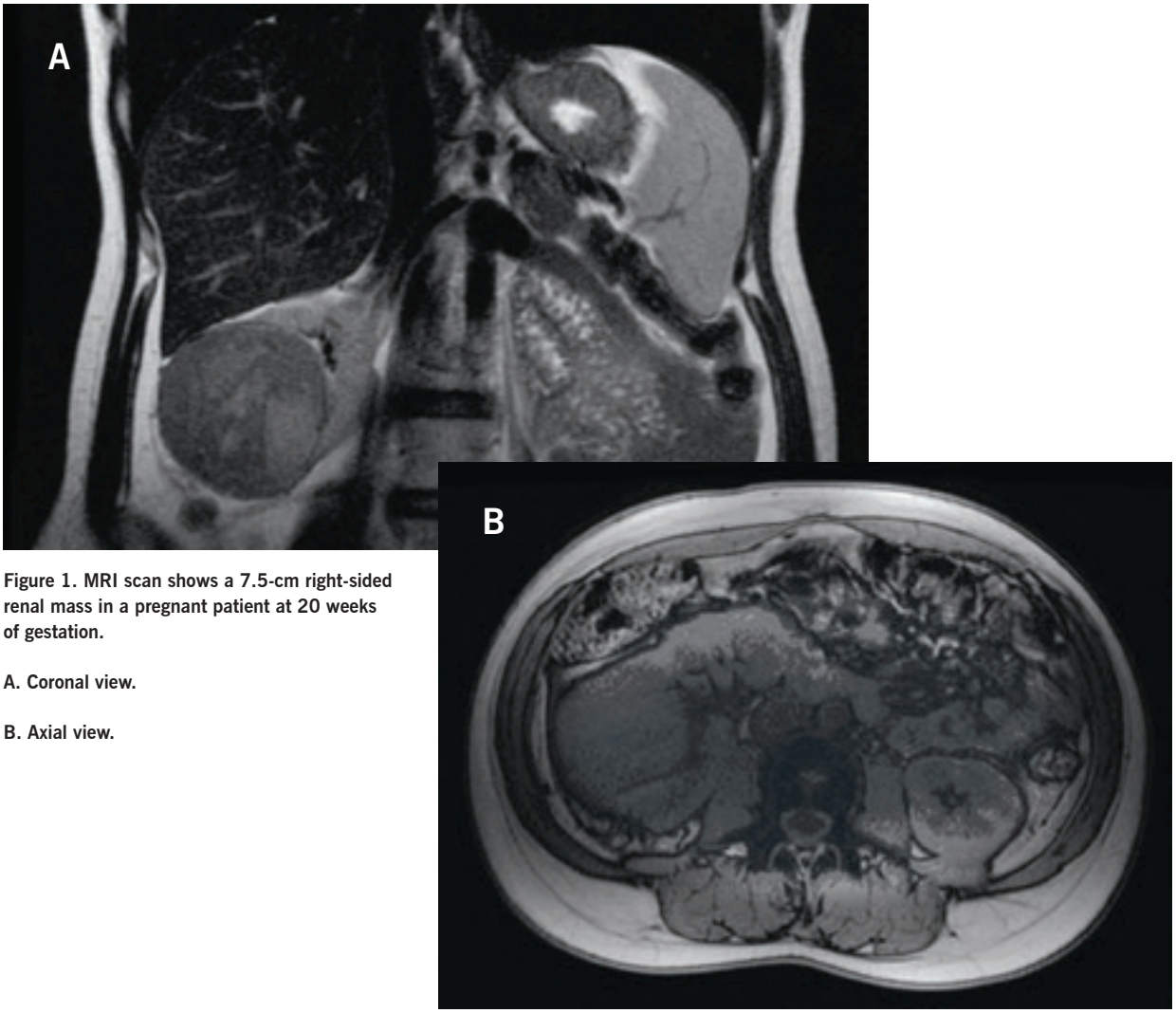



**Figure 1. MRI scan shows a 7.5-cm right-sided renal mass in a pregnant patient at 20 weeks of gestation.**

**A. Coronal view.**

**B. Axial view.**

*Dr. Ramirez (ramired3@ccf.org) is a clinical fellow in the Glickman Urological & Kidney Institute's Department of Urology.*

*Dr. Haber (haberg2@ccf.org; 216.445.4781) is a staff member of the Department of Urology.*

## References

1. *Fazeli-Martin S, Goldfarb D, Novick AC. Renal and adrenal surgery during pregnancy.* Urology. *September 1998; 52(3):510-511.*
2. *Preece P, Mees B, Norris B, et al. Surgical management of haemorrhaging renal angiomyolipoma in pregnancy.* Int J Surg Case Rep. *2015;7C:89-92.*
3. *Reedy MB, Kallen B, Kuehl TJ. Laparoscopy during pregnancy: a study of five fetal outcome parameters with use of the Swedish Health Registry.* Am J Obstet Gynecol. *1997; 177:673-679.*
4. *Boussios S, Pavlidis N. Renal cell carcinoma in pregnancy: a rare coexistence.* Clin Transl Oncol. *2014; 16:122-127.*
5. *Domjan Z, Holman E, Bordas N, et al. Hand-assisted laparoscopic nephrectomy in pregnancy.* Int Urol Nephrol. *2014; 46:1757-1760.*
6. *Sainsbury DC, Dorkin TJ, Macphail S, et al. Laparoscopic radical nephrectomy in first-trimester pregnancy.* Urology. *2004;64:1231.e7-e8.*
7. *Yin L, Zhang D, Teng J, et al. Retroperitoneal laparoscopic radical nephrectomy for renal cell carcinoma during pregnancy.* Urol Int. *2013;90(4):487-489.*
8. *Oelsner G, Stockheim D, Soriano D, et al. Pregnancy outcomes after laparoscopy or laparotomy in pregnancy.* J Am Assoc Gynecol Laparosc. *2003;10:200-204.*
9. *Rollings MD, Chan KJ, Price RR. Laparoscopy for appendicitis and cholelithiasis during pregnancy: a new standard of care.* Surg Endosc. *2004;18(2):237-241.*
10. *Guidelines Committee of the Society of American Gastrointestinal and Endoscopic Surgeons, Yumi H. Guidelines for diagnosis, treatment, and use of laparoscopy for surgical problems during pregnancy.* Surg Endosc. *2008;22:849-861.*
11. *Pearl J, Price R, Richardson W, et al. Guidelines for diagnosis, treatment, and use of laparoscopy for surgical problems during pregnancy.* Surg Endosc. *2011;25:3479-3492.*

# Metabolite of Abiraterone Shows Better Anti-Tumor Activity than Parent Compound Against Castration-Resistant Prostate Cancer

## Key Points

Prostate cancers need androgens to grow, so all metastatic prostate cancers require medical or surgical treatment to block testosterone production.

Almost all metastatic prostate tumors eventually become resistant to hormone deprivation because testosterone production may still occur.

Abiraterone inhibits androgen biosynthesis and is approved to treat metastatic castration-resistant prostate cancer.

Cleveland Clinic research shows that an abiraterone metabolite, Δ4-abiraterone, is significantly better than its parent compound at inhibiting steroidogenesis and tumor growth in an animal model, and has potential as a therapy and biomarker.

A metabolite of an agent approved for use against metastatic prostate cancer may be more effective than the parent drug, abiraterone, a Cleveland Clinic-led research team has discovered. The novel metabolite, known as Δ4-abiraterone (D4A), shows more potent anti-tumor activity than abiraterone in some patients.

Results of the investigation by Cleveland Clinic researcher Nima Sharifi, MD, and colleagues were published July 16 in *Nature*.

"More studies are needed to uncover the exact mechanisms involved, but we predict that direct treatment with D4A could prolong survival in some patients with metastatic prostate cancer," says Dr. Sharifi. "Further studies will also help us develop a potential biomarker profile to predict which patients will respond to abiraterone, which is converted to D4A."

The major significance of the finding regarding abiraterone, says Dr. Sharifi, "is that in addition to its known direct effect, it has this very indirect effect, meaning it's converted to a totally different entity that has its own anti-tumor activities. So when you put them all together, it essentially makes D4A more potent than the parent compound. The way this is being metabolized is very different from the way we traditionally think of drug metabolism."

## Abiraterone and Androgen Synthesis

Prostate cancer is the most common malignancy in men, with about 240,000 new cases diagnosed every year in the United States. Nearly all fatal cases involve castration-resistant tumors, so a considerable amount of research focuses on finding effective treatment for these advanced cancers.

Prostate cancers need androgens to grow, so all metastatic prostate cancers require medical or surgical treatment to block testosterone production. Androgen deprivation, or medical castration, slows the spread of aggressive prostate cancer, with between 80 and 90 percent of tumors responding initially. However, almost all tumors eventually become resistant to hormone deprivation, so it is a temporarily effective treatment, Dr. Sharifi says.

Castration-resistant prostate cancers continue to grow because testosterone production may still occur in the adrenal glands and in the tumor itself.

In previous research, Dr. Sharifi described a genetic mutation that enables prostate cancer cells to produce androgens, thereby providing their own fuel. This mutation in 3β-hydroxysteroid dehydrogenase-isoenzyme-1 (3βHSD1) results in a hyperactivated enzyme, he explains, which "converts precursor steroids to the most potent androgens, and those androgens are responsible for driving disease progression in the setting of castration-resistant prostate cancer."

Regardless of the mechanism of continued growth, however, castration-resistant tumors require alternative therapies.

Abiraterone is an inhibitor of androgen biosynthesis. The U.S. Food and Drug Administration (FDA) approved its use in 2011 in men with metastatic castration-resistant prostate cancer who had undergone previous chemotherapy, including docetaxel. In 2012, the FDA approved abiraterone's use in combination with prednisone in patients without previous chemotherapy.

Abiraterone works by inhibiting cytochrome P45017A1 (CYP17A1), an enzyme needed for androgen synthesis. Abiraterone's specific action is to block enzymatic reactions that allow the conversion of precursor steroids to 5α-dihydrotestosterone (DHT). Tumors require DHT for resistance, so blocking its synthesis improves survival.

## Conversion to Efficacious Metabolite

In the abiraterone study, conducted at Cleveland Clinic's Lerner Research Institute, Dr. Sharifi and his collaborators showed that abiraterone undergoes conversion to the metabolite D4A in both humans and animal models of prostate cancer. The metabolite was found to inhibit three enzymes essential for DHT synthesis, namely 3β-hydroxysteroid dehydrogenase, steroid-5α-reductase and 17β-hydroxysteroid dehydrogenase. D4A also blocked the androgen receptor directly with a higher affinity than did abiraterone, and inhibited androgen-responsive genes.

The degree of conversion of abiraterone to D4A varies among patients. "We think it's possible that the amount of conversion to the metabolite may be in part responsible for either tumor response to the drug or resistance to the drug," Dr. Sharifi says. This means that patients with a higher level of conversion may have better tumor response.

Testing should provide insights, Dr. Sharifi says. "If a patient is on abiraterone, we can draw blood and look for the parent compound as well as the metabolite, and the degree of conversion could be an early biomarker of how well that drug might work."

The metabolite study also showed that D4A has better anti-tumor activity than does abiraterone. Experiments in mouse xenografts showed that inhibition of steroidogenesis and tumor growth was significantly better with D4A than with abiraterone.

The findings about D4A not only help explain the efficacy of abiraterone, but they imply that direct treatment with D4A may achieve better clinical efficacy. "Because D4A is more potent, directly giving this metabolite may have better overall effects, meaning anti-tumor clinical effects, compared with giving the parent compound itself," Dr. Sharifi says.

## Future Research Directions

Dr. Sharifi and his colleagues are pursuing leads their findings have raised. "We're in the process of looking at patients who get abiraterone and respond either with longer survival or longer progression-free survival versus those who don't, to determine if that might correlate with conversion to D4A," he says.

His work on D4A may have implications for other prostate cancer therapies as well. "This may tell us something about how drugs in this class work," says Dr. Sharifi. "There are other drugs that are being investigated in clinical trials whose steroidal structure is similar to abiraterone's, so figuring out how they work — the direct mechanism and the indirect mechanism through metabolites — may help us more appropriately develop these agents."

*Dr. Sharifi (sharifn@ccf.org; 216.445.9750) is an associate staff member in Cleveland Clinic's departments of Hematology and Medical Oncology, Cancer Biology, and Urology. He holds the Kendrick Family Endowed Chair for Prostate Cancer Research and is Associate Professor of Molecular Medicine at Cleveland Clinic Lerner College of Medicine.*

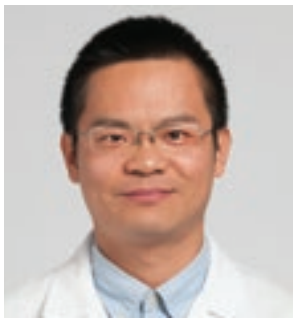
# Neoadjuvant Therapy to Downsize Tumors and Enable Partial Nephrectomy

*by Steven C. Campbell, MD, PhD; Brian I. Rini, MD; Zhiling Zhang, MD; and Juping Zhao, MD*

Steven C. Campbell, MD, PhD

Brian I. Rini, MD

Zhiling Zhang, MD



Juping Zhao, MD

## Key Points

Preservation of renal function is a priority in renal cell carcinoma (RCC) patients with a solitary kidney or pre-existing chronic kidney disease, but it can be difficult or impossible due to unfavorable tumor size and location.

Neoadjuvant tyrosine kinase inhibitor (TKI) can downsize clear cell RCC and enable partial nephrectomy (PN) in some patients who would otherwise require radical nephrectomy, occasionally precluding the need for dialysis.

Complications associated with PN after TKI may increase but most can be managed conservatively and with good outcomes.

Neoadjuvant TKI should be considered selectively, primarily when preservation of renal function is paramount and tumor size and location are particularly unfavorable for PN.

Some patients with renal cell carcinoma (RCC) present extraordinary treatment challenges because of unfavorable tumor size and location that places their remaining parenchymal mass in jeopardy during tumor excision.

In these patients, many of whom have extensive hilar tumor within a solitary kidney, partial nephrectomy (PN) may not be feasible, leaving the patient between a rock and a hard place: either accepting radical nephrectomy (RN) with the need for renal replacement therapy, or proceeding with substantial oncologic risk if the tumor is left in situ.

In other patients with pre-existing chronic kidney disease (CKD) and challenging tumor size and location, PN may be feasible but the amount of parenchymal mass and function that would be lost with the surgery would be unacceptable, placing the patient at increased risk for adverse outcomes (see Figure). A recent analysis showed that new baseline glomerular filtration rate (GFR) after renal cancer surgery is a strong predictor of renal stability and long-term survival, particularly for patients with pre-existing CKD.

We previously reported that sunitinib, a tyrosine kinase inhibitor (TKI), yielded encouraging responses in patients with unresectable locally advanced clear cell RCC. In this population (n = 22), partial responses (> 30 percent reduction in diameter) were seen in 33 percent of patients, and 59 percent were subsequently able to undergo surgical resection. Similar responses were not seen in patients with non-clear cell RCC.

## Can TKI Enable Partial Nephrectomy?

Based on this experience, we prospectively studied the role of pazopanib — another TKI with proven efficacy — in patients with localized clear cell RCC for whom preservation of renal function was essential. Our primary goals were to determine if neoadjuvant TKI could enable PN when it was otherwise impossible, and to optimize the amount of parenchyma that could be saved with the procedure. A secondary endpoint was surgical safety, given that such TKIs can affect wound healing and vascular integrity through their effect on the vascular endothelial growth factor axis.

A total of 25 patients were enrolled: 20 from our center and five from collaborators at Fox Chase Cancer Center. On enrollment, median tumor size was 7.3 cm. About 65 percent of patients had pre-existing CKD or a solitary kidney, and many had both. Eighty percent of patients had RENAL scores of 10-12, consistent with high-complexity tumors. In 13 patients (52 percent) PN was not feasible prior to TKI based on surgeon assessment. Pazopanib dose was 800 mg per day, with adjustment if necessary, and median duration of therapy was eight weeks.

We assessed efficacy of TKI therapy in a variety of ways. Overall, median tumor size was reduced by 25 percent, and median tumor volume was reduced by 46 percent. Median RENAL score was reduced from 11 to 9, and RENAL complexity (high vs. intermediate) was reduced in 10 tumors. Most impressive-

ly, for the 13 patients for whom PN was not possible upfront, downsizing by TKI enabled PN in six (46 percent), thereby precluding the need for dialysis.

## Benefits in Select Patients

Overall, the mean parenchymal volume that could be saved with PN increased from about 100 cc to 175 cc, and functional preservation paralleled this, representing another significant gain with this approach. As the tumor pulled away from the hilum, substantially more parenchyma, and thus function, could be saved during tumor excision and reconstruction (see Figure). Urine leaks were diagnosed in five patients after PN and seven received perioperative blood transfusion, although only one required angioembolization.

Complications thus increased above baseline for most PN series, likely reflecting the challenging patient population, although suboptimal healing related to TKI may also have contributed. Nevertheless, almost all surgical complications were managed conservatively and we achieved good outcomes in all instances.

Our experience suggests that neoadjuvant TKI may provide a benefit in a select subgroup of patients with localized RCC for whom preservation of renal function is vital, and that it may enable PN in some patients who would otherwise require radical nephrectomy.

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

*Dr. Rini (rinib2@ccf.org; 216.444.9567) is a member of Cleveland Clinic Cancer Center's Department of Hematology and Medical Oncology and a Professor of Medicine at Cleveland Clinic Lerner College of Medicine.*

*Drs. Zhang and Zhao are former research fellows in the Urological & Kidney Institute.*

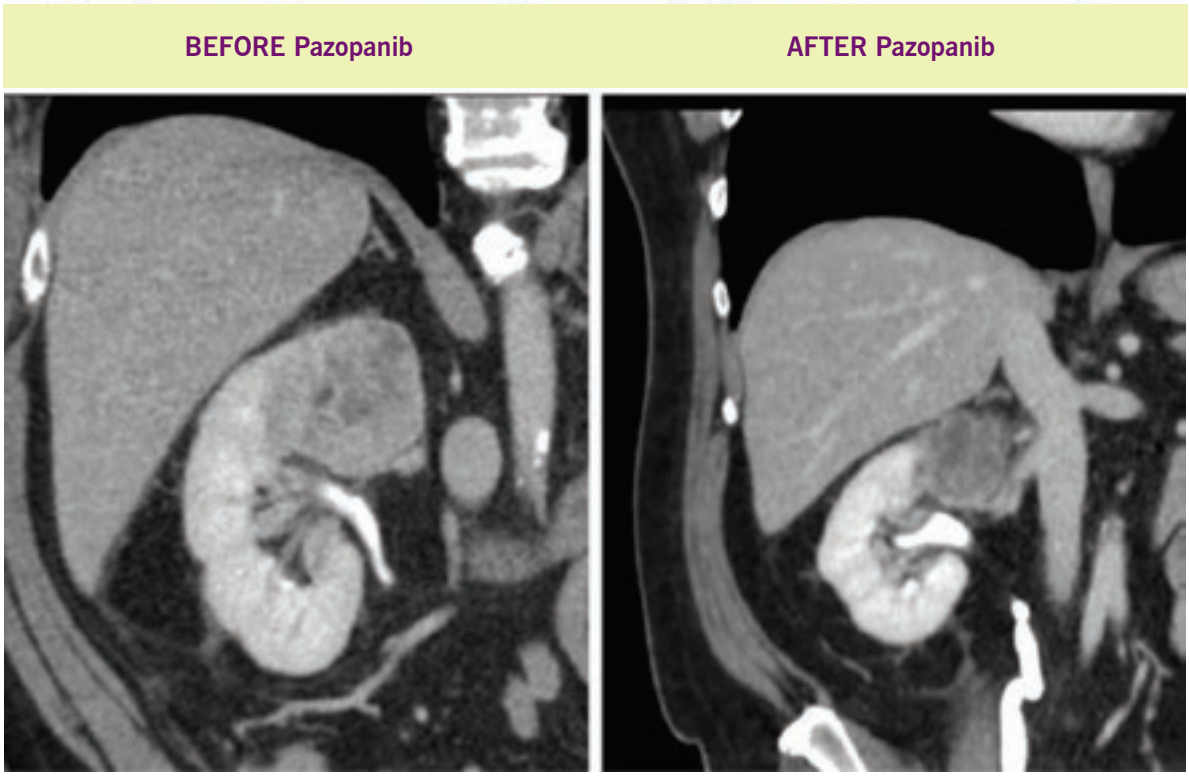



**Figure. A 61-year-old with a solitary right kidney presented with a 5.4-cm mass within the upper pole and extending near the hilum. The RENAL score was 10 and the tumor did not appear to be well-encapsulated. The glomerular filtration rate (GFR) was 38 mL/min/1.73m$^2$. While PN was possible, it would not save optimal amounts of parenchyma and function. After eight weeks of pazopanib, the tumor was downsized to 3.8 cm with a RENAL score of 8, and the tumor pulled away from the hilum. The tumor also appeared well-encapsulated and demonstrated extensive necrosis. PN was performed with cold ischemia time of 38 minutes. Recovery was uneventful. Eighty-two percent of the parenchyma was preserved, and the final GFR was 34 mL/min/1.73m$^2$.**

# Improving Prostate Cancer Survival via Selective Forms of Androgen Deprivation Therapy

*by Hannelore V. Heemers, PhD*

Hannelore V. Heemers, PhD

Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer deaths in men in the United States. Patients who present with localized disease and for whom deferral of treatment is not recommended are treated with surgery or radiation therapy with curative intent.

Some men, however, present with prostate cancer that has spread beyond the confines of the prostate. In others, prostate cancer recurs after prostatectomy or radiation therapy. Men with advanced prostate cancer are given androgen deprivation therapy that targets the action of the androgen receptor.

The androgen receptor is a ligand-dependent transcription factor. Currently, androgen deprivation therapy (ADT) prevents androgen receptor signaling by reducing the availability of its ligand or the ability of the androgen receptor to interact with and be activated by its ligand.

Overall, these forms of ADT are initially effective in inducing remission. However, the extent and duration of remission is variable among patients, and eventually the cancer recurs during ADT. Strikingly, in the vast majority of cases, prostate cancer that recurs under the selective pressure of ADT remains dependent on the androgen receptor for growth.

As with other targeted therapies, the manner in which prostate cancer cells bypass the blocks that have been imposed on the androgen receptor signaling axis often involves adaptations that lead to gain of function for the androgen receptor. With few exceptions, failure of ADT is responsible for the approximately 30,000 American prostate cancer deaths per year.

## Identifying Other Targeting Strategies

We propose that other tactics to target androgen receptor action for prostate cancer treatment should be pursued. It is apparent that the most important part of the androgen receptor signaling axis — namely its transcriptional output, which ultimately controls prostate cancer cell behavior and fate — has not yet been considered for therapeutic intervention.

The transcription function of the androgen receptor and the molecular determinants that control its activity are increasingly evident. During the last decade, systems biology approaches have identified the spectrum of androgen-responsive genes and genomewide androgen receptor binding sites in prostate cancer cells, and gene expression profiling and next-generation sequencing have been performed on clinical prostate cancer specimens obtained at different stages of disease progression.

### Key Points

Androgen deprivation therapy that prevents ligand activation of the androgen receptor is the default treatment for non-organ-confined prostate cancer.

Patients fail androgen deprivation therapy while prostate cancer remains dependent on the androgen receptor.

Selective androgen deprivation therapies that block the transcriptional output of the androgen receptor are needed to improve survival rates for prostate cancer.

## Gaining Androgen Receptor Insights

Collectively, the data and insights from these studies are enabling the preliminary systemic characterization of regulation of the androgen-dependent transcriptome in prostate cancer model systems and the validation of its relevance to clinical situations, specifically the progression of prostate cancer to its lethal stage.

These “big data” projects provide for the first time an incredible opportunity to start isolating androgen receptor action that drives prostate cancer to the lethal stage, and can provide an entirely novel target for therapy.

Increasingly, the androgen receptor is appreciated for its ability to control distinct cellular functions differentially at the molecular level. Conceptually, this gain in knowledge allows us to determine the fraction(s) of androgen action that is most important to prostate cancer progression and to exploit the underlying regulatory mechanisms for therapeutic intervention.

Such an approach could be used to develop forms of androgen ablation that are more selective than current ADT, which may be viewed as “oversized,” i.e., targeting all androgen receptor action, when it may be sufficient to prevent only the fraction that conveys aggressive prostate cancer behavior.

## Focusing on Selective Control

The feasibility of a novel selective form of ADT that interferes with a select fraction(s) of androgen action that drives prostate cancer progression is supported by a body of research. For instance, we have identified fractions of androgen receptor action that selectively control cell migration or lipid synthesis, both of which are features that underlie prostate

cancer progression. Insights into the molecular basis for androgen regulation of these biological processes are leading to the implementation of druggable targets for prostate cancer therapy.

While a one-size form of androgen deprivation therapy may fit all, the tighter fit provided by such treatment options may be more effective and comfortable for the patient.

*Dr. Heemers (heemerh@ccf.org; 216.445.7357) is an associate staff member of the Department of Cancer Biology in Cleveland Clinic's Lerner Research Institute.*

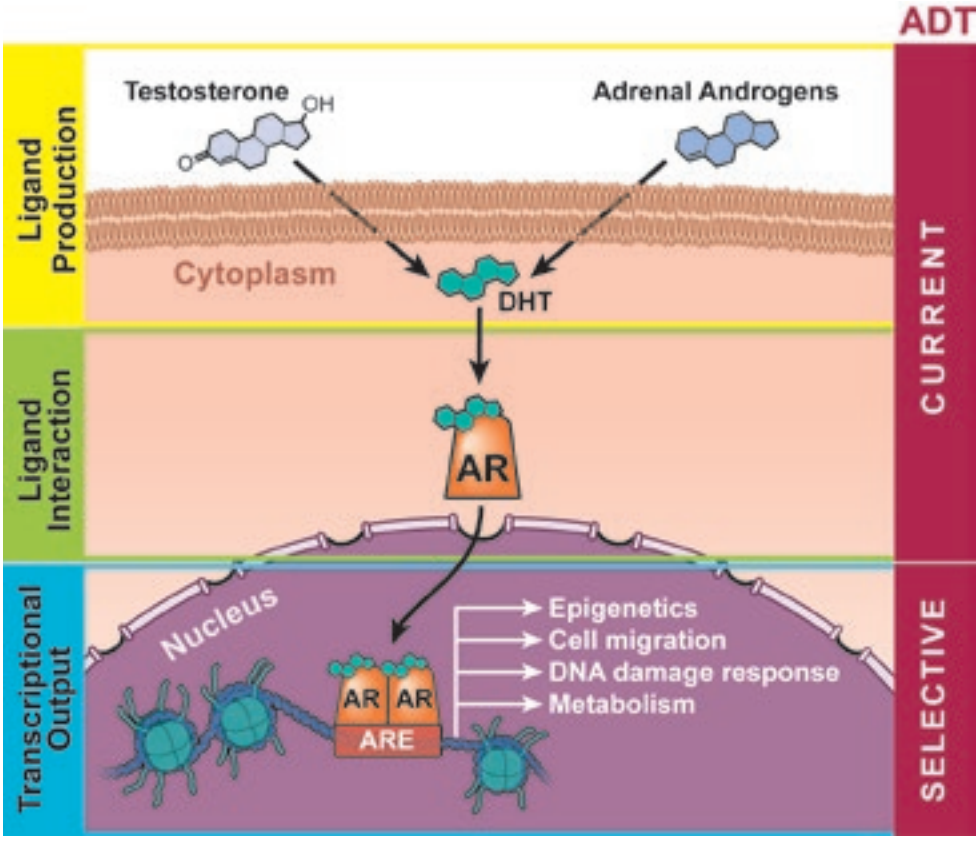



**Figure 1. Targeting androgen receptor (AR) transcriptional output to develop selective forms of androgen deprivation therapy (ADT). Current ADT prevents production of dihydrotestosterone (DHT), the most bioactive androgen, or interferes with the interaction between ARs and DHT. Selective ADT exploits therapeutically distinct AR-dependent cellular processes (cell migration, DNA damage response, etc.) that are associated with prostate cancer progression. From: Elbanna M, Heemers HV. Alternative approaches to prevent androgen action in prostate cancer: Are we there yet? *Discov Med*. 2014 May;17(95):267-274. Used with permission from *Discovery Medicine*.**

**ARE = androgen response element**

# Checkpoint Molecules in Renal Cell Carcinoma Biology

*by Samuel Haywood, MD*

Samuel Haywood, MD

More than 60,000 Americans are diagnosed annually with renal cell carcinoma (RCC), one of the most lethal genitourinary malignancies. Overall mortality rates can reach 20 to 30 percent.

Unfortunately, about one-quarter of patients present with locally advanced or metastatic disease, and approximately 30 percent of cancers will recur after initial treatment. Despite advances in treatment strategies, metastatic renal cell carcinoma (mRCC) largely remains an incurable disease.

Tyrosine kinase inhibitors (TKIs) are the gold standard for treatment of mRCC. While TKIs have been proved to prolong survival, patients eventually develop resistance and experience progression of disease. As such, there is considerable effort underway to develop additional mRCC treatments.

## Probing Immune Suppression Mechanisms

Immunotherapy has shown promise in the treatment of many malignancies, with RCC an excellent example. RCC is one of a few malignancies (along with melanoma and head and neck cancer) associated with known defects in the immune system, and further understanding of this immune suppression would pave the way for improved treatments.

Research conducted in the laboratory of James Finke, PhD, of Cleveland Clinic's Department of Immunology has focused on this issue. A population of cells called myeloid-derived suppressor cells (MDSCs) is present in increased numbers in RCC tumors, resulting in an immunosuppressive environment. This allows cancer cells to escape the body's normal immune response. The presence of MDSCs is associated with poor outcome in RCC.

One proposed immunotherapy for mRCC is a new class of drugs called checkpoint inhibitors. Normally, the immune system has a checkpoint process to prevent excessive immune reactions. In RCC states, a ligand-receptor complex of programmed death-1 (PD-1) and programmed death ligand-1 (PDL-1) is abnormally expressed, and the binding of this complex acts at this checkpoint to suppress the anti-tumor immune response.

Inhibition of this checkpoint interaction "releases the brakes" on the immune system and allows the body to attack the tumor. Preliminary clinical trials of antibodies against PD-1 and PDL-1 have shown promising results in several malignancies, including RCC. However, it is currently unknown if this PD-1/PDL-1 complex is present on MDSCs in RCC. The interaction of TKIs with these checkpoint molecules is also unknown. A series of experiments in the Finke laboratory is underway to further elucidate this relationship.

### Key Points

Despite treatment advances, metastatic renal cell carcinoma remains largely incurable.

Renal cell carcinoma (RCC) is associated with immune system defects, and further understanding of this immune suppression could help improve treatments.

Myeloid-derived suppressor cells (MDSCs) are abundant in RCC tumors, resulting in an immunosuppressive environment and poor treatment outcomes.

The ligand-receptor complex of programmed death-1 (PD-1) and programmed death ligand-1 (PDL-1) is abnormally expressed in RCC and functions as a checkpoint to suppress normal anti-tumor immune response.

Cleveland Clinic research demonstrates the presence of the PD-1/PDL-1 complex on MDSCs within renal tumors, suggesting that checkpoint inhibitors could be effective immunotherapy in RCC.

## Testing the PD-1/PDL-1 Complex

We first obtained blood and tumor samples from patients presenting for resection of localized RCC. A total of seven patients provided blood and 16 patients provided tumor specimens. These were processed and flow cytometry was performed to analyze expression of various cell surface markers.

The analysis demonstrated expression of PDL-1 on MDSCs, both circulating and within the tumor itself. This molecule was present in variable amounts among patients, but 10 to 20 percent of all MDSCs expressed PDL-1. With respect to PD-1, this receptor was found to be expressed on T cells in peripheral blood and within the tumor milieu. Its presence was seen on both CD4 T-helper cells and CD8 cytotoxic lymphocytes, and initial analysis suggests upregulation of PD-1 expression within the tumor environment as compared with circulating blood. Taken together, the results of this first experiment definitively demonstrate the presence of this important complex on MDSCs within the kidney cancer setting.

The second phase of the study examined the effect of the PD-1/PDL-1 complex on RCC patients treated with TKI therapy. Tumor samples were obtained from RCC patients in three groups: no treatment prior to surgical resection (control),

neoadjuvant treatment with sunitinib and neoadjuvant treatment with axitinib. Immunohistochemistry was performed on these tumor samples to assess for levels of immune cell infiltrate as well as the PD-1 molecule. Initial analysis with a small pilot sample demonstrated increased immune cells infiltrating the tumors treated with TKIs as well as modest decreased expression of the immunosuppressive PD-1 molecule. Review and data analysis of the entire cohort is continuing.

## Future Directions

Immunotherapy holds much promise for improving treatment of mRCC. In particular, checkpoint inhibition of the PD-1/PDL-1 axis is an evolving area of research with direct clinical applications. Ongoing studies will further elucidate the interaction between the immune system, RCC and immunotherapeutic treatments, and this knowledge will help researchers design new treatment strategies for these patients.

*Dr. Haywood (haywoos3@ccf.org) is a resident in the Glickman Urological & Kidney Institute's Department of Urology.*

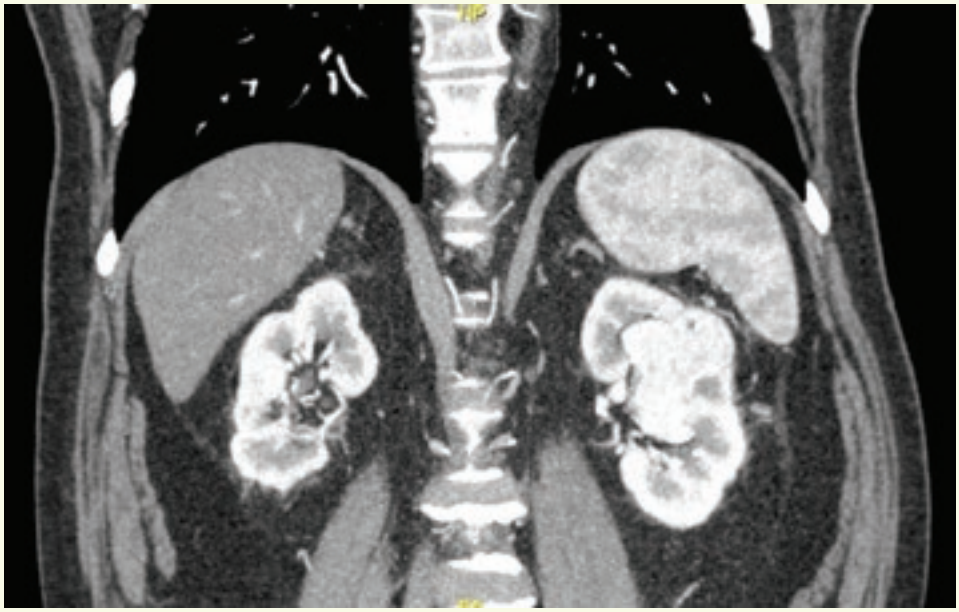


**Figure. Diagnostic imaging depicts renal cell carcinoma.**

# New Multidisciplinary Clinic Focuses on Glomerular Diseases

## Key Points

Because glomerulonephritis is rare, few physicians develop expertise treating it.

Cleveland Clinic has established the Glomerular Diseases Clinic to provide multidisciplinary care for patients with glomerulonephritis, glomerulosclerosis and related conditions.

The clinic provides evaluation, treatment and access to clinical trials.

Cleveland Clinic has launched the Glomerular Diseases Clinic to provide multidisciplinary care that meets the unique needs of patients with glomerulonephritis, glomerulosclerosis and related conditions. It is one of only a handful of such programs in the United States.

The Glomerular Diseases Clinic, part of Cleveland Clinic's nephrology program, is staffed by five nephrologists: James Simon, MD; Jonathan Taliercio, DO; Evamaria Anvari, MD; Juan Calle, MD; and Richard Fatica, MD. This team also meets about three times a month with a pathologist to review biopsies and treatment plans and to discuss advances in the field.

"We work as a multidisciplinary group," says Dr. Simon.

Since many patients with lupus have glomerular disorders, Drs. Taliercio and Anvari coordinate their care with Cleveland Clinic rheumatology specialists.

## An Uncommon Diagnosis

Because glomerulonephritis is an unusual condition, few physicians develop expertise treating it, Dr. Simon says. Presenting symptoms can include high blood pressure, dark cola-colored urine, sudden swelling in the legs and fluid retention. Some patients lack symptoms and are referred after a test reveals protein or blood in their urine. Some patients self-refer seeking a second opinion.

"In the course of evaluating these patients, we often diagnose other conditions, such as cancer or hepatitis C, and we can refer them to other Cleveland Clinic specialists to manage these conditions," says Dr. Simon.

Patients generally are treated with immunosuppressant therapies such as prednisone.

## Ongoing Research Studies

One major benefit of a dedicated glomerular disorders clinic is the access it provides patients to the latest clinical trials, Dr. Simon notes.

The Glomerular Diseases Clinic staff is involved in several studies, including:

**MENTOR (Membranous Nephropathy Trial of Rituximab):** Patients with idiopathic membranous nephropathy are randomly assigned to a trial of cyclosporine (given as a pill) or rituximab (given intravenously). The goal is to reduce protein loss in urine without encountering the risks typically associated with steroid therapy. Participants will be compared at 24 months (12 months after stopping the medication).

**ATHENA:** This is an observational trial designed to characterize the natural decline of renal function markers such as glomerular filtration rate, creatinine, proteinuria and β-2 microglobulin in Alport syndrome patients. Dr. Simon is hopeful this study will lead to a drug trial within about a year.

**NEPTUNE (The Nephrotic Syndrome Study Network):** This is an observational study of patients with nephrotic syndrome who undergo a medically indicated kidney biopsy. The primary study outcomes being followed are changes in the amount of urine protein and kidney function.

*To refer a patient to Cleveland Clinic's Glomerular Diseases Clinic, please call 855.REFER.123.*

# Implantable Cardioverter-Defibrillator Is Associated with Reduced Mortality in Some Chronic Kidney Disease Patients *by Georges Nakhoul, MD*

Georges Nakhoul, MD

Chronic kidney disease (CKD) is a worldwide public health problem that affects millions of Americans. Patients with CKD have an increased risk of mortality in general, and cardiovascular mortality in particular. Specifically, as the stage of CKD progresses, patients are more prone to developing sudden cardiac death (SCD).

## Key Points

Chronic kidney disease (CKD) is associated with increased cardiovascular mortality, particularly from sudden cardiac death (SCD).

Analysis of Cleveland Clinic's registry of more than 50,000 CKD patients shows that placement of an implantable cardioverter-defibrillator is associated with lower mortality in patients with stage 3 CKD, but not in those with stage 4 CKD.

Recent advances in medicine and technology have led to the development of implantable cardioverter-defibrillators (ICDs), which are devices capable of detecting arrhythmias and delivering corrective electric shocks.

In the general population, the benefits of ICDs in preventing sudden cardiac death are now well-proven. Since patients with CKD appear to die more frequently from SCD, the intuitive assumption is that this population would gain significantly from ICDs. Unfortunately, the major studies that established the indications for ICD placement excluded patients with chronic kidney disease, so the benefits in this population remain uncertain.

## Examining ICD Benefits in CKD Populations

In the last few years, Cleveland Clinic has developed a large CKD registry comprising more than 50,000 patients. The registry is serving as a key research tool, shedding light on numerous matters related to CKD care.

We used[1] our CKD registry to identify patients who had an ICD placed for primary prevention between Jan. 1, 2001, and Oct. 31, 2011.

Demographic details were extracted from the electronic health record (EHR). The primary outcome of interest (all-cause mortality) was ascertained from our EHRs and linkage of our CKD registry with the Social Security Death Index. Patients were followed from their date of study entry (date of second qualifying estimated glomerular filtration rate (eGFR) or first ICD) until Oct. 31, 2011.

We then developed a propensity score of the likelihood of receiving an ICD, utilizing the following variables: age, sex, race, diabetes, hypertension, malignancy, body mass index, coronary artery disease, coronary revascularization, congestive heart failure, ventricular arrhythmia, cerebrovascular disease, eGFR, left ventricular ejection fraction, and use of renin-angiotensin system blockers, statins and beta blockers. We used one-to-one greedy matching with 0.1 caliper width to match patients with an ICD to those without.

We included 1,053 patients who had an ICD placed for primary prevention. We identified 9,435 potential controls for those with an ICD. Patients with an ICD were more likely to be younger, to be men, and to have lower ejection fraction, diabetes, congestive heart failure and coronary artery disease than were those with no ICD. As expected, there was a higher incidence of arrhythmia in the ICD group. We were able to match 631 of 1,053 patients (60 percent) with an ICD with 0.1 calipers.

Among the 1,262 matched cases and controls, there were 578 deaths during a median follow-up of 2.9 years. Figure 1 shows a Kaplan-Meier plot of survival by ICD among matched patients with different eGFR categories. After propensity score matching, ICD was associated with significantly lower mortality among those with an eGFR < 60 mL/min/1.73 $m^2$ in both the unadjusted and adjusted models.

We found a significant interaction ($p = 0.04$) between ICD and an eGFR of 45-59 mL/min/1.73 $m^2$ and an eGFR of 30-44 mL/min/1.73 $m^2$, in which patients with an ICD and an eGFR within these two intervals had a significantly lower hazard of mortality, with hazard ratios of 0.58 (95 percent confidence interval [CI], 0.44-0.77) and 0.65 (95 percent CI, 0.50-0.85), respectively. No such association was noted among those with an eGFR < 30 mL/min/1.73 $m^2$.

## ICD Placement in CKD: Should We Be More Selective?

The major finding from our study is that the presence of an ICD was associated with lower mortality in patients with stage 3 CKD, but not among patients with stage 4 CKD.

Our study is one of the few to examine the benefits of ICD per CKD stage and offers the advantage of a large number (the largest to our knowledge) of patients with eGFR < 30 mL/min/1.73$m^2$. More importantly, it is so far the only study that includes a control group.

Confirming the survival benefits of ICD placement in stage 3 CKD patients is crucial because this category constitutes the vast majority of non-dialysis-dependent CKD. We believe that the lack of protective effects of ICDs among stage 4 CKD patients could be due to the higher presence of comorbidities in this cohort.

While preliminary evidence appears to support this hypothesis, it is too early to draw definitive conclusions. However, our results suggest that ICD implantation should be considered carefully in patients with advanced CKD. Additional clinical trials examining the benefits and other complications of ICDs are warranted to support ICD placement in stage 4 CKD populations.

In summary, in a large cohort matched for demographics, comorbidities, and cardiac and kidney function, the presence of an ICD was associated with lower mortality in those with stage 3 CKD, but not in those with stage 4 CKD.

*Dr. Nakhoul (nakhoug@ccf.org; 216.445.4926) is an associate staff member of the Glickman Urological & Kidney Institute's Department of Nephrology and Hypertension.*

## Reference

1. *Nakhoul GN, Schold JD, Arrigain S, et al. Implantable cardioverter-defibrillators in patients with CKD: a propensity-matched mortality analysis.* Clin J Am Soc Nephrol. *2015 Jul 7;10(7):1119-1127.*

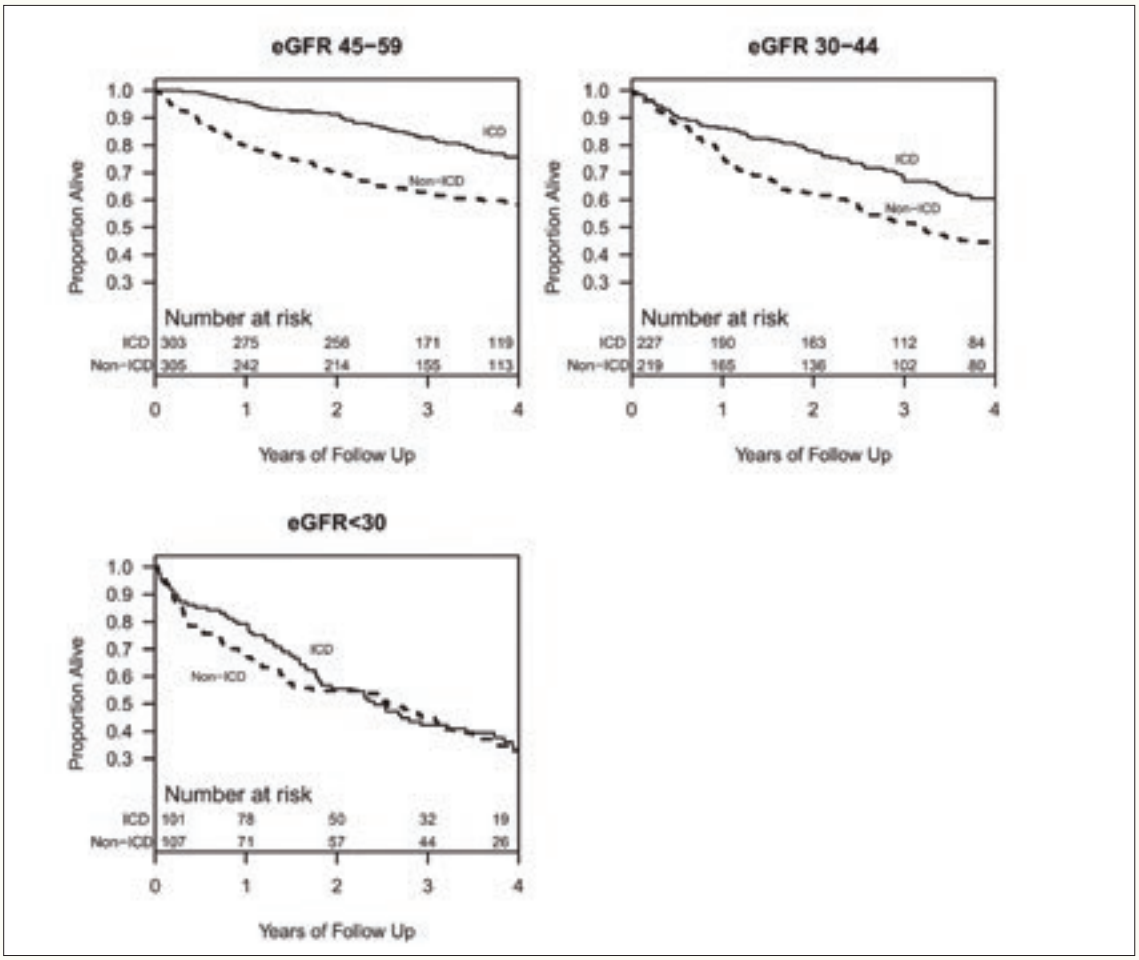



**Figure 1. Kaplan-Meier curves showing survival of those with and without an implantable cardioverter-defibrillator (ICD) for various estimated glomerular filtration rate (eGFR) categories. Republished with permission of the *Clinical Journal of the American Society of Nephrology*, from: Implantable cardioverter-defibrillators in patients with CKD: a propensity-matched mortality analysis. Nakhoul GN, Schold JD, Arrigain S, et al. 2015 Jul 7;10(7):1119-1127. Permission conveyed through Copyright Clearance Center, Inc.**

# Landmark SPRINT Hypertension Trial Favors More Aggressive Blood Pressure Control *by George Thomas, MD, MPH, FACP*

## Key Points

Hypertension increases risk for heart disease, stroke, heart failure and kidney disease, but there has been debate about the optimal blood pressure goal for hypertensive patients.

The Systolic Blood Pressure Intervention Trial (SPRINT) evaluated the effects of aggressive versus standard blood pressure control efforts in older patients with cardiovascular disease or risk factors, with particular emphasis on those with chronic kidney disease.

SPRINT's results show that intensive blood pressure management in these patients significantly reduced cardiovascular disease rates and mortality risk compared with the standard approach.

Intensively managing high blood pressure in older adults to achieve systolic levels below commonly recommended hypertension targets significantly reduces cardiovascular disease rates and mortality risk, according to the results of a landmark federally sponsored study.

Hypertension is highly prevalent in the adult population in the United States and is an established risk factor for heart disease, stroke, heart failure and kidney disease. Observational studies show a progressive increase in cardiovascular risk associated with blood pressure (BP) levels above 115/75 mm Hg.

While it is well-established that reducing elevated BP lowers cardiovascular risk, the optimal BP goal for patients with a diagnosis of hypertension and who are being treated has been a matter of some debate. Should clinicians try to lower BP to "optimal levels," i.e., less than 120/80 mm Hg? Would such an approach be beneficial or harmful? Would it be costly or burdensome to patients?

Current clinical practice, endorsed by hypertension guidelines, is to lower systolic blood pressure (SBP) to less than 140 mm Hg in most patients. The 2014 report from the Joint National Committee (JNC 8) recommends relaxing BP goals in elderly patients to SBP of less than 150 mm Hg, citing lack of evidence for more aggressive control.

Cleveland Clinic's Department of Nephrology and Hypertension was involved in the Systolic Blood Pressure Intervention Trial (SPRINT), a multicenter, randomized controlled trial sponsored by the National Institutes of Health. SPRINT was designed to answer the following question: "Will more aggressive BP control to SBP < 120 mm Hg (intensive group) reduce the risk of cardiovascular, kidney and cognitive outcomes, compared with the current standard practice of BP control to SBP < 140 mm Hg (standard group)?"

## A Sizable Study Cohort

The study enrolled 9,361 volunteers age 50 and above with established cardiovascular disease or cardiovascular risk factors. It placed particular emphasis on patients with chronic kidney disease (CKD) who had estimated glomerular filtration (eGFR)rates of 20-50 mL/min/1.73 $m^2$ and patients age 75 years and older. Patients with diabetes, stroke or polycystic kidney disease were *not* included in the study (as other studies aimed to answer the BP control question in these patients).

The primary outcome was the first occurrence of a myocardial infarction, acute coronary syndrome, stroke, heart failure or cardiovascular disease death. Secondary outcomes included all-cause mortality, decline in kidney function or development of end stage renal disease, decline in cognitive function, and small vessel cerebral ischemic disease.

The study's median follow-up period was 3.2 years. Average age of participants was 68 years; 28 percent were older than 75. Thirty-six percent were female and 30 percent were black. Twenty-eight percent had baseline CKD (9.5 percent of participants had an eGFR > 45 mL/min/1.73 $m^2$).

## Significant Risk Reductions

The results indicate there was a significant 30 percent lower incidence for primary outcome and a 25 percent lower risk of death among participants in the intensive group compared with the standard group.

The lower incidence for primary outcome was primarily driven by a reduction in heart failure. The benefits extended to those older than 75 and to those with CKD.

Adverse events, including hypotension, hyponatremia and a decline in renal function in those without a history of CKD, were more common in the intensive group. Based on National Health and Nutrition Examination Survey data from 2007 to 2012, it is estimated that 7.6 percent or 16.8 million U.S. adults would meet eligibility criteria for SPRINT. Other study results are pending, including cognitive outcomes and additional details on long-term renal function.

## An Impact on Future Guidelines

In summary, results from this well-designed trial provide scientific evidence favoring aggressive blood pressure control in patients older than 50 with established cardiovascular disease or cardiovascular risks (*without* a history of diabetes or stroke).

These results will obviously influence future hypertension guidelines and clinical practice. The benefits and risks of intensive blood pressure control have to be weighed carefully, rather than using a blanket approach to intensify treatment in all older adults.

At this time, from available evidence, it is unclear whether intensive blood pressure control would show a similar benefit in diabetics, younger patients and low-risk individuals.

*Dr. Thomas (thomasg3@ccf.org; 216.636.5420) is Director of the Center for Blood Pressure Disorders in the Glickman Urological & Kidney Institute's Department of Nephrology and Hypertension, and an Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine. He is Cleveland Clinic's principal investigator for the SPRINT trial.*

# Cancer Found to Cause More Chronic Kidney Disease Deaths than Previously Believed *by Joseph Nally, MD*

Joseph Nally, MD

For many years, nephrologists have been aware of the importance of monitoring chronic kidney disease (CKD) patients for cardiovascular disease and its risk factors. However, a new study[1] shows that for some non-dialysis-dependent CKD patients, cancer also is a major cause of mortality. For some patients, it actually poses a greater risk than does cardiovascular disease.

These findings are derived from a retrospective review of approximately 39,000 CKD patient records led by researchers in the Department of Nephrology and Hypertension in Cleveland Clinic's Glickman Urological & Kidney Institute.

The study found that the two leading causes of mortality were heart disease, in about 35 percent of patients, and cancer, in about 32 percent. These two causes account for two-thirds of deaths in these patients, a higher rate than in the general population.

This study is groundbreaking, as it is the first time that cause-specific mortality in patients with non-dialysis-dependent CKD has been reported in the United States.

The association between low glomerular filtration rate (GFR) and an elevated risk of death, cardiovascular events and hospitalization has been known for more than a decade,[2] but no one has actually examined the specific causes of death. The renal community believed that cardiovascular death rates would be much more pronounced than what our data showed. Many experts in the field predicted that heart disease might account for considerably more than 50 percent of the deaths.

## Two Key Findings

We reviewed the records of 33,478 white and 5,042 black patients with CKD who lived in Ohio between January 2005 and September 2009. The mean patient age was 72.8 $\pm$ 11.8 years. Fifty-six percent of patients were female. A total of 6,661 patients died during the study's time frame.

The registry's highly detailed information on aspects such as demographics and comorbidities enabled us to make two key findings, with implications for screening and disease management.

### Key Points

Chronic kidney disease (CKD) is associated with a heightened risk of death, but details regarding the differences in causes have not been well-studied, particularly in patients with mild to moderate CKD.

An analysis using a large CKD registry reveals that heart disease and cancer are the leading causes of death among non-dialysis-dependent CKD patients, with reduced kidney function linked to a higher risk for cardiovascular mortality.

Black patients with mild to moderate CKD have a higher risk of cardiovascular deaths than do white CKD patients.

The study findings have implications for screening and disease management.

One is that there are more cancer deaths than cardiovascular-related deaths in patients who have mild kidney disease — that is, those with a GFR of 45 to 59. But as kidney function decreases and a patient's GFR falls below 30, there are twice as many deaths from heart disease than from cancer — 39.6 percent versus 20 percent, respectively. This is the first time it has been shown that with mild kidney disease, more people died of cancer than of heart disease.

The second important finding was that both black and white CKD patients have the same mortality rates when the data are fully adjusted for all other comorbid diseases. However, black patients die more often from cardiovascular disease than from malignancy overall.

## Implications for Screening

The key message of these findings is that while nephrologists and others caring for CKD patients need to maintain an emphasis on cardiovascular risk management, they also must be vigilant about screening patients with mild kidney disease for cancer.

No one type of cancer was found to be more common than another. All of the usual cancers were represented, such as colon, breast and lung. The risk was spread across the board.

Our findings also illustrate the need for better monitoring and management of heart disease risk in black CKD patients. Further studies should be undertaken to determine the mechanisms underlying these patients' higher rates of cardiovascular-related mortality.

## A Valuable Data Source

There is another important message to be learned from this research. Previous cause-specific mortality research utilized

the Social Security Death Index as the gold standard. Due to changes in health privacy laws, as well as political considerations, that information has not been available since November 2011.

The new standard became the National Death Index, which requires a fee for its information. This severely restricts researchers' ability to access these data.

However, our team learned in the course of its work that the National Death Index gathers its information from all 50 states. Colleagues in Cleveland Clinic's Quantitative Health Sciences group, notably Jesse Schold, PhD, and Susana Arrigain, MA, found that they could access Ohio Death Index information free of charge, and that it provides data on cause-specific deaths.

Our team validated the Ohio Death Index against Cleveland Clinic's electronic medical records and other sources, so we knew it was accurate.

Working with the Ohio Death Index allowed our team to produce this significant manuscript exploring cause-specific deaths from CKD. This is an important lesson, and we encourage other researchers to explore whether their states' death indexes are as accessible as Ohio's.

*Dr. Nally (nallyj@ccf.org; 216.444.8897) is the Director of the Center for Chronic Kidney Disease and a staff member of the Department of Nephrology and Hypertension in the Glickman Urological & Kidney Institute. He is also a staff member of the Transplant Center and a Clinical Professor of Medicine at Cleveland Clinic Lerner College of Medicine.*

## References

1. *Navaneethan SD, Schold JD, Arrigain S, Jolly SE, Nally JV Jr. Cause-Specific Deaths in Non-Dialysis-Dependent CKD.* J Am Soc Nephrol. *2015 Oct;26(10):2512-2520.*
2. *Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization.* N Engl J Med. *2004 Sep 23;351(13):1296-1305.*

# Successful Diagnosis and Management of Urological Symptoms Caused by Pelvic Floor Spasm

*by Daniel Shoskes, MD, MSc, FRCS(C)*

## Key Points

Pelvic floor spasm is a common contributing factor in genital pain and lower urinary tract symptoms experienced by patients with chronic pelvic pain syndrome or interstitial cystitis.

Diagnosis of pelvic floor spasm is relatively simple using a slightly modified digital rectal exam to palpate pelvic floor muscles.

The mainstay of successful treatment is pelvic floor physical therapy consisting of myofascial release, posture improvement and muscle-stretching exercises directed by an experienced, specially trained therapist.

The skeletal muscles of the pelvic floor support and surround the bladder, prostate, vagina and rectum. Much as spasm of neck and shoulder muscles can lead to tension headaches, spasm of the pelvic floor can lead to genital pain and lower urinary tract symptoms (LUTS).

Pain can be felt in the penis, testicles, perineum (sensation of "sitting on a golf ball"), lower abdomen and lower back. Women may experience dyspareunia and men may have post-ejaculatory pain and erectile dysfunction.[1] Indeed, more than 50 percent of men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and patients with interstitial cystitis have pelvic floor spasm on exam, which can be an independent driver of their ongoing symptoms.[2]

The diagnosis is not difficult but does require a slight modification of the usual digital rectal exam.[3] In men, the muscles of the pelvic floor can be palpated anteriorly to either side of the prostate and laterally during the rectal exam. In women, these muscles can be palpated during a vaginal exam.

Pelvic floor spasm is felt as bands of tight muscle, and trigger points are felt as knots of muscle that are often painful on palpation and usually re-create the patient's symptoms. Indeed, we believe a common cause of misdiagnosis of prostatitis comes from pain experienced during the rectal exam that is assumed to be due to the prostate but is actually caused by palpation of extraprostatic muscles.

## Diagnosing with UPOINT

We have developed a phenotyping tool for men and women with either CP/CPPS or interstitial cystitis/painful bladder syndrome (IC) called UPOINT that identifies six clinically diagnosed domains (urinary, psychosocial, organ-specific, infection, neurologic systemic, tenderness of pelvic floor muscles) .[4] Multimodal therapy is then directed at only the positive phenotypes (antibiotics for infection, alpha blockers or antimuscarinics for urinary symptoms, etc.).

We have found that this approach significantly improves or resolves symptoms in 84 percent of men with CP/CPPS.[5] In our clinic, roughly two-thirds of men have pelvic floor spasm,[5] which is higher than the 51 percent found in a multicenter National Institutes of Health-sponsored study.[2] We suspect that we see more men with pelvic floor spasm in a referral practice because so few urologists assess for this problem and men who don't have it end up being successfully treated with other medical therapies.

## Relaxing Muscles with Physical Therapy

The mainstay of treatment for pelvic floor spasm is physical therapy (PT) that consists of myofascial release, posture improvement and muscle-stretching exercises.[6] The goal is to help relax the muscles, not to strengthen them. Therefore, Kegel exercises, which are often inappropriately applied as "generic physical therapy," can make the symptoms worse.

Pelvic floor PT improves symptoms in about 80 percent of cases,[7] although in an underpowered study comparing pelvic PT with conventional Western massage, there was no difference in the CP/CPPS cohort.[8] For patients who have persistent pain and trigger points despite the appropriate PT, trigger point injection of a local anesthetic can be an effective adjunct.[9] We recently have begun to offer patients this option.

Because many of our patients are nonlocal, we sometimes face the challenge of finding a way to provide appropriate PT for their pelvic floor spasm because many therapists are unfamiliar with myofascial release.

## Does Specialized Physical Therapy Help?

To determine whether PT guided by therapists who specialize in pelvic floor spasm actually impacts outcomes, we recently performed a study.[10] We identified patients with pelvic floor spasm from our CPPS registry who were seen more than once between 2010 and 2014. Patient phenotype was assessed with the UPOINT system and symptom severity with the National Institutes of Health Chronic Prostatitis Symptom Index (CPSI).

A 6-point drop in CPSI defined patient improvement. We identified 82 patients who fit the criteria, with mean age of 41.6 years (range 19-75 years) and median symptom duration of 24 months (3-240 months). Mean initial CPSI was 26.8 (10-41), median number of positive UPOINT domains was three (1-6) and 27 (32.9 percent) were local residents.

At follow-up, nine patients had refused pelvic floor PT (PFPT), 24 received PFPT outside our institution and 48 had PFPT from experienced therapists at Cleveland Clinic. Mean change in CPSI was $1.11 \pm 4.1$ for patients who refused PFPT, $-3.46 \pm 6.7$ for those who received outside PFPT and $-11.3 \pm 7.0$ for patients who received PFPT at Cleveland Clinic ($p < 0.0001$). Individual improvement was seen in one (11 percent) PFPT-refusal patient, 10 (42 percent) outside-PFPT patients and 38 (79.2 percent) Cleveland Clinic patients ($p < 0.0001$). Using multivariable analysis, only Cleveland Clinic PFPT (odds ratio [OR] 4.23, $p = 0.002$) and symptom duration (OR 0.52, $p = 0.03$) predicted improvement.

## Summing Up

In conclusion, pelvic floor spasm is a common contributing factor in pain and LUTS experienced by patients diagnosed with CPPS or IC. It is simple to diagnose, and the mainstay of successful treatment is PFPT directed by a therapist well-versed in the condition.

*Dr. Shoskes (shosked@ccf.org; 216.445.4757) is a staff member of the Glickman Urological & Kidney Institute's Department of Urology and of the Transplant Center. He is also a Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

## References

1. *Anderson RU, Wise D, Sawyer T, et al. Sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome: improvement after trigger point release and paradoxical relaxation training.* J Urol. *2006 Oct;176(4 Pt 1):1534-1538.*

2. *Shoskes DA, Berger R, Elmi A, et al. Muscle tenderness in men with chronic prostatitis/chronic pelvic pain syndrome: the chronic prostatitis cohort study.* J Urol. *2008 Feb;179(2):556-560.*

3. *Westesson KE, Shoskes DA. Chronic prostatitis/chronic pelvic pain syndrome and pelvic floor spasm: can we diagnose and treat?* Curr Urol Rep. *2010 Jul;11(4):261-264.*

4. *Shoskes DA, Nickel JC, Rackley RR, et al. Clinical phenotyping in chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: a management strategy for urologic chronic pelvic pain syndromes.* Prostate Cancer Prostatic Dis. *2009;12(2):177-183.*

5. *Shoskes DA, Nickel JC, Kattan MW. Phenotypically directed multimodal therapy for chronic prostatitis/chronic pelvic pain syndrome: a prospective study using UPOINT.* Urology. *2010 Jun;75(6):1249-1253.*

6. *Anderson RU, Sawyer T, Wise D, et al. Painful myofascial trigger points and pain sites in men with chronic prostatitis/chronic pelvic pain syndrome.* J Urol. *2009 Dec;182(6):2753-2758.*

7. *Anderson RU, Wise D, Sawyer T, et al. 6-day intensive treatment protocol for refractory chronic prostatitis/chronic pelvic pain syndrome using myofascial release and paradoxical relaxation training.* J Urol. *2011 Apr;185(4):1294-1299.*

8. *FitzGerald MP, Anderson RU, Potts, J et al. Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes.* J Urol. *2013 Jan;189(1 Suppl):S75-S85.*

9. *Moldwin RM, Fariello JY. Myofascial trigger points of the pelvic floor: associations with urological pain syndromes and treatment strategies including injection therapy.* Curr Urol Rep. *2013 Oct;14(5):409-417.*

10. *Polackwich AS, Li J, Shoskes DA. Patients with Pelvic Floor Muscle Spasm have a Superior Response to Pelvic Floor Physical Therapy at Specialized Centers.* J Urol. *2015 Oct;194(4):1002-1006.*

# Renal Transplantation Is Occurring Later Among Patients with Congenital Urinary Tract Disorders

*by Hadley Wood, MD; David Goldfarb, MD; and Jesse Schold, PhD*

Hadley Wood, MD

David Goldfarb, MD

Jesse Schold, PhD

## Key Points

Congenital urinary tract disorders disproportionately cause chronic kidney disease in children.

A review of more than a decade of renal transplant statistics shows that patients with congenital uropathies and nephropathies trended toward later age at first transplant.

The review also shows equivalent 10-year graft survival between patients with congenital uropathies and those with chronic pediatric kidney disease.

Those trends of later transplantation and improved graft survival may result from improved screening, care and intervention; better transplant donor and recipient selection; and improved post-transplant care and surveillance.

Kidney transplantation remains the gold standard for treating children with end-stage renal disease (ESRD), providing a known survival advantage compared with hemodialysis management.

Congenital disorders, such as anomalies of the upper and lower urinary tract and hereditary nephropathies, are disproportionately responsible for the development of chronic kidney disease (CKD) in children. In the United States, approximately 60 percent of pediatric CKD is attributed to such congenital disorders.

We hypothesized that advancements in the management of patients with congenital urinary tract disorders may slow renal demise and result in delayed renal transplant within these patients. Furthermore, such advances could translate into improved renal transplant graft and patient survival.

## Checking Transplant Recipient Data

To test our hypothesis, we used the Scientific Registry of Transplant Recipients (SRTR) database of transplant statistics collected by the Organ Procurement and Transplantation Network, which is a collection of hospitals and organ procurement organizations across the United States. Since 1987, the SRTR has maintained comprehensive information on all solid organ transplants in the country, and includes current and past information on the full spectrum of transplant activity. Data include information on organ donors, candidates and recipients as well as organ-specific and patient outcomes.

The SRTR was queried to identify first renal transplant and graft and patient survival data within congenital uropathy (CU) and patients with congenital pediatric kidney disease (CPKD) between 1996 and 2012.

Those in the CPKD group were substantially older at age of first transplant than were those with CU, resulting in differences between the two groups in renal transplant donor and recipient variables. On age-matched comparison, most variables were not significantly different between the two groups, including cognitive ability, body mass index and rates of diabetes across all age groups. A notable exception was hypertension. Among those 35 to 49 years old, individuals with CPKD had higher rates of hypertension compared with CU patients (72 percent vs. 81 percent, $p < 0.0001$). Among those 12 to 17 years old, those with CU had higher rates of hypertension compared with CPKD patients (46 percent vs. 40 percent, $p = 0.018$).

## Trend Toward Later Age at First Transplant

The average age of first transplant did not significantly change during the study interval (Figure 1). However, analysis of individual age groups reveals several significant trends (Figures 2 and 3).

When considering graft survival (Figure 4) at five years, both groups demonstrated approximately 90 percent survival; however, at 10-year follow-up, CU patients had better graft survival than did CPKD patients (80.7 percent vs. 75.9 percent, $p < 0.001$). When considering patient survival after renal transplant, the groups again had similar survival at five years (93.2 percent for CU patients vs. 95 percent for CPKD patients, $p > 0.05$). Correspondingly, at 10 years, CU patients had significantly better patient survival than did CPKD pa-

tients (82.3 percent vs 77 percent, $p < 0.001$). When comparing CU and CPKD patients within age groups, however, graft and patient survival differences were not significant.

This study demonstrates that patients with congenital uropathies and nephropathies indeed trended toward later age at first transplant during the 16-year period we examined in the SRTR database. Furthermore, after matching CU and CPKD patients for age, we demonstrated equivalent 10-year graft survival between the two groups.

## What's Behind the Improved Outcomes?

We postulate that these findings can be explained by one or more of the following changes during the study period:

- Improved prenatal screening and care
- Improved early nephrological intervention and care for afflicted patients
- Improved donor and recipient selection
- Improved post-transplant medical care and surveillance

Among patients with CPKD, subsequent management strategies include appropriate hypertension management, hormone supplementation, protein replacement, nutritional supplementation and, when appropriate, medical therapies such as steroid or immunosuppressive agents. Care for patients with CU such as those with posterior urethral valves, prune belly syndrome, congenital neuropathic bladders, obstructive megaureters and significant ureteral reflux includes appropriate use of anticholinergics, intermittent catheterization, antibiotics and appropriate surgical intervention.

*Dr. Wood (woodh@ccf.org; 216.444.2146) is a staff member of the Glickman Urological & Kidney Institute's Center for Genitourinary Reconstruction and an Assistant Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

*Dr. Goldfarb (goldfad@ccf.org; 216.444.8726) is Surgical Director of the Urological & Kidney Institute's Renal Transplantation Program and a staff member of the Department of Urology and of the Center for Ethics, Humanities and Spiritual Care. He is also a Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

*Dr. Schold (scholdj@ccf.org; 216.444.6254) is an assistant staff member in Cleveland Clinic's Department of Quantitative Health Sciences.*

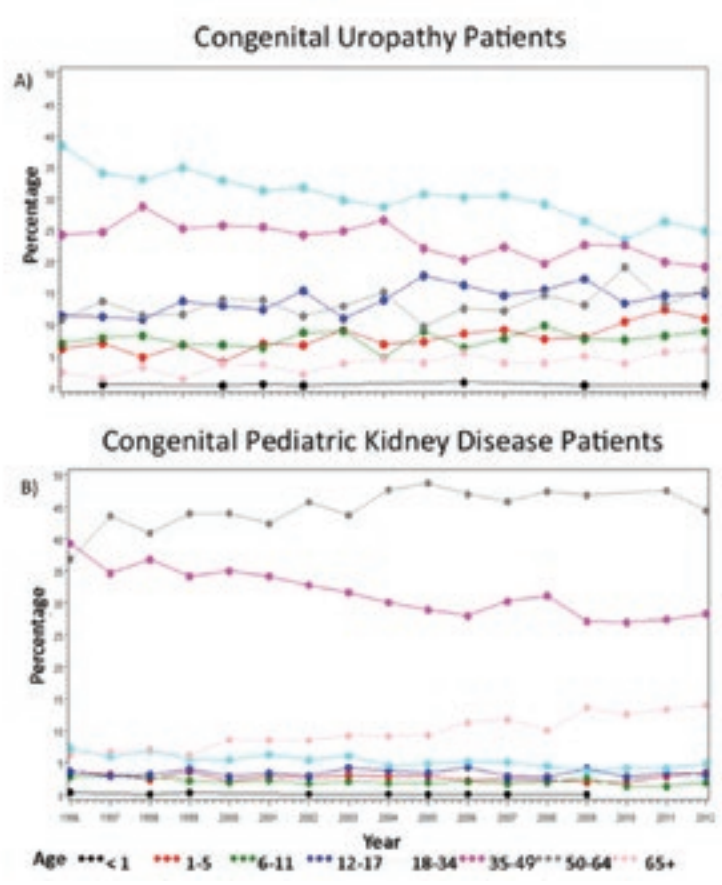



**Figure 1. Age at first renal transplant as a percentage of all renal transplants over time among (A) congenital uropathy and (B) congenital pediatric kidney disease patients.**

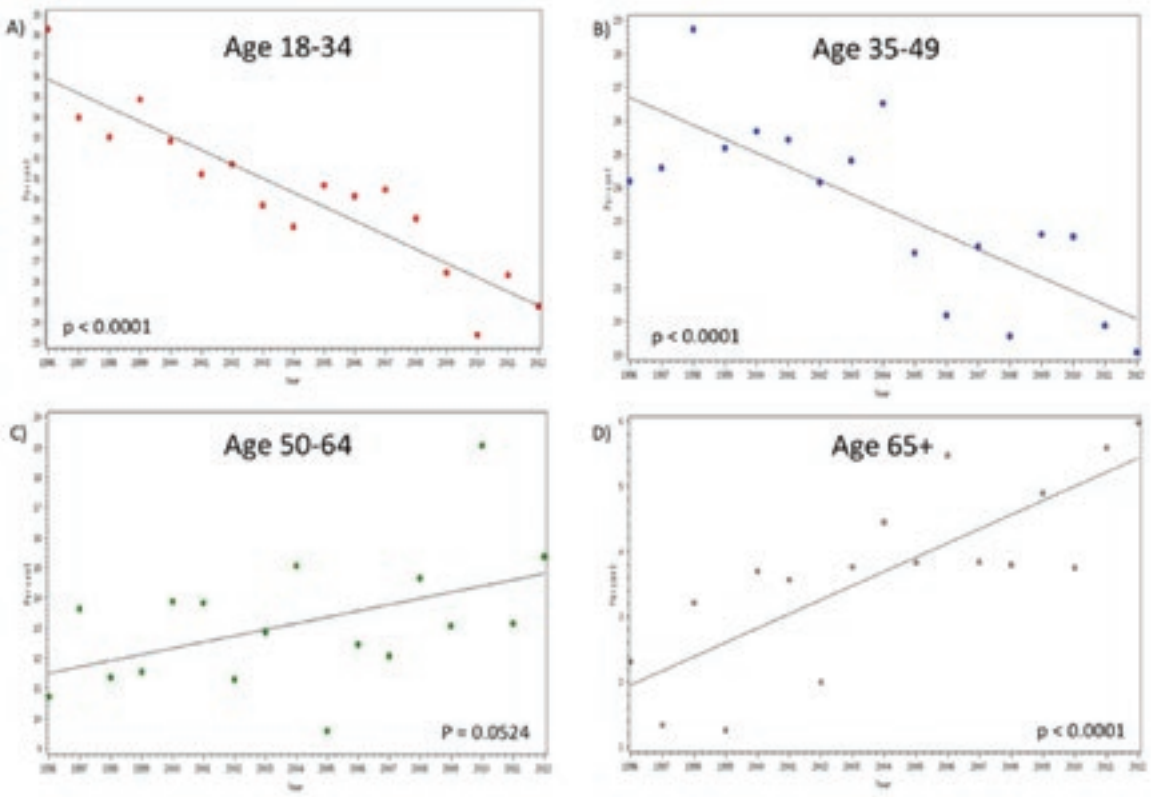



**Figure 2. Percentage of congenital uropathy patients undergoing first renal transplant over time between the ages of (A) 18-34, (B) 35-49, (C) 50-64 and (D) 65+ years.**

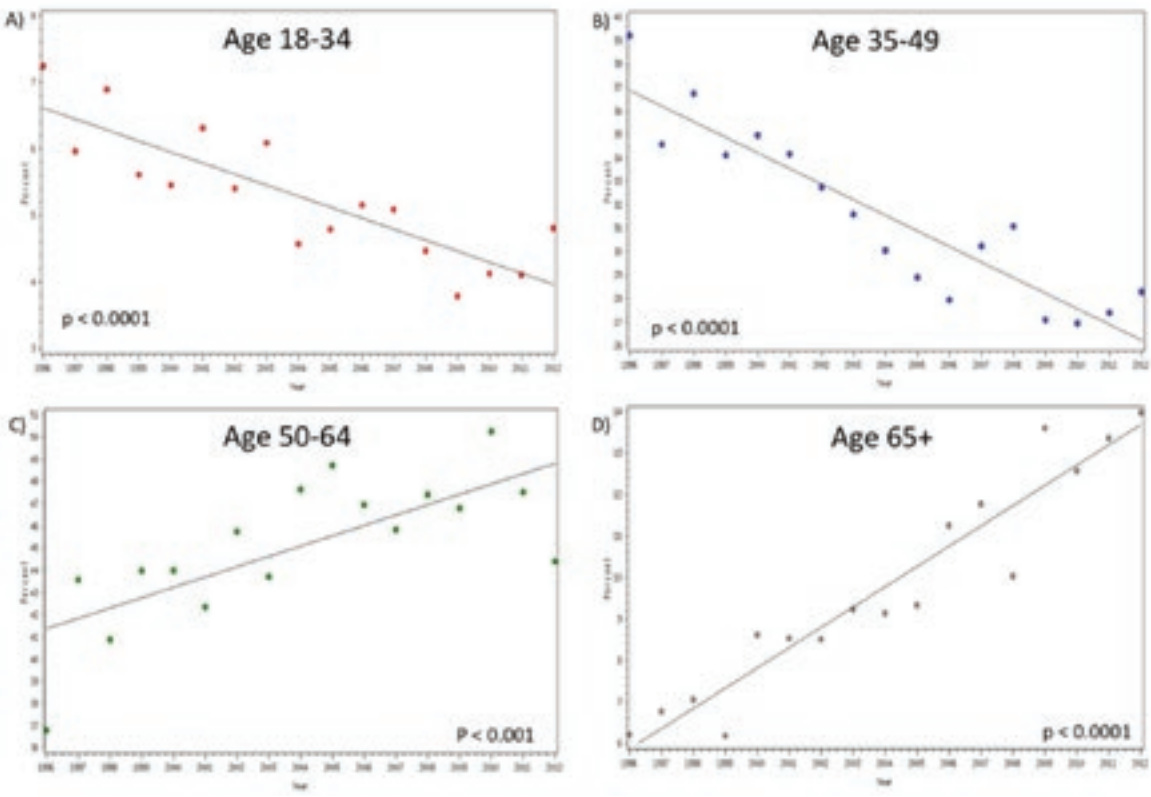



**Figure 3. Percentage of congenital pediatric kidney disease patients undergoing first renal transplant over time between the ages of (A) 18-34, (B) 35-49, (C) 50-64 and (D) 65+ years.**

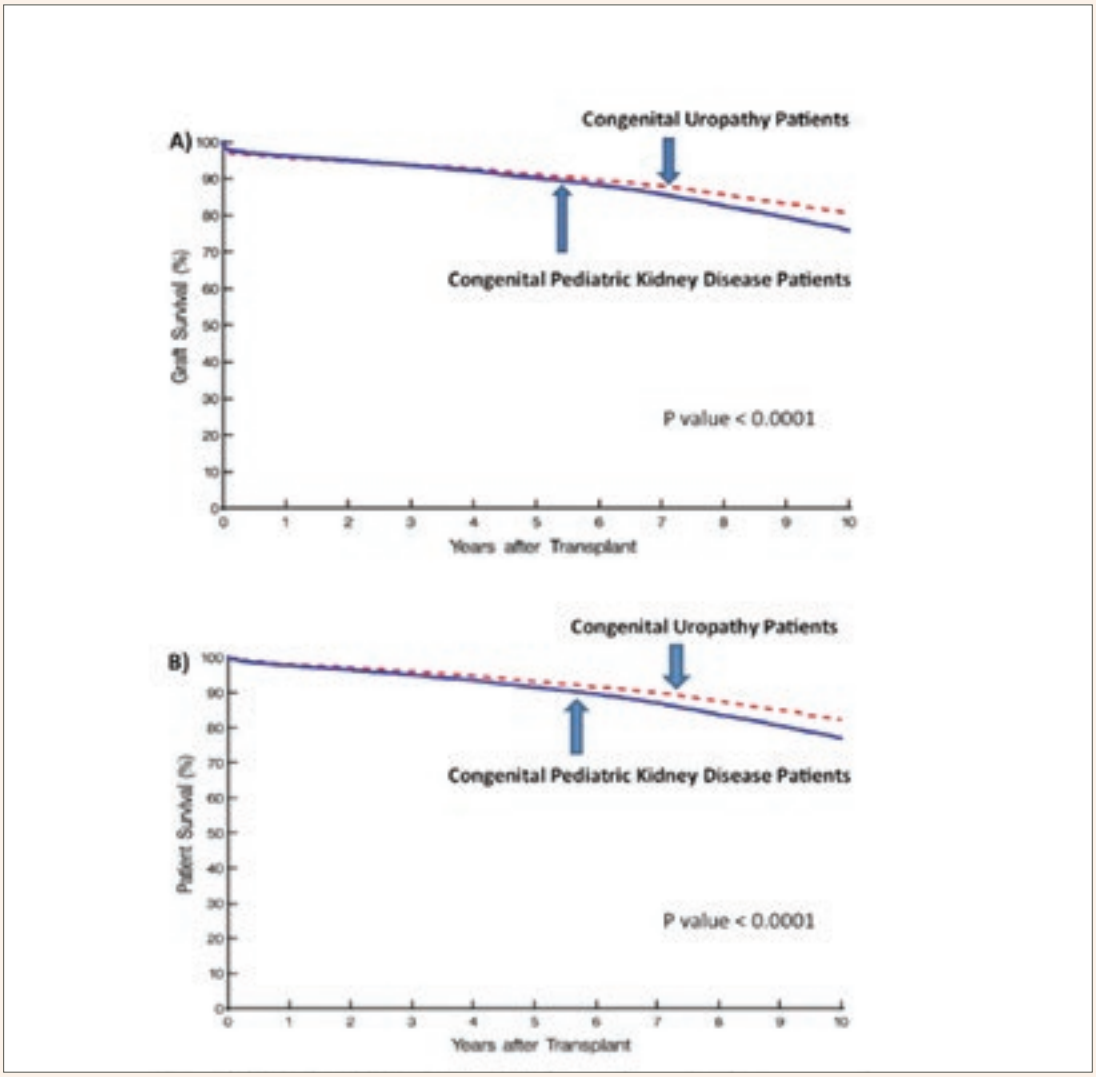



**Figure 4. (A) Graft and (B) patient survival after renal transplant by group over time.**

# Comparative Cost-Effectiveness Analysis of Vasovasostomy Techniques: A Model for Critical Evaluations of Surgical Procedures

*by Edmund Sabanegh Jr., MD*

Edmund Sabanegh Jr., MD

With continued growth in healthcare costs, there is a strong push for providers to look critically at per-case costs to identify opportunities for efficiencies. This is particularly important in the arena of elective procedures, where patients may bear a significant financial burden in the form of high deductible insurance plans, copayments and noncoverage.

One of our areas of focus in Cleveland Clinic's Department of Urology has been to critically analyze our procedural costs, with an eye toward reducing variable costs without compromising the efficacy of the procedure. Our most recent efforts have involved a careful comparative analysis of our costs for reproductive microsurgery.

## Vasectomy Reversal

Vasectomy remains a major contraceptive technique throughout the world, with more than 500,000 vasectomies performed in the United States each year. For couples who desire conception after vasectomy, vasectomy reversal with microsurgical vasovasostomy remains the gold standard in terms of outcomes and safety, with as many as 6 percent of vasectomized men choosing to pursue this approach.

For most patients, these surgeries are expensive and usually not covered by insurance plans. Costs are primarily driven by lengthy microsurgical procedure times and expensive specialized sutures.

Multiple variations in reconstructive approach have been described for vasovasostomy, but the formal two-layer microsurgical technique (Figure 1) remains the gold standard, producing excellent outcomes with respect to patency and pregnancy rates.

Large multicenter trials have shown equal efficacy for a simpler, modified one-layer approach (Figure 2). Because of the greater microsurgical precision, the formal two-layer anastomosis tends to have longer operative times, with requirements for more microsurgical suture (10-0 vs. 9-0) than the modified one-layer repair.

## Affordable Microsurgery — Every Suture Counts

We conducted a comparative cost analysis of 106 patients on whom one of the two different techniques were performed between 2010 and 2015. The two groups were statistically similar in age and time since vasectomy. Specific attention was given to operative times, suture requirements and postoperative outcomes (semen parameters). Cost and surgical outcomes are summarized in Figure 1.

### Key Points

Insurance plans typically do not cover vasovasostomy, meaning patients bear a significant cost and highlighting the need for efficiencies.

Vasovasostomy costs are driven mainly by operative time and the need for specialized sutures.

A modified one-layer vasovasostomy approach is as effective as the standard two-layer approach and requires less operative time and microsurgical suture.

A comparative cost analysis shows the one-layer reconstruction has lower disposable and overall cost than two-layer vasovasostomy, without compromising efficacy.

Modified one-layer microsurgical reconstruction resulted in shorter operative times and lower disposable and overall cost when compared with formal two-layer vasovasostomy. These efficiencies were accomplished without compromising the efficacy of the procedure as defined by semen parameters.

## The Buck Stops Here

Ultimately, our challenge across the medical profession remains to deliver the highest-quality affordable care. Our comparative cost analysis of vasectomy reversal is just one step in our journey to make procedures more available to patients who are shouldering an increasing economic burden in healthcare.

*Dr. Sabanegh (sabanee@ccf.org; 216.445.4473) is Cleveland Clinic's Associate Chief of Staff, Chairman of Glickman Urological & Kidney Institute's Department of Urology and Director of the Center for Male Fertility. He is also a Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

## *Additional Reading*

*Safarinejad M, Lashkari M, Asgari S, Farshi A, Babaei A. Comparison of macroscopic one-layer over number 1 nylon suture vasovasostomy with the standard two-layer microsurgical procedure.* Human Fertil. *2013;16(3):194-199.*

*Sharma V, Le BV, Sheth KR, et al. Vasectomy demographics and postvasectomy desire for future children: results from a contemporary national survey.* Fertil Steril. *2013; 99(7):1880-1885.*

*Nyame Y, Babbar P, Almassi N, Polackwich A, Sabanegh Jr E. Comparative Cost-Effectiveness Analysis of Modified 1-Layer versus Formal 2-Layer Vasovasostomy Technique.* J. Urol. *2015 Sep 24. pii: S0022-5347(15)04802-8. [Epub ahead of print]*

**Figure 1. Comparative cost and surgical outcomes for vasovasostomy techniques.**

| | Median Formal two-layer | Median Modified one-layer | *p* value |
|---|---|---|---|
| **Patient age (yrs)** | 40.0 | 42.5 | 0.46 |
| **Time since vasectomy (yrs)** | 8.0 | 9.5 | 0.47 |
| **Operating room time (min)** | 165 | 120 | 0.006 |
| **Cost** | | | |
| Suture ($) | 632 | 42 | < 0.001 |
| Operating room costs ($) | 2,700 | 1,900 | 0.006 |
| Total variable cost ($) | 3,332 | 1,942 | 0.001 |
| **Sperm concentration (million/cc)** | 18.2 | 21.1 | 0.76 |

**Figure 2. Formal two-layer vasovasostomy.**

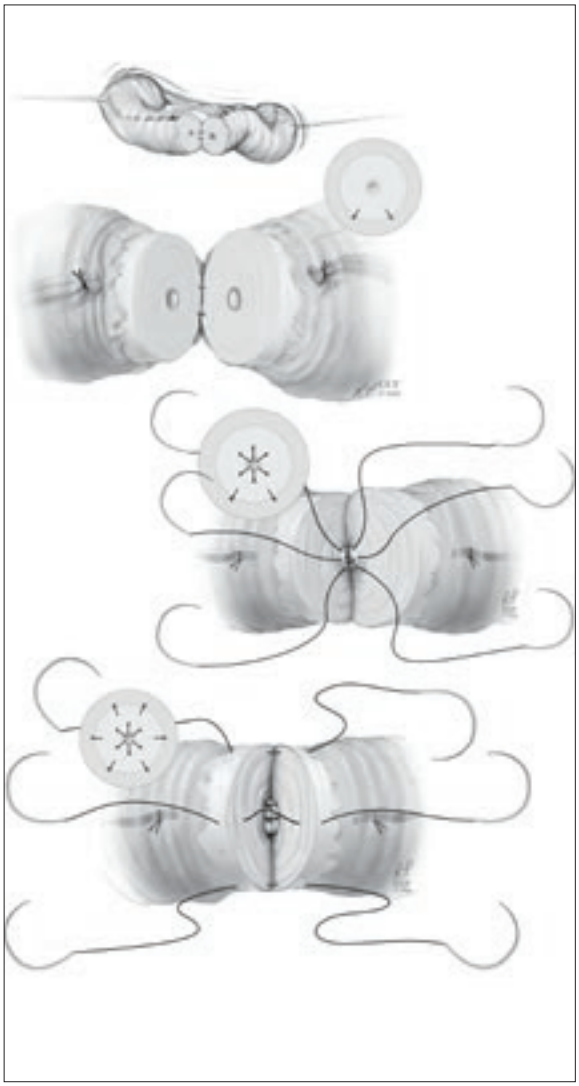
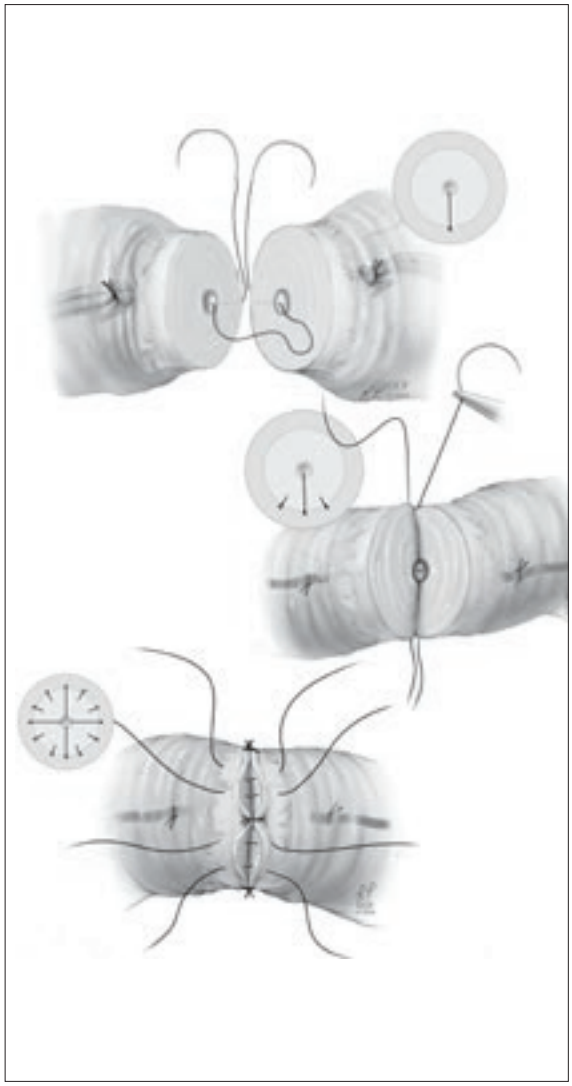


**Figure 3. Modified one-layer vasovasostomy.**



Reprinted with permission from Elsevier from Nyame YA, Babbar P, Almassi N, Polackwich AS, Sabanegh E. Comparative Cost-Effectiveness Analysis Modified 1-Layer versus Formal 2-Layer Vasovasostomy Technique. *Urol*. 2015 Sep 24. pii: S0022-5347(15)04802-4808. [Epub ahead of print.]

# Stone Removal to Thwart Recurrent UTI: A 50-50 Proposition

*by Manoj Monga, MD*

## Key Points

The relationship between asymptomatic nonobstructive renal calculi and urinary tract infection (UTI) is poorly understood, raising challenges for management of patients with recurrent infections.

Cleveland Clinic researchers conducted a retrospective chart review to assess whether surgical removal of nonobstructing asymptomatic stones impacted recurrent UTI.

The review found that only about half of patients with recurrent UTIs and asymptomatic renal calculi are infection-free after stone extraction.

Patients with risk factors for recurrent UTIs after stone extraction should be counseled that stone extraction may not eradicate their infections.

New evidence indicates that kidney stone extraction in patients with recurrent urinary tract infection (UTI) and asymptomatic renal calculi may not render such patients infection-free.

The relationship between asymptomatic nonobstructive renal calculi and UTI is not well-understood. A specific challenge facing urologists is the management of patients with recurrent UTI — defined as three or more infections in a year or two or more in 6 months — who have asymptomatic nonobstructing renal calculi. Stone extraction is often proposed for such patients, with the presumption that the stone acts as a nidus for recurrent infections. No studies to date, however, have examined the effect of surgical stone extraction on recurrent UTI.

## Seeking to Improve Outcomes

Informed consent and informed decision-making require that patients have realistic expectations about the outcomes of possible management options. To assess whether removal of nonobstructing asymptomatic stones has an impact on recurrent UTI, and to identify predictors of patients who may be rendered infection-free by stone extraction, investigators in Cleveland Clinic's Glickman Urological & Kidney Institute performed a retrospective chart review[1] of patients with recurrent UTI who underwent surgical stone extraction and were rendered stone-free with the aim of eradicating the infection.

Evaluation of recurrent UTI included imaging (ultrasound screening followed by computed tomography confirmation) by the patient's referring physician, infectious disease specialist or urologist.

Patients were divided into two groups:

- Those with no evidence of infection recurrence one year after stone removal
- Those with evidence of a recurrence of infection within one year of stone removal

Univariate analysis was performed using the Wilcoxon signed-rank test and Fisher's exact test. A logistic regression was used to test variables during multivariate analysis.

One hundred twenty patients with recurrent urinary tract infections and a nonobstructive renal stone were identified from the chart review. Fifty-eight (48 percent) remained infection-free after surgery, with a mean follow-up of 14 months. Sixty-two (52 percent) had a recurrence of infection, at a mean time from surgery of 12 months.

Choice of surgical management was extracorporeal shock-wave lithotripsy in 32 percent, ureteroscopy in 7 percent and percutaneous nephrolithotomy in 61 percent. There were no significant differences of treatment modality between the two groups ($p = 0.4$).

*Escherichia coli* was the predominant infecting organism in the two groups.

On univariate analysis, there was no significant impact on risk of infection recurrence by age, sex, body mass index, prostate size, steroid use, malignancy, diabetes mellitus,

immunosuppression, stone composition, stone volume, preoperative creatinine level or type of surgery.

## Risk Factors for UTI Recurrence

An increased risk of infection recurrence post-procedure was associated with:

- African-American race (2 percent vs. 22 percent, odds ratio [OR] 13.7, $p = 0.0009$)
- Hypertension (28 percent vs. 52 percent, OR 2.8, $p = 0.007$)
- When stratified by sex, males with type 2 diabetes (7 percent vs. 43 percent, OR 1.73, $p = 0.01$)

Infections consisting solely of *E. coli* were more likely to resolve post-procedure (36 percent vs. 16 percent, OR 0.33, $p = 0.01$).

On multiple logistic regression, African-American race ($p = 0.01$) and hypertension ($p = 0.003$) remained significant predictors of unsuccessful clearance of infection, and *E. coli*-only infection ($p = 0.01$) was a significant predictor of infection clearance.

Among the patients with recurrent UTIs postoperatively, 82 percent had infections with the same preoperative organism, while in 18 percent, there was a change in bacterial species cultured.

## A Need for Patient Counseling

The data demonstrate that only about half of patients with recurrent UTIs and asymptomatic renal calculi may be rendered infection-free after stone extraction.

Patients with risk factors for recurrent infections after stone extraction should be counseled that stone extraction may not eradicate their infections. Although *E. coli* is not a urease-producing organism that causes struvite stones, UTIs with this bacteria may resolve with stone extraction. With this knowledge, patients can make informed decisions about proceeding to surgery or choosing other options to manage their recurrent UTIs.

*Dr. Monga (mongam@ccr.org; 216.445.8678) is Director of the Glickman Urological & Kidney Institute's Stevan B. Streem Center for Endourology and Stone Disease.*

## *Reference*

1. *Omar M, Abdulwahab-Ahmed A, Chaparala H, Monga M. Does Stone Removal Help Patients with Recurrent Urinary Tract Infections?* J Urol. *2015 Oct;194(4):997-1001.*

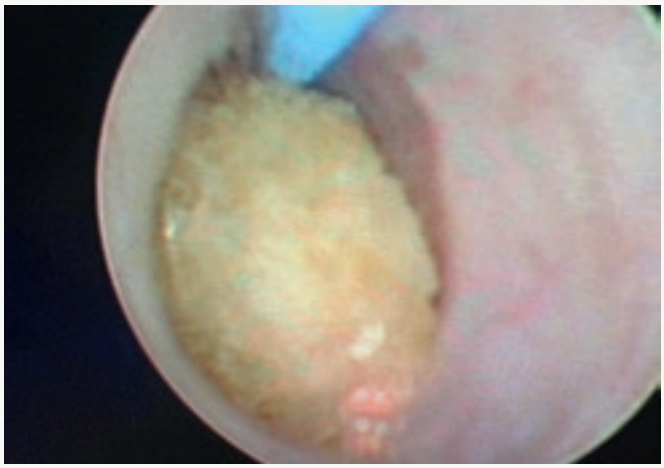


**Figure 1. Laser fragmenting calculus.**

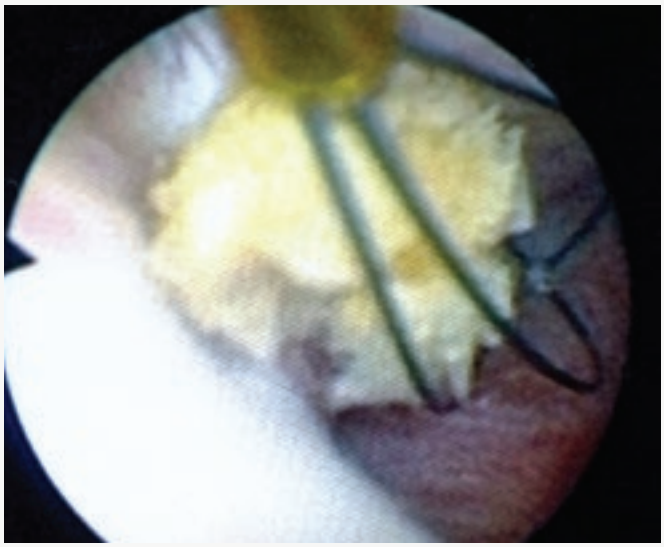


**Figure 2. Basket extraction of stone fragments.**

# Autologous Progenitor Cells for the Treatment of Female Stress Urinary Incontinence *by Courtenay Moore, MD*

Courtenay Moore, MD

Urinary incontinence affects as many as 50 percent of women and can result in significant social and economic burden, with an estimated $19.5 billion spent in 2000 on the treatment of incontinence.[1]

Stress urinary incontinence (SUI), the most common type of incontinence, is defined by the International Continence Society as "the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing," and affects as many as 35 percent of adult women.[2,3]

Current treatment options for SUI include weight loss, pelvic floor physical therapy, incontinence pessaries, bulking agents and slings, all of which aim to restore normal anatomy.

## Testing a Regenerative Approach

Potential alternatives to these restorative therapies are regenerative therapies, which use autologous progenitor cells to regenerate the urinary sphincter.

Two phase 2 clinical studies have shown that autologous muscle-derived stem cells are safe and effective in the treatment of female SUI.[4]

We are currently conducting and enrolling patients in a phase 3, multicenter, double-blind placebo-controlled trial investigating the safety and efficacy of using autologous muscle-derived stem cells for urinary sphincter repair in women with SUI.

Subjects undergo a quadricep femoris muscle biopsy under local anesthesia. The muscle cells are then processed and injected transurethrally into the urinary sphincter. Results will be compared with those of patients who receive a placebo injection. The primary outcome measure is the number of leaks due to stress incontinence episodes occurring during a 12-month period.

To be considered for inclusion, women must be ages 18 years and older with demonstrable SUI on cough stress test, Q-tip angle less than 30 degrees, body mass index less than 35 and no history of neurologic disease.

### Key Points

Stress urinary incontinence (SUI) causes significant social and economic burdens for patients.

Current SUI therapies use various approaches intended to restore normal pelvic anatomy.

Regenerative therapies are a potential alternative, using autologous progenitor cells to regenerate the urinary sphincter.

Cleveland Clinic is participating in a phase 3 multicenter randomized trial to test the safety and efficacy of autologous muscle-derived cells for urinary sphincter repair to treat SUI.

*For more information regarding this study and potential patient enrollment, please contact Andrea Aaby at aabya@ccf.org or 216-444-1152.*

*Dr. Moore (moorec6@ccf.org; 216.444.8043) is a staff member of the Glickman Urological & Kidney Institute's Department of Urology and the Ob/Gyn & Women's Health Institute's Department of Urogynecology. She is also an Associate Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

## References

*1. Hu TW, Wagner TH, Bentkover JD, et al. Costs of urinary incontinence and overactive bladder in the United States: a comparative study.* Urology. *2004;63(3):461-465.*

*2. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society.* Urology. *2003 Jan; 61(1):37-49.*

*3. Luber KM. The definition, prevalence, and risk factors for stress urinary incontinence.* Rev Urol. *2004;6 Suppl 3:S3-S9.*

*4. Peters KM, Dmochowski RR, Carr LK et al. Autologous muscle derived cells for treatment of stress urinary incontinence in women.* J Urol. *2014 Aug;192(2):469-476.*

# Facilitating More Transplants with Kidney Exchanges and Chains

*by Stuart Flechner, MD*

Stuart Flechner, MD

It took 26 hospitals and 2.5 months. But as of March 26, 2015, 35 people received kidneys from 35 donors in the largest kidney transplant chain to date in the United States. Cleveland Clinic surgeons removed or transplanted kidneys for four of the 70 participants.

A member center of the National Kidney Registry (NKR) since 2011, Cleveland Clinic has successfully transplanted 34 kidney recipients (and counting) through an NKR paired exchange or chain.

## Trading for More Compatible Kidneys

The NKR helps those waiting for a transplant swap a kidney from their willing but less compatible donor for a more compatible kidney from another donor. The less compatible kidney is then used to transplant a better matching recipient elsewhere. The exchange is a win for everyone.

Participants most often trade kidneys in pairs. However, occasionally, an altruistic (or nondirected) donor will set off a cascade of transplants, with each recipient required to have a partner donor willing to "pay it forward" by contributing a kidney to the chain.

## Better Matches Mean Better Outcomes

Potential kidney recipients who register with the NKR through a member center have a better chance of finding a compatible donor more quickly. The more precise the HLA antigen match, the more likely the success of the graft.

Better donor-recipient matches have contributed to these improved outcomes reported by the NKR:

- NKR graft survival (98 percent at one year; 93.2 percent at three years) exceeds that of other U.S. living donor transplants (97 percent at one year; 91.7 percent at three years).
- NKR patient survival (99.2 percent at one year; 97.2 percent at three years) exceeds that of other U.S. living donor transplants (98.5 percent at one year; 96.5 percent at three years).

### Key Points

Kidney transplant chains involving multiple paired donors and recipients help overcome compatibility issues and increase the percentage of living donor transplants, which improve success rates and shorten patient waitlist times.

The National Kidney Registry (NKR) facilitates paired exchange transplants.

Cleveland Clinic is a top center for transplants through the NKR and has transplanted dozens of recipients through NKR paired exchanges.

## How Kidney Exchange Works at a Top NKR Center

Cleveland Clinic is one of the top centers for transplants through the NKR, with 10 transplants in 2014 (six already in 2015). We were also one of the most successful centers in 2014, with 100 percent of NKR patients matched and transplanted. That achievement is partly due to careful selection of both donors and recipients who are ready for immediate transplant.

At Cleveland Clinic:

- Our transplant selection committee vets each donor and recipient. We ensure they are well-informed of the process so there are no late dropouts. We keep their transplant evaluations updated at all times.
- We enter medical information for each donor-recipient pair on the NKR website. When matches are made, we thoroughly review the other pair's medical records and exchange blood samples for donor crossmatching.
- All transplants performed in 2014 were ABO compatible, and all recipients had a negative crossmatch with their donor. It's only in extreme situations that we ever accommodate weak incompatibilities.

Through our living donor evaluation process, if we identify someone willing to start a chain by becoming an altruistic donor, we enter them individually on the NKR website. One altruistic donor can trigger from two to more than 30 transplants around the nation. In trade, at the end of the chain, we receive a donor kidney back for one of our patients.

## Paired Exchange: Helping More People

More NKR paired exchanges will increase the percentage of living donor transplants, which have significantly higher success rates than deceased donor transplants. In addition, finding a living donor can shorten a patient's time on the

waitlist. (Average wait time for a deceased donor kidney is currently three to five years.) Receiving a kidney from a living donor also frees deceased donor kidneys for others, making the waitlist move faster.

At Cleveland Clinic, we immediately introduce the NKR paired exchange when evaluating new patients and donors for kidney transplant. Almost any live donor-recipient pair should seek out paired exchange if they are incompatible (or only moderately compatible) but otherwise viable candidates for transplant.

The NKR's paired exchange program helps unlock incompatibilities in other pairs and ultimately helps many patients. It's a community effort. Also, any altruistic donor should consider starting a chain through the NKR in order to help as many patients as possible and expand the impact of his or her gift.

*Dr. Flechner (flechns@ccf.org; 216.445.5772) is a staff member of the Glickman Urological Institute's Department of Urology and of the Transplant Center. He is also a Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

## Renal Transplant Program Achieves Graft-Survival Milestone

*by David Goldfarb, MD*

David Goldfarb, MD

Every six months, the Scientific Registry for Transplant Recipients (SRTR) posts center-specific outcomes for all transplant centers in the United States. The reports are extremely detailed and include comprehensive information regarding each center's transplant candidates, waitlists and transplant outcomes compared with other programs regionally and nationally. One of the reports' most important features is the center's graft and patient survival data.

### Key Points

The Scientific Registry for Transplant Recipients (SRTR) regularly compiles center-specific outcome reports for all U.S. transplant centers.

In the January-June 2015 SRTR report, Cleveland Clinic's kidney transplant program had the best risk-adjusted three-year adult living-donor graft survival of any program in the country for transplants performed between Jan. 1, 2009 and June 30, 2011.

The outcome results from the transplant program's focus on high-quality multidisciplinary care.

While Cleveland Clinic's kidney transplant program consistently performs well in all categories, Figure 1 (see P. 50) highlights a significant achievement from the January-June 2015 SRTR report. The figure is a national center-by-center comparison of adult patient three-year survival with a functioning living-donor graft for renal transplants performed between Jan. 1, 2009, and June 30, 2011.

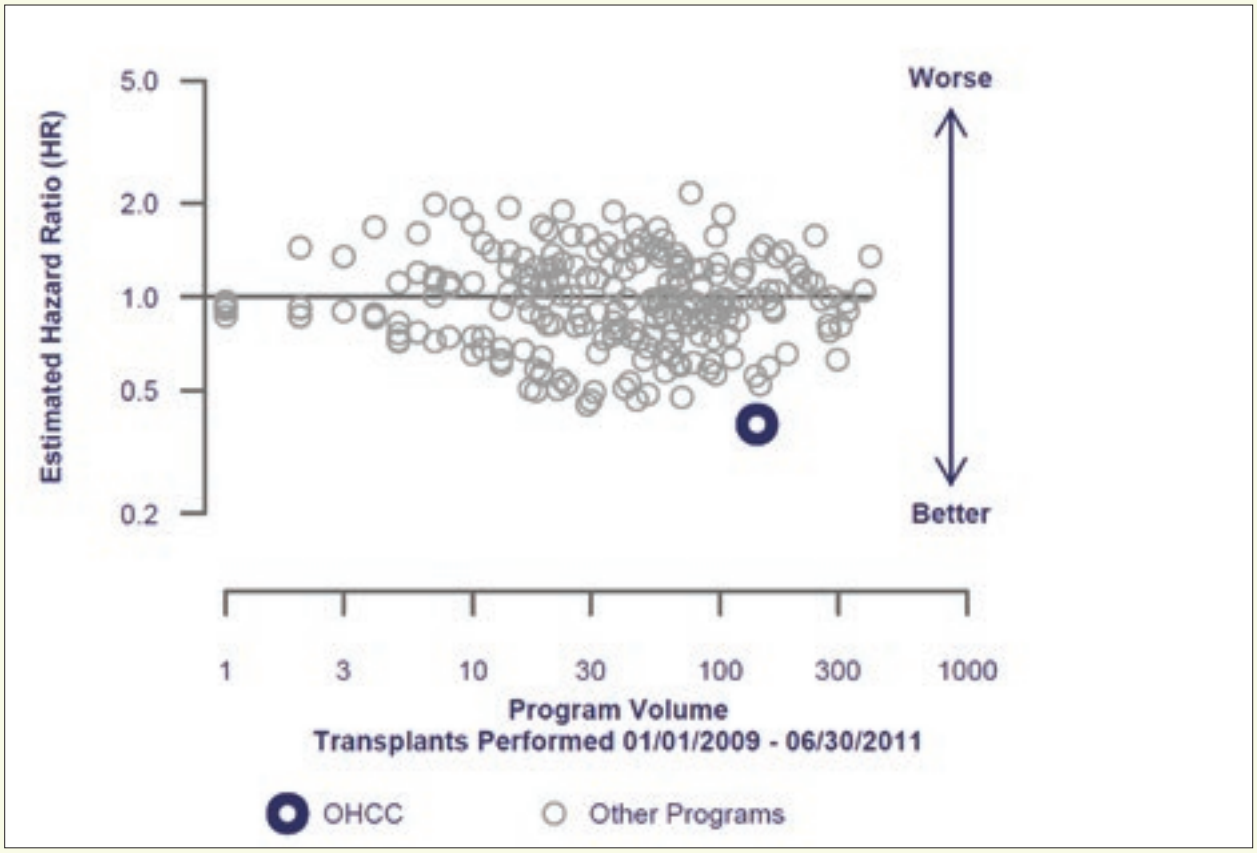
The large open circle at the bottom of the figure represents Cleveland Clinic's hazard ratio for three-year living-donor graft survival. The fact that the hazard ratio is at the far right of the figure indicates that we are one of the larger-volume living-donor kidney transplant programs in the country. The fact that it is the lowest circle on the figure indicates that Cleveland Clinic's kidney transplant program had the best risk-adjusted graft survival of any program in the United States during the reporting period. A lower number here indicates a lower risk for graft loss.

These results are due to our program's emphasis on quality. Important factors for establishing quality include careful attention to donor/recipient evaluation, skilled coordination of multidisciplinary care (physicians, nurse coordinators, social workers, dietitians, pharmacists and administrative personnel), expert surgical services for all procedures and, finally, diligent long-term follow-up of transplant recipients through our dedicated transplant nephrology group.

This accomplishment is the result of dedicated care across the entire team, with the goal of achieving the highest-quality result.

*Dr. Goldfarb (goldfad@ccf.org; 216.444.8726) is the Surgical Director of the Glickman Urological & Kidney Institute's Renal Transplant Program and a staff member of the Department of Urology and of the Center for Ethics, Humanities and Spiritual Care. He is also a Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

**Figure 1. Adult (18+) three-year survival with a functioning living-donor renal graft.**

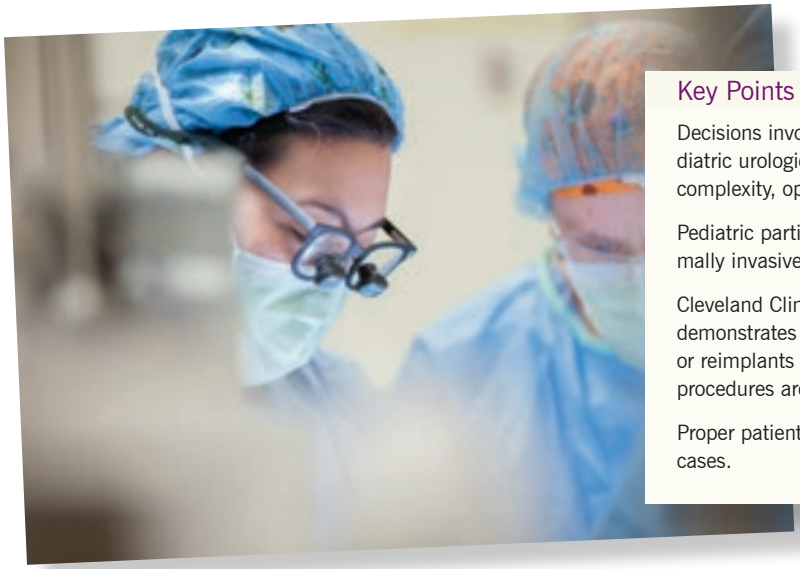



From Scientific Registry of Transplant Recipients January-June 2015 report for Cleveland Clinic, accessed at srtr.org/csr/archives/201412/OHCCTX1KI201412NEW.pdf. OHCC = Cleveland Clinic.

51



# First Robotic Pediatric Partial Nephrectomy Case at Cleveland Clinic Demonstrates Safety in a Properly Selected Patient *by Audrey Rhee, MD*



## Key Points

Decisions involving whether to use a robotic approach in pediatric urologic surgeries require consideration of procedure complexity, operative time, postsurgical recovery and cost.

Pediatric partial nephrectomies are rarely managed minimally invasively.

Cleveland Clinic's first robotic pediatric partial nephrectomy demonstrates that in addition to reconstructive procedures or reimplants in the pediatric population, extirpative robotic procedures are a safe option.

Proper patient selection is vital for successful robot-assisted cases.

The robotic approach in pediatric urologic surgery is constantly under scrutiny. This stems from the fact that many reconstructive procedures can be performed in less operative time using an open approach, with similarly small sum-total incisions. Pediatric patients who undergo open urologic procedures rarely remain hospitalized more than two days postoperatively unless they are older and more muscular. Thus, the patient selection and procedure performed must justify the cost and approach in robotic cases.

Here we review the first pediatric robot-assisted partial nephrectomy performed at Cleveland Clinic. The patient, a 9-year-old female, initially presented with epigastric pain. She was ultimately diagnosed with chronic pancreatitis; however, imaging incidentally revealed a complex left upper pole cystic lesion. This 1.1 x 0.8-cm T1 and T2 hypointense, nonenhancing lesion consistent with a renal cyst was in the superior pole of the left kidney. Septations and calcifications were present.

Notably, the patient had a duplex collecting system on the left kidney; however, this was not associated with a dysplastic upper pole or dilated ureter. Nor did it appear to be consistent with a calyceal diverticulum.

## A Decision to Proceed Robotically

After extensive counseling, we offered the patient's parents the options of watchful waiting or excision of the lesion. Given the complexity of the lesion, the parents were interested in pursuing excision but were not keen on an open approach. Our pediatric urology and minimally invasive teams reviewed the patient's medical imaging and determined that the procedure could be performed robotically.

Retrograde pyelograms confirmed the duplex collecting system and that the upper pole lesion was not merely a dysplastic upper pole. An open-ended ureteral catheter was left in place in the lower pole ureter for identification purposes.

The robot was docked using a 12-mm camera port, 8-mm standard robotic arm ports and a 12-mm assistant port. We carefully defatted the left kidney and dissected the hilum. A laparoscopic ultrasound confirmed our preoperative findings. We applied a bulldog clamp to the renal artery and excised the renal lesion in its entirety. The renorrhaphy was closed in a running horizontal mattress fashion. Total warm ischemia time was 13 minutes.

## A Good Outcome and Lessons Learned

The patient did well after surgery and was discharged the next day with a stable complete blood count. The pathology report confirmed a benign renal cortical cyst.

The patient obtained a follow-up ultrasound that demonstrated a healthy left kidney with no residual lesions. Two years postoperatively, her images are consistently unchanged. Her small abdominal incisions are well-healed and well-concealed.

Heminephrectomies in this pediatric patient population have been reported. However, blood loss is markedly less in a nonfunctioning upper pole than in a potentially vascular and malignant lesion. Partial nephrectomies are less common and few are managed minimally invasively.

This case demonstrates that in addition to reconstructive procedures such as pyeloplasty or reimplants in the pediatric population, extirpative robotic procedures are also a safe

option. Had this child undergone an open approach, her recovery would likely have been much longer, given her age and size. Additionally, her incision would have been much larger.

Proper patient selection is the cornerstone of success in robot-assisted cases.

*Dr. Rhee (rheea@ccf.org; 216.636.9483) is an associate staff member of the Glickman Urological & Kidney Institute's Department of Urology and of the Center for Pediatric Urology at Cleveland Clinic Children's.*

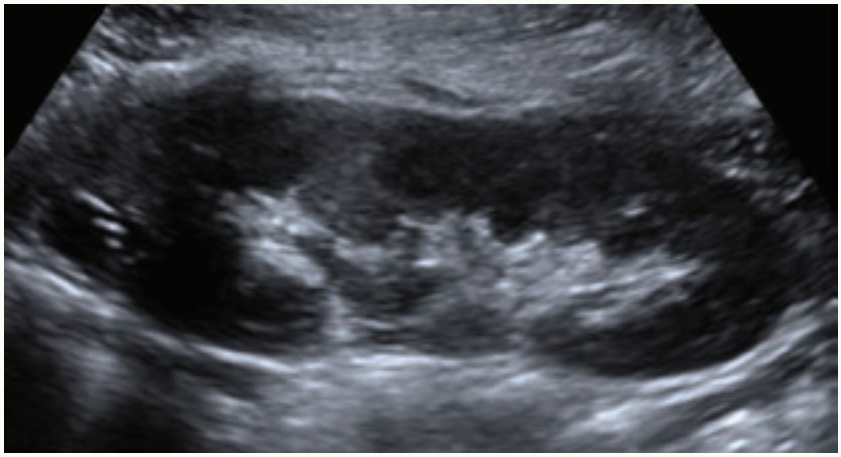
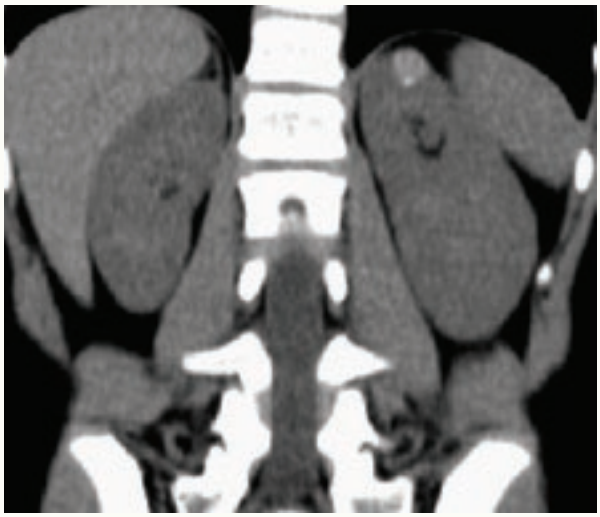
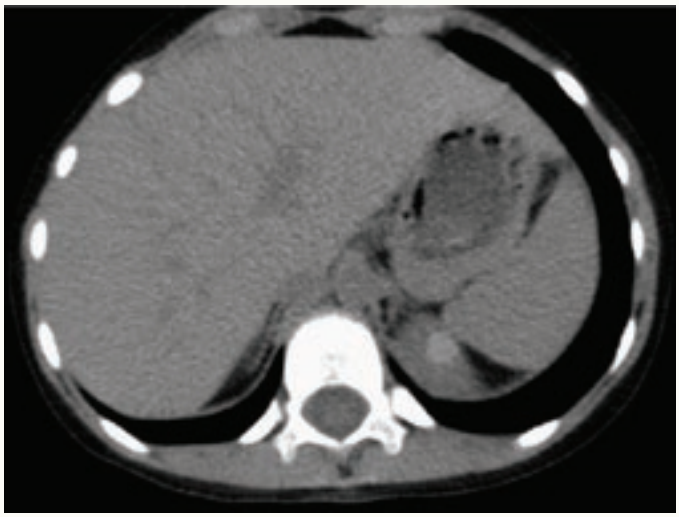


**Figure 1. Preoperative ultrasound of the left kidney, sagittal view, showing a 1.6 x 1.1 x 0.9-cm cystic lesion in the upper pole. There is increased echogenicity within the periphery that may reflect calcifications.**





**Figures 2 and 3. Preoperative CT scan images, axial and coronal views, showing a 9 x 9 x 12-mm hyperdense (80 HU) round endophytic lesion in the upper pole of the left kidney, with a 3-mm peripheral calcification inferiorly. No layering fluid levels are seen within the lesion.**

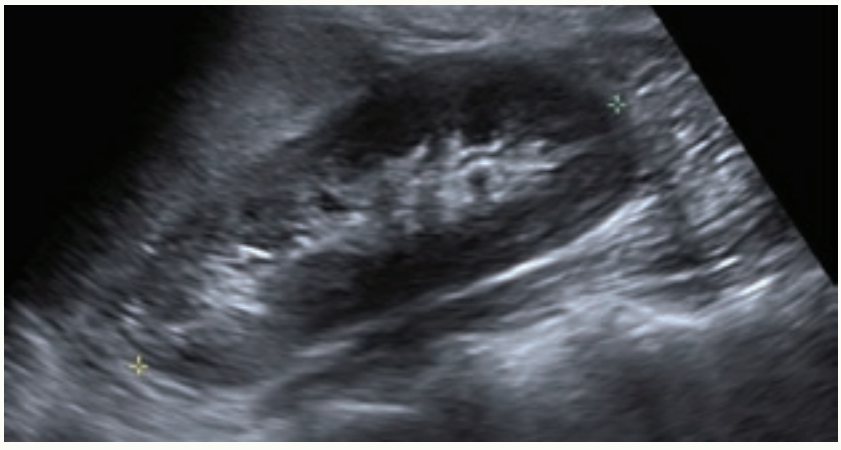


**Figure 4. Ultrasound of left kidney, sagittal view, two years postoperatively. Previously noted cystic lesion is not seen at the superior pole, and there is no evidence of hydronephrosis.**

## Resources for Physicians

### Physician Directory

**clevelandclinic.org/staff**

### Same-Day Appointments

To help your patients get the care they need, right away, have them call our same-day appointment line, **216.444.CARE (2273)** or **800.223.CARE (2273)**.

### Track Your Patients' Care Online

Establish a secure online Dr**Connect** account at **clevelandclinic.org/drconnect** for real-time information about your patients' treatment.

### Critical Care Transport Worldwide

To arrange for a critical care transfer, call **216.448.7000** or **866.547.1467**. **clevelandclinic.org/criticalcaretransport.**

### Outcomes Data

View Outcomes books at **clevelandclinic.org/outcomes.**

### CME Opportunities

Visit **ccfcme.org** for convenient learning opportunities from Cleveland Clinic's Center for Continuing Education.

### Executive Education

Learn about our Executive Visitors' Program and two-week Samson Global Leadership Academy immersion program at **clevelandclinic.org/executiveeducation**.

### About Cleveland Clinic

*Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,200 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 90 northern Ohio outpatient locations (including 18 full-service family health centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.*

*In 2015, Cleveland Clinic was ranked one of America's top five hospitals in* U.S. News & World Report's *"Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 10 hospitals in 13 specialty areas, and the top hospital in heart care (for the 21st consecutive year).*

## 24/7 Referrals

### Referring Physician Center and Hotline

**855.REFER.123 (855.733.3712)**

clevelandclinic.org/refer123

Live help connecting with our specialists, scheduling and confirming appointments, and resolving service-related issues.

### Physician Referral App

Download today at the App Store or Google Play.

## Stay Connected with Cleveland Clinic's Glickman Urological & Kidney Institute

### Consult QD — Urology and Nephrology

A blog featuring insights and perspectives from Cleveland Clinic experts. Visit today and join the conversation. **ConsultQD.clevelandclinic.org/urology-nephrology**

Facebook for Medical Professionals
**Facebook.com/CMEClevelandClinic**

Follow us on Twitter
**@CleClinicMD**

Connect with us on LinkedIn
**clevelandclinic.org/MDlinkedin**

On the Web at **clevelandclinic.org/Glickman**

*Urology & Kidney Disease News*
Vol. 25 / Winter 2016

*Urology & Kidney Disease News* is a publication of Cleveland Clinic's Glickman Urological & Kidney Institute.

*Urology & Kidney Disease News* is written for physicians and should be relied on for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

Cleveland Clinic's Urology and Nephrology Programs Are Ranked No. 2 in the U.S. — *U.S. NEWS & WORLD REPORT*



clevelandclinic.org/UKDNews

Cleveland Clinic

**Every life deserves world class care.**

9500 Euclid Ave., Cleveland, OH 44195

Cleveland Clinic is a nonprofit, multispecialty academic medical center integrating clinical and hospital care with research and education for better patient care. More than 3,200 staff physicians and researchers in 120 medical specialties provide services through 27 patient-centered institutes. Cleveland Clinic's health system comprises a main campus, eight regional hospitals and more than 90 outpatient locations, with 18 family health centers in northern Ohio, and medical facilities in Florida, Nevada, Toronto and Abu Dhabi. Cleveland Clinic is consistently ranked among the top five hospitals in America (*U.S. News & World Report*).
*clevelandclinic.org*



15-URL-045