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On the cover and above: Construction is under way on the Glickman Tower, the future home of the Glickman Urological and Kidney Institute. The newly formed institute includes the departments of Urology, Regional Urology, and Nephrology and Hypertension.
On April 16, 2007, the Cleveland Clinic Board of Governors approved the establishment of a new multidisciplinary institute, termed the Glickman Urological and Kidney Institute. Our administration is moving toward a new paradigm in which clinical areas are organized around organ and disease systems, rather than individual specialties, with the aim of enhancing both patient care and academic collaboration. The Glickman Urological and Kidney Institute is the second institute to be created around this new model and represents a coalescence of urologists, kidney and pancreatic transplant surgeons, nephrologists, hypertension specialists, dialysis physicians and scientists working in these areas. I am delighted to have been appointed as Chairman of this new institute, which will further enable us to enhance the practice and science of medicine in these related disciplines, not only at the main Cleveland Clinic campus but throughout our entire hospital system.

The new institute will be housed in the Glickman Tower, which is currently under construction. This 10-story facility will be the tallest building on the Cleveland Clinic campus and will comprise more than 200,000 square feet of space. The tower is scheduled for completion in October 2008.

Where the urology program at Cleveland Clinic is concerned, our paramount objective remains to provide the highest quality of care for adult and pediatric patients with routine or complex urological disorders. Our activities comprise a unique combination of high-volume and challenging clinical material, extensive clinical scientific activities, and credible laboratory research within an environment that is nurturing the future leaders of our specialty. Our professional staff of 69 urologic physicians and scientists offers expertise in every urologic subspecialty area and comprises the largest full-time urology faculty in the United States.

The demand for clinical services offered by our urology program continues to increase, reflecting the strong regional and national reputation of our physician staff. During 2006, we performed more than 16,000 operations and recorded more than 90,000 outpatient visits. During the past 18 months 12 new faculty members were recruited to join our urology program. These include Andrew Stephenson, M.D. (urologic oncology), Ed Sabanegh, M.D. (male infertility), Courtenay Moore, M.D. (female urology), Jeffrey Palmer, M.D. (pediatric urology), Sawsan Alkass, M.D. (female urology), John Rabets, M.D. (renal and pancreas transplantation), Michael Gong, M.D. (urologic oncology), Khaled Fareed, M.D. (general urology), Gaurang Shah, M.D. (general urology), Robert Stein, M.D. (laparoscopic surgery), Nivedita Dhar, M.D. (urologic oncology) and Kamrooz Sanii, M.D. (general urology).

In August 2006, the World Congress of Endourology meeting was held at Cleveland Clinic under the direction of Inderbir Gill, M.D., who served as the Congress President. This meeting attracted 1,700 urologists from around the world and was the largest medical meeting ever held at Cleveland Clinic; 300 of these urologic attendees remained with us at Cleveland Clinic for an additional week of academic activities following completion of the Congress.

Our faculty members share a passion for discovery and a deep commitment to providing the best possible clinical and investigative training for our residents and post graduate fellows. During 2006, our faculty contributed 244 scientific publications to peer-reviewed medical journals. There are currently 100 ongoing prospective clinical research studies and 43 ongoing laboratory research projects. We are supporting our academic mission through all available funding sources, including peer-reviewed grants, philanthropy and industry. Urology faculty members currently serve as principle investigators of NIH or NCI grants totaling more than $22 million.

The programmatic development of our urology program remains a collaborative effort between our subspeciality-based, academically oriented faculty and high-quality community general urologists. In addition to our main campus activities, our faculty members now provide medical and surgical care at 18 satellite locations in Northeast Ohio. Going forward, the Glickman Urological and Kidney Institute will house two separate urology departments, a Department of Urology comprising main campus faculty and a Department of Regional Urology comprising faculty who are predominantly based in outreach locations. Search committees have been formed to identify a chairman for each of these new departments.

This is indeed an exciting time for the faculty and trainees of our urology program and the entire Glickman Urological and Kidney Institute. We are proud of our past, energized by our ongoing activities and passionate about our future. We are pleased to share current activities with our colleagues and friends in this issue of Urology News.

Andrew C. Novick, M.D.
PSA dogma centered on a “normal” threshold of 4.0 ng/mL during the first decade following its approval for prostate cancer screening. Healthy patients above this cutoff were believed to be at risk for prostate cancer and usually were recommended to undergo biopsy. Patients with levels below this cutoff were reported to have normal readings and were reassured that they had no prostate cancer and that follow-up in a year or more was appropriate.

However, many centers began to recognize that the relatively empiric cutoff of this newly discovered protein had the substance of the emperor’s proverbial new clothes. Even in the early 1990s, it was often quoted that up to one-fourth of men with prostate cancer had a “normal” PSA, and it was even more widely accepted that the majority of men with PSA in the range of 4.0-10.0 ng/mL did not have cancer identified if biopsy was performed. Thus, those men with cancer below the cutoff seemed inaccurately categorized as having normal values, and those above the cutoff were mischaracterized as having abnormal values. The egregious example of classifying one man with a PSA of 3.9 as normal while another with a PSA of 4.1 was deemed abnormal was ill-conceived at best. Their risk of a biopsy identifying cancer is identical.

Recognizing this cutoff myth, we are moving forward with colleagues in Pathology and Laboratory Medicine to eliminate this—or any—artificial cutoff defining a “normal” PSA value. Relying on amassing data and referencing key series, the following verbiage is planned to accompany all PSA reports, listing no “normal range”:

Published data from the Prostate Cancer Prevention Trial demonstrated that there is no PSA level below which the risk of having prostate cancer is zero. For an individual patient, the significance of a PSA level should be interpreted in a broad clinical context, including age, race, family history, digital rectal exam, prostate size, results of prior prostate biopsy, and use of 5 alpha reductase inhibitors. Considering the high incidence of asymptomatic cancer in the general population that may not pose an ultimate risk to the patient, the decision to recommend urological evaluation or prostate biopsy should be individualized after considering all of these factors.

The risk that a patient will have prostate cancer detected if a biopsy is performed at various levels of PSA is listed in the table below:

<table>
<thead>
<tr>
<th>PSA Range</th>
<th>Relative Risk for Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.0 ng/mL</td>
<td>8.8%*</td>
</tr>
<tr>
<td>1.1-2.0 ng/mL</td>
<td>17%*</td>
</tr>
<tr>
<td>2.1-3.0 ng/mL</td>
<td>23.9%*</td>
</tr>
<tr>
<td>3.1-4.0 ng/mL</td>
<td>26.9%*</td>
</tr>
<tr>
<td>&gt;4 ng/mL</td>
<td>45.5%**</td>
</tr>
</tbody>
</table>


This change is long overdue and will require substantial education of both primary care physicians and patients. It will be made clear that there is no PSA level at which a biopsy is mandated. The decision to consider biopsy should entail an understanding of the baseline risk of finding significant cancer compared to the known risk of finding cancer if performing biopsy with disregard to PSA level. In addition, some tumors present minimal risk to the patient, so biopsy risks identifying cancer in some patients who would have been better off without knowing these low-risk tumors existed.

We anticipate concern that changing the reporting of PSA to reflect prostate cancer risk instead of an artificial cutoff may increase PSA anxiety and the number of prostate biopsies. That is clearly not the intent of this initiative. Rather, the intent is to accurately report PSA values with a meaningful interpretation of their implication instead of reporting an artificial—relatively meaningless—cutoff. Interpreting PSA in the context of all the above factors will help advance the understanding and management of prostate cancer risk and diagnosis.
Andrew C. Novick, M.D., Awarded Barringer Medal for Outstanding Achievement

Andrew C. Novick, M.D., Chairman of Cleveland Clinic’s Glickman Urological and Kidney Institute, was awarded the Barringer Medal for outstanding achievement at the annual meeting of the American Association of Genitourinary Surgeons (AAGUS) in Scottsdale, Ariz.

AAGUS is an association of leading academic urologists from the United States, Canada and around the world, which is dedicated to the study of diseases of the genitourinary system. The Barringer Medal is awarded only periodically and represents one of the highest honors that can be bestowed in the specialty of urology. Dr. Novick is the first Cleveland Clinic urologist ever to receive this award.

“I am honored to have been chosen as a recipient of the Barringer Medal,” Dr. Novick says. “It is always gratifying when one’s work and achievements are recognized by peers whose dedication to the field of urology I also deeply respect.”

David M. Barrett, M.D., Senior Councilor for AAGUS, says “Dr. Novick is clearly a candidate for the Barringer Medal. He is one of the most prominent, distinguished urologists in the country today and is reflective of the quality of individuals who are members of the American Association of Genitourinary Surgeons.”

Staff Grants, Awards and Appointments

Robert Fairchild, Ph.D., was awarded $1.9 million over 5 years for “Acute Humoral Rejection of Renal Allografts.” Funded by the National Institute of Allergy and Infectious Diseases/NIH.

Eric Klein, M.D., has been appointed Editor-in-Chief of UROLOGY®.

Firouz Daneshgari, M.D., was awarded the 2007 Zimskind Award from the Society of Urodynamics and Female Urology.


Resident and Fellow Awards

Hadley Wood, M.D., received the 2007 Elisabeth Pickett Research Award from the Society of Women in Urology.

Una J. Lee, M.D., won a travel award to the Society for Urodynamics and Female Urology (SUFU). Dr. Lee also won a basic science poster award from the SUFU.

Una J. Lee, M.D., also received 2nd prize for the Resident Research Presentations at the 2007 Ohio Urological Society Meeting in March 2007.

Ryan C. Hedgepeth, M.D., won the Bruce Hubbard Stewart Memorial Award for Humanistic Medicine.

Brian R. Lane, M.D., Ph.D., received the George and Grace Crile Traveling Fellowship Award.

Inderbir S. Gill, M.D., Jihad Kaouk, M.D., Mihir M. Desai, M.D., and their team won 3 of the 5 outstanding paper awards at the 22nd Annual Meeting of the Engineering and Urology Society, May 2007:

- **Flexible robotic retrograde renoscopy.** M. Desai, M. Aron, I. Gill, G.P. Haber, O. Ukimura, J. Kaouk, G. Stahler, F. Barbagli, C. Carlson, F. Moll
- **KTP laser robotic nerve-sparing radical prostatectomy.** T. Gianduzzo, J. Kaouk, J. Colombo Jr., G.P. Haber, C. Magi-Galluzzi, J. Hafron, M. Aron, I. Gill
- **Percutaneous cryoablation of kidney lesions under combined real-time ultrasound and 3-D CT scan navigation.** G. P. Haber, O. Ukimura, J. Colombo Jr., Y. Lin, P. Koenig, T. Gianduzzo, M. Aron, C. Magi-Galluzzi, I. Gill, J. Kaouk

New Staff

The Glickman Urological and Kidney Institute welcomes the following new staff members:

Nivedita Dhar, M.D., a specialist in urologic oncology, bladder cancer and urinary diversion and general urology, received her medical degree from St. Louis University School of Medicine in Missouri. Dr. Dhar completed her fellowship at the University of Bern Faculty of Medicine in Switzerland. She completed her internship at State University of New York at Buffalo Affiliated Hospitals, where she was also a resident. Dr. Dhar also underwent residency training at Cleveland Clinic.

Kahled Fareed, M.D., a specialist in urologic oncology and general urology, received his medical degree from Assiut University School of Medicine in Egypt, where he also completed a urology residency. Dr. Fareed conducted postdoctoral research in prostate disease and molecular biology before completing residencies in general surgery and urology at the University of Texas Southwestern Medical Center in Dallas.

Michael Gong, M.D., a laparoscopic urologic oncologist, received his medical degree from the University of Chicago, along with a doctorate in molecular genetics and cell biology. He completed his residency at Stanford University Hospitals and his fellowship in urologic oncology at Memorial Sloan-Kettering Cancer Center. Prior to joining Cleveland Clinic Dr. Gong practiced at The Ohio State University Medical Center and Memorial Sloan Kettering.

John Rabets, M.D., a specialist in kidney transplant, renal oncology and general urology, received his medical degree from the University of Pennsylvania School of Medicine in Philadelphia. He completed his internship and residency at Cleveland Clinic. Dr. Rabets recently completed a fellowship in the Division of Transplantation at the University of Maryland Medical Center in Baltimore.

Online Access to Your Patient’s Treatment Progress

Whether you are referring from near or far, our eCleveland Clinic service, DrConnect, can streamline communication from Cleveland Clinic physicians to your office. This new online tool offers you secure access to your patient’s treatment progress at Cleveland Clinic. With one-click convenience, you can track your patient’s care using the secure DrConnect Web site. To establish a DrConnect account, visit eclevelandclinic.org or e-mail drconnect@ccf.org.

Outcomes Data Available

The latest edition of outcomes data from the Cleveland Clinic Glickman Urological and Kidney Institute is available. Our outcomes booklet also offers summary reviews of medical and surgical trends and approaches. Charts, graphs and data illustrate the scope and volume of procedures performed each year. To view outcomes booklets for the Cleveland Clinic Glickman Urological and Kidney Institute as well as many other Cleveland Clinic medical and surgical disciplines, visit clevelandclinic.org/quality.
Donation Expands Robotics Program

Hunter Douglas donated $1 million in support of the Center for Advanced Robotic and Image-Guided Surgery, which is housed in the Glickman Urological and Kidney Institute. The donation will advance the research, education and innovations of robotic and image-guided surgery at Cleveland Clinic.

Kamrooz Sanii, M.D., received his medical degree from Shiraz University Faculty of Medicine in Iran. He completed his internship at State University of New York Health Science Center in Brooklyn and his residency at the University of Pittsburgh Medical Center.

Gaurang Shah, M.D., received his medical degree from Gujarat University in India. He completed a residency in urology at the State University of New York Upstate Medical University in Syracuse.

Dr. Shah completed fellowships at the Royal College of Surgeons of Edinburgh and Glasgow, Scotland. He also served as a visiting fellow at Wayne State University in Detroit and as a clinical fellow at New York University Medical Center.

Robert Stein, M.D., is a specialist in laparoscopic surgery. He earned his medical degree from the University of Pennsylvania School of Medicine in Philadelphia and completed residencies in general surgery and urology at the University of Pittsburgh.

Dr. Stein recently completed a fellowship in advanced laparoscopy and endourology at Cleveland Clinic.

Cleveland Clinic Excels in Latest U.S. News Rankings

Urology ranked No. 2 in the nation; kidney disease ranked No. 5

The Cleveland Clinic Glickman Urological and Kidney Institute's urology program was ranked among the top 2 urology programs in the United States for the 8th consecutive year by U.S. News & World Report. The institute’s kidney disease program ranked 5th in the nation.

The 2007 “America’s Best Hospitals” survey recognized Cleveland Clinic as one of the nation’s best hospitals overall, ranking the hospital as No. 4 in the country. Cleveland Clinic ranked in all 16 specialties surveyed by the magazine. Twelve of its specialties were listed among the top 10 in the United States. All Cleveland Clinic specialties placed in the nation’s top 20.

For details, visit clevelandclinic.org.
Upcoming Preceptorships

**October 22-23, 2007**

3rd Annual National Urology Resident Preceptorship in Reconstructive Urologic Surgery

Directors: Kenneth Angermeier, M.D., Drogo Montague, M.D., and Jonathan Ross, M.D.

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

Please check our Web site for more details on these programs as they become available: clevelandclinic.org/urology

**April 28-30, 2008**

7th Annual National Urology Resident Preceptorship Program in Female Pelvic and Reconstructive Surgery

Director: Firouz Daneshgari, M.D.

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

**Fall 2008**

National Urology Preceptorship

Director: Jeffrey S. Palmer, M.D., F.A.A.P., F.A.C.S.

This program is designed for general urologists, pediatric urologists, urologists-in-training and allied healthcare professionals who are involved with the care of children with urologic conditions.

Upcoming Conferences

**September 13-14, 2007**

Uro-Oncology Mini Symposium

Director: Amr Fergany, M.D.

Global Patient Services
3rd Floor, Intercontinental Hotel and Bank of America Conference Center

This mini-symposium will provide lectures, live surgeries and interactive presentations.

**September 28, 2007**

Reproductive Medicine Symposium

Director: Edmund Sabanegh, M.D.

Cleveland Clinic Lerner Research Institute
NA5-087 Amphitheater

This course will provide an update on the most current, state-of-the-art diagnostic and treatment options for the management of infertility. The lectures will focus on a multidisciplinary approach to both male and female factor management.

**October 12, 2007**

Practical Considerations in GU Prosthetic Surgery

Directors: Drogo K. Montague, M.D., and Kenneth Angermeier, M.D.

Glickman Urological and Kidney Institute
Bruce H. Stewart Conference Room – A100

This one-day course targeted to practicing urologists will feature lectures and live video transmission from the OR of artificial urinary sphincter and inflatable penile prosthesis cases.

This course is by invitation and will hold 15 participants.

**March 13-15, 2008**

Ambulatory Urology Symposium

Director: J. Stephen Jones, M.D., F.A.C.S.

This course is intended to update urologists on ambulatory urology from both a practical and medical standpoint. The focus will be to target the two-track system that urology continues to develop and focus on.
PSA-Induced Pathological Stage Migration is Slowing

Eric A. Klein, M.D.*

Will Rogers once observed that when the Okies moved from Oklahoma to California in the 1930s the average IQ of both states simultaneously went up. This effect, known as the “Will Rogers Phenomenon,” suggests that some gains in the effectiveness of anticancer therapies over the last several decades actually result from diagnosing the disease at an earlier stage rather than an increase in the effectiveness of curative therapies. Nowhere has this been more important than for prostate cancer, for which the introduction of PSA in 1987 resulted in a substantial migration to earlier-stage disease at diagnosis. PSA screening also has resulted in a pathological stage migration so that for a given PSA and grade of tumor, a man in 2006 has a higher chance of having organ-confined disease than he would have 10 years earlier. This phenomenon has resulted in improved disease-free survival after radical prostatectomy in more recent years that cannot be completely attributed to improvements in therapy.

In a follow-up to an earlier study (Declining rates of extra-capsular extension after radical prostatectomy: evidence for continued stage migration. J Clin Oncol. 1999 17:3167), we re-examined rates of non-organ-confined disease at radical prostatectomy as a surrogate for the chance for cure to see if stage migration has continued. We examined 3,364 surgical specimens spanning the early and late PSA eras (1987 to 2005) for this study. We found a substantial drop in the overall rate of non-organ-confined disease from 79.3% in 1987 to 24.7% in 2005. More interestingly, we found that the rate of year-to-year change in this outcome has changed substantially with time. Immediately after the initial implementation of PSA screening, the likelihood of having non-organ-confined disease decreased at an annual percentage change of 2.91 between 1987 and 1992. As PSA screening became widespread, the rate of change accelerated more than 5-fold to -16.88 percent per year between 1992 and 1995. In the most recent PSA era, stage migration has continued at a slower rate of -4.18 percent per year. Compared to an estimate of 12% absolute change in the proportion of cases with non-organ confined disease 1992 and 1993, we estimate only a 1.1% absolute change between 2004 and 2005.

The decline in the absolute rate of stage migration in the late PSA era is clinically significant. Previous work has shown the year of surgery to be a predictor of outcome for prostate cancer patients, an observation that has been attributed to pathological stage migration. The slowing of stage migration affects this observation, and indeed recent nomograms in outcome prediction have shown that the year of surgery is not a significant predictor of outcome for patients treated after 1998. Furthermore, the declining effects of stage migration suggest that improvements in cure can no longer depend on patients presenting with earlier stage disease and will require new therapeutic approaches for continued improved cure rates. Further studies at the population level are needed to confirm these findings.

* The research was done in collaboration with Fei Dong, a third-year student at Case Western Reserve University School of Medicine.

Key Points

The slowing of stage migration has shown that the year of surgery is not a significant predictor of outcome for prostate cancer patients treated after 1998.

The declining effects of stage migration suggest that improvements in cure can no longer depend on patients presenting with earlier stage disease and will require new therapeutic approaches for continued improved cure rates.
In recent years, office-based saturation biopsy (SB) has become our standard diagnostic approach in the challenging cohort of patients with substantial risk factors for prostate cancer who have had previously negative biopsy. In addition to its utility for diagnosis, SB in patients with microfocal disease has been shown to more accurately predict prostate tumor volume and grade compared to traditional biopsy schemes, thereby allowing the selection of suitable candidates for active surveillance (AS). Cleveland Clinic evaluated the use of a staging SB to evaluate suitability for a delayed curative intervention protocol in patients with presumed low-grade, low-volume prostate cancer on initial diagnostic biopsy.

Our current practice is to perform all biopsies with a periprostatic block in the office. Patients undergoing their first biopsy have 12 cores taken, whereas patients previously biopsied undergo a 20-core SB. Thus, all surveillance biopsies were 20-core. Biopsies in either setting are focused laterally and at the apex in the peripheral zone (Figure 1).

We identified 58 low-risk patients managed with AS on this protocol who had undergone staging surveillance SB. Median age was 69 years (range 51 – 83), with a median PSA of 5.1 ng/mL (range 0.5 – 47). All but 5 patients had a Gleason score of ≤ 6 (Table 2). Nineteen (37%) patients had undergone prior negative biopsies, and as a result were initially diagnosed through SB. The remainder had been diagnosed with a 12 or fewer core biopsy. The results of the initial diagnostic biopsies are shown in Table 1.

Patients who are being considered for an AS protocol undergo staging SB typically within 24 months following their initial diagnosis. Patients are subsequently followed with serum PSA levels and digital rectal examination (DRE) every 6-12 months, and are restaged with a second staging SB only if the initial staging biopsy suggests a greater risk of disease progression. Patients younger than 60 years old,

### Key Points

- Our study data support our practice of pathologically staging patients with saturation biopsy (SB) prior to institution of prolonged active surveillance.
- SB may lead to a more accurate assessment of extent and grade of disease in men with prostate cancer on an active surveillance (AS) protocol compared to traditional biopsy.
- Half of patients whose initial diagnosis was made by 12 or fewer cores were found to have higher-grade or higher-volume disease on staging saturation biopsy. Patients originally diagnosed with SB were highly unlikely to have significantly greater risk tumor than that identified at diagnosis.

In our series, almost two-thirds of patients who pursue an AS protocol delay or avoid local therapy.

![Figure 1: Number and locations of cores sampled for saturation biopsy.](image-url)
those with a change in findings of DRE or increased serum PSA may undergo repeat staging SB. There is no consensus on indications for initiation of local therapy for patients managed with AS, but we include a substantial increase in serum PSA (typically >2.0 ng/mL above baseline, but individualized), a change in the DRE, an increase in Gleason score, or 50% increase in tumor volume on staging biopsy, or if the patient desires treatment.

Staging SB was performed a median of nine months after the initial biopsy (range 1-20 months). Eight patients had a third biopsy on the protocol, and one patient had a fourth. The results of the staging SB are given in Table 1. Twenty patients (38%) were defined as having upstaging of disease at the staging biopsy, and no patient was found to have upstaging at second or third follow-up SB. Five patients were found to have a higher Gleason score, 5 patients had 50% or greater increase in disease volume, and 10 patients had both an increase in Gleason score and volume. Of the 45 patients with an initial Gleason score ≤6, thirteen patients (29%) were upgraded, 12 to a Gleason score 7 and one to a Gleason score 8. All patients with these findings were advised to proceed with local therapy. Nine patients (17%) had no evidence of disease at staging SB.

Patients who were upstaged had a higher percentage of biopsy cores involved. Only two of the 19 patients (11%) initially diagnosed on SB were upstaged on repeat staging SB, compared to 18 of the 33 patients (55%) who were diagnosed using a traditional biopsy scheme. Our data indicate that patients originally diagnosed with SB were more likely to have a smaller volume of disease on subsequent staging biopsy. This further supports our practice of pathologically staging patients with SB prior to making a commitment on the safety of delaying local curative therapy.

The number of cores for SB has varied widely in the literature, with numbers as high as 54 reported. We believe that our scheme of 20 cores widely sampling the entire gland, including traditionally lower yield areas such as the transition zone, offers a compromise between adequate examination of the prostate and the decreasing yield of over sampling. Prior to 2004 our routine was to perform a 24-core SB; however, we showed that parasagittal (medial) biopsies did not provide any additional diagnostic yield, and therefore decreased the total number of parasagittal biopsies from 8 to 4. A BJU International review of the publications regarding SB showed that the literature supports the concept that obtaining greater than 20-24 cores added little or no additional information in either in vivo or in vitro investigation. Although our follow-up is limited in duration, we have demonstrated that this approach offers a significantly greater understanding of the patient’s tumor burden. There is the small potential that prognosis may change with up to 12 months delay prior to the staging biopsy. However, delays of this duration or longer have not been shown to lead to a worsening of prognosis in reports of patients who choose active treatment.

For references, please e-mail the editor.

Table 1. Biopsy data

<table>
<thead>
<tr>
<th></th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial diagnostic biopsy (n=66)</strong></td>
<td></td>
</tr>
<tr>
<td>Number of cores taken</td>
<td>12 (6-28)</td>
</tr>
<tr>
<td>Number of positive cores</td>
<td>1 (1-8)</td>
</tr>
<tr>
<td>Maximum % of core involved</td>
<td>10 (5-100)</td>
</tr>
<tr>
<td><strong>Staging saturation biopsy (n=58)</strong></td>
<td></td>
</tr>
<tr>
<td>Number of cores taken</td>
<td>20 (10-24)</td>
</tr>
<tr>
<td>Number of positive cores</td>
<td>2 (0-17)</td>
</tr>
<tr>
<td>Maximum % of core involved</td>
<td>17.5 (0-100)</td>
</tr>
<tr>
<td>Number of patients with NED (%)</td>
<td>9 (17%)</td>
</tr>
<tr>
<td>Number of patients upstaged* (%)</td>
<td>20 (38%)</td>
</tr>
</tbody>
</table>

NED: No evidence of disease at staging saturation biopsy

* Upstaging is defined as higher bGAs or tumor volume than initial diagnostic biopsy

Table 2. Statistical comparison of data from initial diagnostic biopsy in patients who had stable or upstaging of disease on staging saturation biopsy.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Stable (n=36)</th>
<th>Upstaged (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± S.D.)†</td>
<td>69 ± 6.6</td>
<td>69 ± 8.8</td>
<td>0.79</td>
</tr>
<tr>
<td>iPSA (mean ± S.D.)†</td>
<td>5.7 ± 3.6</td>
<td>5.3 ± 1.7</td>
<td>0.66</td>
</tr>
<tr>
<td>Initial biopsy ≥ 20 cores‡</td>
<td>17 (52%)</td>
<td>2 (9.5%)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Number of cores positive on initial biopsy (mean ± S.D.)†</td>
<td>1.7 ± 1.5</td>
<td>1.8 ± 1.1</td>
<td>0.46</td>
</tr>
<tr>
<td>Bilateral disease‡</td>
<td>5 (16%)</td>
<td>5 (24%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Maximum % of core affected (mean ± SD)</td>
<td>15 ± 20</td>
<td>27 ± 25</td>
<td>0.02*</td>
</tr>
<tr>
<td>Gleason &gt; 6‡</td>
<td>3 (8.6%)</td>
<td>2 (9.1%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

† Wilcoxon/Kruskal Wallis test
‡ Fisher Exact test
* Statistically significant
The American Cancer Society estimates that 18 percent of cancers worldwide are caused by infectious agents (The Cancer Atlas, www.cancer.org). Causative agents include bacteria, such as *H. pylori*, which account for about two-thirds of the worldwide incidence of stomach cancer; viruses such as hepatitis B and C, which cause 85 percent of liver cancers; and human papilloma virus (HPV), which causes cervical and oropharyngeal cancers (and for which the FDA has approved a preventive vaccine).

Substantial epidemiologic evidence suggests that prostate cancer may also be initiated or promoted by microbial infections. For example, studies have shown that men with a history of prostatitis or sexually transmitted infections are at increased risk of prostate cancer, as are those with serum antibodies that indicate prior exposure to *trachoma vaginalis* or human herpes virus type 8.

**New retrovirus identified**

In 2006, we reported the discovery of a novel retrovirus, XMRV, in the prostate of a subset of men genetically susceptible to prostate cancer because of an allelic variant in the RNASEL gene (Urisman A et al. *PLos Pathogens* 2006; 2(3):e25. Epub). RNASEL encodes for the antiviral enzyme RNaseL and is a candidate for the HPC1 gene on chromosome 1q25. When normally expressed, RNaseL helps prevent the spread of viral infections in mammals as part of the innate immune system.

Prostate infections with XMRV, located in cancer-associated fibroblasts in the stroma adjacent to tumor, were found almost exclusively in men homozygous for a reduced-activity variant of RNaseL. Since that discovery, we have been working to characterize the oncogenic potential of XMRV in vitro.

**Integration required for viral replication**

A prerequisite for retroviruses to replicate, and thus to also cause cancer, is the ability to integrate into the host genome. For retroviruses that contain an oncogene in the viral DNA – known as transducing viruses – integration allows for expression of the oncogene and results in tumor development.

Non-transducing retroviruses can sometimes cause cancer when the viral genome integrates nonspecifically in host DNA by activating a nearby cellular oncogene. XMRV lacks an oncogene, and therefore its oncogenic potential could be linked to its sites of integration in host DNA. Cellular oncogenes as well as other genes near the sites of XMRV provirus integration could be dysregulated – thus contributing, directly or indirectly, to prostate cancer.

**Integration sites pinpointed in infected men**

In collaboration with Samson A. Chow, Ph.D., of the University of California, Los Angeles, we have recently identified the chromosomal integration sites for XMRV in several infected men (Dong B et al. *Proc Natl Acad Sci* 2007; 104:1655-60). XMRV, like its cousin MuLV that causes leukemia in mice, appears to have a predilection for insertion near transcriptionally activated genes near their promoter regions.

Of the nearby genes identified in these men, one is a suppressor of androgen receptor transactivation (APPBP2), one has been associated with lymphomas in mice (NFATC3), and one functions as a transcriptional transactivator (CREB5).

These observations lay the groundwork for understanding how XMRV may be related to the development or progression of prostate cancer. Additional work is focused on developing diagnostic tests that may allow for better risk assessment than PSA alone, correlation of viral load with disease parameters (including age of onset, tumor grade and stage) and seroprevalence studies.

Our ultimate goal, if XMRV can be defined as a cause of prostate cancer or its progression, is to develop a preventive vaccine.
Prostate
clevelandclinic.org/urology

Khaled Fareed, M.D.

The management of patients with elevated PSA and negative TRUS-guided biopsies is difficult. The probability of detecting cancer with a repeat biopsy ranges from 10-34% (Table). Unfortunately, PSA has a positive predictive value that is inadequate, resulting in many unnecessary evaluations. As such, patients and clinicians face a dilemma after a negative first set of biopsies. The decision to repeat a biopsy is fraught with patient pain and anxiety as well as increased cost and a delay in definitive management in those patients with prostate cancer.

As increasingly younger patients with lower PSA levels are undergoing biopsy, the number of negative biopsies will increase. Likewise, even patients with two negative biopsies can have up to a 29% chance of unidentified malignancy, typically low-volume in some series.

Several centers have adopted a so-called saturation biopsy (prostate mapping) for prostate cancer detection. We are currently collaborating with Drs. Claus Roehrborn and Shahrokh Shariat and their team at the University of Texas Southwestern Medical Center to evaluate the utility, timing and optimal scheme of saturation biopsy intended to detect clinically significant prostate cancer.

Cleveland Clinic is collaborating with University of Texas Southwestern Medical Center to evaluate the utility, timing and optimal scheme of saturation biopsy intended to detect clinically significant prostate cancer. By linking the saturation biopsy findings with the post-radical prostatectomy databases in the two centers, we will be able to determine how representative saturation biopsy was compared to the post-radical, whole-mount pathology. Establishing the accuracy of saturation biopsy compared to the post-prostatectomy biopsy may allow for possible selection of patients with low disease volume for future targeted therapy.

We will also examine the diagnostic potential of different biological (PSA velocity, density, free PSA, etc.), and pathological (PIN, ASAP, inflammation, etc.) markers in detecting cancer on repeat biopsy. This will allow for careful selection of patients who undergo saturation biopsy based on their biological profiles and the results for their prior biopsies.

### Key Points

- Cleveland Clinic is collaborating with University of Texas Southwestern Medical Center to evaluate the utility, timing and optimal scheme of saturation biopsy intended to detect clinically significant prostate cancer.

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### Cancer detection rates on repeat prostate biopsy, review of literature.

<table>
<thead>
<tr>
<th>Author/source</th>
<th>Population</th>
<th>2nd biopsy</th>
<th>3rd biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keetch et al. J Urol 151: 1571, 94(2)</td>
<td>Screening, yearly f/u</td>
<td>88 / 427</td>
<td>19</td>
</tr>
<tr>
<td>Roehrborn et al. Urology 47: 347, 96(1)</td>
<td>Clinic-Select</td>
<td>28 / 123</td>
<td>23</td>
</tr>
<tr>
<td>Ukiruma et al. Urology 50: 66, 97(13)</td>
<td>Clinic-Select</td>
<td>33/193</td>
<td>17</td>
</tr>
<tr>
<td>Fleshner et al. J Urol 158: 505, 97(5)</td>
<td>Clinic-Select</td>
<td>39/130</td>
<td>30</td>
</tr>
<tr>
<td>Rietberger et al. J Urol 160: 2121, 98</td>
<td>Screening/ EORTC</td>
<td>49/442</td>
<td>11</td>
</tr>
<tr>
<td>Letran et al. J Urol 160: 426, 98</td>
<td>Clinic PSA 2-15 ng/ml</td>
<td>15/51</td>
<td>29</td>
</tr>
<tr>
<td>Borboroglu et al. J Urol 163:158, 00(14)</td>
<td>Clinic-Select</td>
<td>17/57</td>
<td>30</td>
</tr>
<tr>
<td>Djavan et al. J Urol 163: 1144, 00(15)</td>
<td>PSA 4-10 ng/ml All had 2nd TRUS</td>
<td>83/820</td>
<td>10</td>
</tr>
<tr>
<td>Gerard et al. Urology 55: 553, 00</td>
<td>Clinic-Select</td>
<td>1637/6380</td>
<td>25.7</td>
</tr>
<tr>
<td>Slawin et al. J Urol 165: 1554, 01(16)</td>
<td>Clinic-Select</td>
<td>27/111</td>
<td>24.3</td>
</tr>
<tr>
<td>Stewart et al. J Urol 166:86, 01(14)</td>
<td>Clinic-Select</td>
<td>77/224</td>
<td>34</td>
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</tbody>
</table>
There has been considerable debate about the utility of pelvic lymph node dissection (PLND) when performing a radical prostatectomy (RP). Because of PSA-induced stage migration, recent large RP series in the United States report the incidence of positive lymph nodes around 4-5%, compared to historical rates as high as 40%. In low-risk disease, generally defined as Gleason score ≤6, PSA ≤10 ng/mL and clinical stage T1 or T2a, the incidence drops to <1%. Currently reported practices vary from those who always perform an extended PLND to those who employ a predictive nomogram in their decision making, to those who are increasingly not performing a PLND in low-risk disease. Although some recent reports suggest a benefit in delaying biochemical failure in those with intermediate or high-risk disease with extended PLND, there is a growing consensus that PLND is not beneficial in those with favorable tumor characteristics who are at low risk of nodal metastases.

We examined biochemical failure rates in a cohort of 336 patients with favorable tumor characteristics, defined as PSA ≤10 ng/mL, biopsy Gleason score ≤6, 1992 and AJCC stage T1 or T2, who underwent radical prostatectomy between 1995 and 1999. These patients were divided into two groups: those who underwent a limited PLND (PLND group, n=140) and those who did not (no PLND group, n=196) as determined by surgeon discretion. For the PLND group, the boundaries of dissection included the undersurface of the external iliac vein, pelvic sidewall, obturator nerve, bifurcation of the common iliac artery and inguinal ligaments bilaterally.

The majority of the patients (71.7%, n=241) had organ-confined disease and 57% (n=193) had pathologic Gleason score ≤6. Only one of the 140 patients undergoing PLND had positive lymph nodes (0.7%). Median PSA follow-up for the PLND and no PLND groups were similar at 94.5 and 88 months.

### Key Points

- We believe that the accumulated data strongly suggest that pelvic lymph node dissection can be safely omitted in patients with low-risk prostate cancer without affecting the chance for long-term cure.
- Randomized clinical trials are needed to assess the benefits and risks of limited vs. extended PLND in those with intermediate and high-risk disease.

**Figure.** Kaplan-Meier survival analysis of men with low-risk prostate cancer stratified according to lymph node dissection status.
months, respectively (Mann-Whitney p=0.14). The Kaplan-Meier estimate of biochemical relapse-free rate for the entire cohort was 86.1% at 10 years. Thirty-nine of the 336 (11.7%) patients developed biochemical failure during the follow-up interval, 18 (8.7%) in the no PLND group, and 21 (13.6%) in the PLND group (chi square p=0.26). There were no clinical failures in the no PLND group; 2 patients (0.6%) from the PLND group developed distant metastases. There were no local or pelvic nodal failures in either group. All cause mortality was 5.4% (n=18) for the entire cohort. On univariate analysis, PLND was not an independent predictor of outcome (Wald p=0.33). Kaplan-Meier estimates showed no differences in biochemical relapse-free survival between groups at 10 years (88 vs. 84%, log rank p=0.33) (Figure).

The potential benefits of PLND with radical prostatectomy are providing adequate staging for prognosis, identifying patients who would benefit from adjuvant treatment, and the potential for therapeutic or survival advantage by removing limited metastases that are confined to the excised nodes. However, patients with low-risk disease have such a low incidence of positive nodes that these benefits probably do not outweigh the downsides of PLND, which include a complication rate of 1-4% and extra cost associated with a longer operative time. This study does not address whether an extended lymph node dissection in low-risk prostate cancer can improve overall biochemical disease-free survival. We note, however, that the overall biochemical relapse-free survival rate in this series for the no PLND group (88%) compares favorably to that reported by other contemporary series that included routine limited PLND. These data support the omission of PLND for patients with favorable tumor features at the time of radical prostatectomy without compromising the chance for cure.

Salvage Radiation Therapy for Recurrent Prostate Cancer

Andrew Stephenson, M.D.

While radical prostatectomy successfully controls the cancer in the majority of men, the cancer will return in approximately 25% of patients. In its earliest stages, most men with recurrent cancer will only have a rising prostate-specific antigen (PSA) level identified on serial blood tests, without any evidence of cancer on physical examination or biopsy or visible on radiologic imaging studies. Men with a rising PSA level after surgery are at substantial risk of developing bone metastasis and dying from prostate cancer. An estimated 30,000 patients annually will develop PSA recurrence after radical prostatectomy.

A critical issue in managing patients with a PSA recurrence after surgery is determining whether patients have recurrent cancer in the prostatic bed or if a rising PSA level indicates the presence of microscopic metastatic disease. This is a critical distinction as men with local recurrence may potentially be cured of their disease with salvage external-beam radiation therapy. Approximately 50% of patients may be cured of their recurrent prostate cancer when pelvic radiation therapy is administered at the first signs of PSA recurrence. On the other hand, androgen-deprivation hormone therapy may effectively palliate patients with metastatic disease for several years, but it is not curative.

Men with recurrent disease that has spread outside the pelvic region are unlikely to benefit from radiation therapy. Thus, it is imperative to identify patients who are likely to benefit from salvage radiation therapy because there may be treatment-related side effects such as urinary incontinence, irritative bowel and bladder symptoms, and erectile dysfunction. Unfortunately, neither imaging studies nor biopsy strategies have proven to be useful in distinguishing patients with locally recurrent vs. metastatic prostate cancer.

Key Points

Glickman Urological and Kidney Institute researchers conducted a study to develop a nomogram that would predict the likelihood a patient will be free of disease at 6 years after salvage radiation therapy.

Numerous studies have shown that nomograms are more accurate at predicting outcomes than clinical judgment. This will be useful for medical decision-making for patients with a rising PSA level after radical prostatectomy.

A substantial proportion of patients with high-grade cancer and a rapidly rising PSA were found to be free of disease after salvage radiation therapy if they were treated early in the course of recurrent disease when the serum PSA first reached detectable levels.

Men with recurrent disease that has spread outside the pelvic region are unlikely to benefit from radiation therapy. Thus, it is imperative to identify patients who are likely to benefit from salvage radiation therapy because there may be treatment-related side effects such as urinary incontinence, irritative bowel and bladder symptoms, and erectile dysfunction. Unfortunately, neither imaging studies nor biopsy strategies have proven to be useful in distinguishing patients with locally recurrent vs. metastatic prostate cancer.

continued on next page
To better identify patients with PSA recurrence who are likely to benefit from radiation therapy, researchers at the Glickman Urological and Kidney Institute analyzed the outcome of more than 1,500 patients from 18 North American referral centers who received radiation therapy for recurrent prostate cancer after radical prostatectomy. The purpose of this study was to develop a prediction nomogram to predict the likelihood a patient will be free of disease at 6 years after salvage radiation therapy. Nomograms are statistical models that provide individualized outcome predictions based on a patient’s unique set of cancer characteristics. Numerous studies have shown that nomograms are more accurate at predicting outcomes than clinical judgment. The nomogram utilizes 11 disease parameters to predict the outcome for the individual patient (see Figure). This nomogram is likely to be useful for medical decision making for patients with a rising PSA level after radical prostatectomy.

An important finding of this study was that a substantial proportion of patients with high-grade cancer and a rapidly rising PSA or short PSA doubling time were free of disease after salvage radiation therapy if they were treated early in the course of recurrent disease, when the serum PSA first reached detectable levels. It is known that these patients with these features are at the highest risk of dying from prostate cancer. Thus, salvage radiation therapy may offer these patients a second chance for cure of their aggressive prostate cancer.

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New Mechanism to Vaporize Prostatic Tissue

James Ulchaker, M.D.

A new device known as the Evolve SLV™ (biolitec, East Longmeadow, Mass.) recently received FDA approval to treat benign prostatic hyperplasia (BPH). Our initial experience using this technology at the Glickman Urological and Kidney Institute appear very promising.

The device uses diode laser energy to produce a beam of energy that is emitted at a 980 nanometer wavelength at a power up to 120 watts. The energy beam, at this wavelength, is absorbed by both water and hemoglobin. Thus, when placed in contact with prostatic tissue, it produces prostatic vaporization in a bloodless fashion.

The procedure is normally performed in an outpatient surgical setting. A laser fiber is passed thru a 23 Fr continuous flow, short-beaked cystoscope using a saline irrigant. The entire prostatic channel, including the bladder neck, is then vaporized in a controlled, bloodless fashion. Care is taken to avoid damage to the urethral sphincter. The procedure lasts from 30 to 90 minutes, depending on the individual prostate size.

When the procedure has been completed, the patient is discharged home with a catheter, which normally is left in place overnight. However, discharge home without a catheter is possible in select cases.

The first thing that improves is the force of the man’s urinary stream; however, he will have some urgency and frequency for a few weeks postoperatively. Initial results appear promising.

The procedure also has been performed successfully in men with significant lower urinary tract symptoms who have prostate cancer, as well as men who have had their prostate cancers treated with radiation therapy. These men are at a significantly higher risk for the complications of incontinence or scarring, and thus this technology may have increased utility in this subgroup of patients.

We continue to strive for the ideal device to vaporize prostatic tissue. Whether this mechanism can be efficiently used on larger volume prostates and stand the durability test of time remains to be determined. But for now, we are encouraged with the Evolve SLV™ system’s early results and will continue to investigate and report on the data in the future.

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Key Point

The biolitec Evolve SLV™, which produces prostatic vaporization in a bloodless fashion, shows promise in the treatment of BPH.

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Figure 1. Lateral lobe prostatic hypertrophy causing obstruction of urinary flow.

Figure 2. Vaporized prostatic urethra following the use of the Evolve SLV™ 980 laser.

Figure 3. Closed urethral sphincter following prostatic vaporization.
Salvage Prostate Cryoablation

**J. Stephen Jones, M.D., F.A.C.S.**

Patients with recurrent prostate cancer following definitive radiation therapy have limited treatment options. Salvage prostatectomy is rarely utilized based on complication rates. Androgen blockade is often administered, but accumulating evidence suggests significant side effects can occur without potential for cure.

Similarly, salvage cryoablation has historically been associated with a high incidence of complications. However, newer reports suggest that the complication rates, while still appreciable, are manageable in the majority of patients. Urologists at Cleveland Clinic have treated more than 50 men in the past three years with salvage cryoablation and currently offer this option to healthy men with apparent organ-confined prostate cancer recurrence following radiation therapy options. Although follow-up disease control data are limited to date, initial complication rates are definable and appear to be lower than those for salvage prostatectomy. More importantly, Kaplan-Meier (KM) analysis of salvage patients in series followed for longer duration indicates that disease control is possible even in the salvage setting. It is well-recognized that disease-free survival is much greater in patients with PSA <10 and PSA velocity <2.0 ng/mL/year, so we currently believe this setting is most appropriate for consideration of salvage cryoablation.

Salvage cryoablation patients at Cleveland Clinic experience significantly higher complication rates than those expected with primary treatment, but less than complications associated with salvage prostatectomy. One to three months duration of significant pain occurs in 19% of patients, typically associated with urethral slough. The pain with slough usually resolves rapidly, but radiated tissue heals slowly, so these patients may require a urethral catheter or SP tube for several months while this heals. The risk of persistent incontinence is less than 10%. Although this risk is real, the majority of these patients wear one pad or fewer per day, and the risk is notably lower than that expected with salvage prostatectomy. Major complications such as fistula have been reduced to 2% or less in all recent salvage cryoablation series, similar to the Cleveland Clinic experience.

National data from the CryoOnline Database demonstrate that these outcomes are to be expected in widespread application as well. For 277 patients followed for mean 21.6 months with 47 having at least five-year follow-up, KM analysis demonstrated five-year actuarial biochemical disease-free rates of 58.9% using the ASTRO definition. The positive biopsy rate was 6.0%. The rectal fistula rate was 1.2%.

As a result of both institutional and national registry data, we now offer salvage cryoablation as a treatment option for patients with biopsy-proven recurrence of prostate cancer at least two years after definitive radiation or brachytherapy. Using argon-based cryoablation, this offers a potentially curative option following failed radiation therapy and is associated with a morbidity profile lower than that of previous technology. Side effects are still higher with salvage cryoablation than for primary cryoablation, and we currently perform primary cryoablation approximately twice as often.

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**Key Points**

- Recent limited follow-up disease-control data show that initial complication rates for salvage cryoablation of the prostate appear to be lower than those for salvage prostatectomy.
- Kaplan-Meier analysis shows that disease control can be obtained in the salvage setting.
- Cleveland Clinic now offers salvage cryoablation as a treatment option for patients with prostate cancer recurrence at least two years after definitive radiation or brachytherapy.
Salvage Robotic Prostatectomy

Jihad H. Kaouk, M.D.

Biochemical recurrence after primary therapy for localized prostate cancer with external beam radiotherapy or permanent prostate brachytherapy radiation therapy occurs in approximately 40-50% of patients. Uncontrolled local disease is a significant risk factor for metastatic progression, cancer-specific mortality and considerable morbidity, and local salvage therapy represents the only approach with curative potential. However, in the United States nearly 90% of these men will receive systemic androgen ablation with fewer than 2% of patients treated with salvage radical retropubic prostatectomy (RP).

Historically, salvage RP has been associated with major complication rates of 33-50%, 15% risk of rectal injury and incontinence rates of 58-65%. However, surgeons reported improvement in the complication rates and morbidity associated with salvage RP in recent series. Nonetheless, salvage RP remains a technically demanding procedure and is still associated with higher than normal complications rates when compared to standard RP series. These improved results led us to study if there is a role for salvage robotic surgery in the management of locally recurrent prostate cancer after radiation therapy.

A total of four patients underwent a robotic prostatectomy following permanent interstitial brachytherapy. To assess the feasibility of performing robotic surgery on previously irradiated prostates, our initial two patients underwent a robotic cystoprostatectomy for treatment of bladder cancer. These patients also had a history of brachytherapy for prostate cancer. Subsequently, two consecutive patients underwent salvage prostatectomies following local treatment failure. Selection criteria for salvage robotic radical prostatectomy include life expectancy greater than 10 years, the presence of clinically localized disease and a negative evaluation for systemic disease.

Robotic cystoprostatectomies and salvage radical prostatectomies were all successfully completed. Mean operative time for the salvage prostatectomy cases was 125 minutes with a mean estimated blood loss of 50cc. Mean length of hospital stay was 2 days. There were no intraoperative or postoperative complications. Both cases of salvage prostatectomy were continent at 3 months follow-up.

In our limited experience, robotic salvage was very effective. The benefits of pneumoperitoneum and excellent surgical exposure prevented significant blood loss. In our series there were no rectal injuries. The plane between the rectum and prostate was clearly identified with the magnified 3-D vision. The precision of the wrested robotic instrumentation allowed the dense posterior attachments to be sharply divided, thus avoiding rectal injuries.

Our initial results demonstrate that salvage robotic prostatectomy is technically possible and minimizes perioperative morbidity.

For references, please e-mail the editor.

Key Points

<table>
<thead>
<tr>
<th>Improvements were reported in the complication rates and morbidity of contemporary salvage radical retropubic prostatectomy (RP).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvage RP remains a technically demanding procedure and is still associated with higher than normal complications rates when compared to standard RP series.</td>
</tr>
<tr>
<td>Our limited experience found robotic salvage prostatectomy to be effective and to minimize perioperative morbidity.</td>
</tr>
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</table>
Robotic Radical Prostatectomy Using Laser Energy: A Promising Technique for Better Nerve-Sparing

Jihad H. Kaouk, M.D., and Inderbir S. Gill, M.D.

Various hemostatic methods have been employed during nerve-sparing robotic assisted and laparoscopic radical prostatectomy, while attempting to minimize collateral tissue injury, particularly to the cavernous nerves. Such techniques include ultrasonic shears, bipolar diathermy, laparoscopic clips and lateral vascular pedicle control with laparoscopic bulldog clamps.

Monopolar and bipolar diathermy and ultrasonic shears have been shown to adversely affect cavernous nerve function. Vascular clips and clamps may interfere with dissection and dislodge as dissection proceeds. In particular during robotic surgery, the surgeon, being out of the operative field, is dependent on the skill of the surgical assistant at the patient’s side to place the clips accurately.

In contrast to conventional surgical methods, laser energy potentially allows for precise dissection with good hemostasis and minimal adjacent tissue injury. Several surgical lasers have been described, particularly in the neurosurgical literature, where functional preservation of adjacent neural tissue during operative dissection is paramount. The potassium-titanyl-phosphate (KTP) laser offers superior cutting qualities with minimal tissue penetration (typically <1mm). In addition, the 3-D vision and improved precision provided during robotic surgery further enhance the fine dissection and minimal collateral tissue injury afforded by the laser energy.

**Key Points**

- In contrast to conventional surgical methods, laser energy potentially allows for precise dissection with good hemostasis and minimal adjacent tissue injury.
- The potassium-titanyl-phosphate (KTP) laser offers superior cutting qualities with minimal tissue penetration. The 3-D vision and improved precision provided during robotic surgery further enhance the fine dissection and minimal collateral tissue injury afforded by the laser energy.

**Laboratory Study**

We completed a study in the canine model to examine the technical feasibility of laser nerve-sparing robotic radical prostatectomy. In one study, we compared potency outcomes using KTP laser, ultrasonic shears (US) or clips and cold scissors (C&S) after laparoscopic unilateral nerve bundle mobilization. The peak intracavernosal pressure response to nerve stimulation recorded as a percentage of mean arterial pressure (ICP%MAP) was similar for the KTP and C&S groups but was significantly decreased for the US group (KTP 92%, C&S 96%, US 49% (Figure 1).

In another canine study, 10 robotic radical prostatectomies were performed solely with KTP laser without any additional hemostatic maneuvers using the da Vinci® S Surgical System (Intuitive Surgical, Sunnyvale, Calif.) and a

![Figure 1](image-url)
prototype robotic laser instrument (Figure 2). Pre- and post-
ICP%MAP (median pre 98.5%, post 77.0%, p = 0.12) were not 
significantly different. Similarly, pre- and post-hemoglobin 
(median pre- 14.4g/dL, post- 12.6g/dL, p = 0.06) and hemato-
crit measurements (pre 45.1%, post 40.2%, p = 0.06) were not 
significantly different. There was no postoperative hemor-
rhage. Acute laser-induced necrosis due to thermal spread 
was 0.5-1.0 mm (Figure 3).

Initial Clinical Series

Laser nerve-sparing robotic radical prostatectomy was 
performed in 10 patients using a KTP laser unit delivering 
12W through a 300µm fiber. This represents the first series 
ever completed using such technology.

All 10 procedures were successfully completed solely 
with laser energy. The absence of tremor afforded by the 
robotic system improved the precision of the laser and 
enabled narrow cutting widths to be achieved. In addition,
the Endowrist® (Intuitive Surgical) technology of the laser 
instrument enabled the laser beam to be delivered from a 
variety of angles, thus allowing the tissues to be specifically 
targeted and, therefore, optimized tissue cutting and ves-
sel coagulation. The 4th robotic arm allowed the operating 
surgeon to optimally retract the tissue for dissection. This, 
in conjunction with the laser tool, allowed the primary sur-
gon to operate with less reliance on the surgical assistant.

The mean (range) perioperative values were: prostate 
weight 63.2 g (41-102) operation time 217 min (179-266), 
blood loss 290 ml (100-900), hemoglobin decrease post sur-
gery 2.2 g/dl (1.5-4.1), hematocrit decrease 6.83 % (4.5-10.8), 
hospital stay 39.9 hrs (21-64), and total laser dissection time 
65.9 min (38-104). Eight patients had pT2 disease and 2 
had pT3. All surgical margins were negative. There were no 
complications noted in this series.

KTP laser nerve-sparing robotic radical prostatectomy had no 
significant effect on cavernous nerve function in the canine 
model and was feasible and safe in the clinical human set-
ing. Long-term assessment of potency outcomes is under 
way to determine the value of this novel technique specifi-
cally to potency preservation after radical prostatectomy.
Cleveland Clinic surgeons performed more than 1,800 laparoscopic surgeries for urologic cancers between 1997 and 2006. This large body of work provides a broad and deep database, allowing the determination of perioperative complication rates and the risk factors associated with specific complications. We have recently completed a study whose data provides information for preoperative patient counseling, stratification of patients into risk categories, and the opportunity to modify procedural techniques to meet specific risks and minimize complications.

The 1,867 laparoscopic procedures examined for the study include radical and partial nephrectomies, nephroureterectomies, radical prostatectomies and radical cystectomies. Complications were categorized as intraoperative or postoperative.

Intraoperative complications include bleeding sufficient to require transfusion or conversion to an open procedure, and injury to any surrounding organs or anatomic structures. (Conversion to an open procedure was not considered a complication in and of itself because such conversions result from either intraoperative complications or unexpected and/or insurmountable anatomic findings encountered after the procedure was initiated.) Some postoperative complications include ileus, gastrointestinal bleeding, deep vein thrombosis, pulmonary embolism, pulmonary edema, atrial fibrillation, myocardial infarction, syncope, acute renal failure, urinary retention, urinary leakage, rectal fistula, bowel injury, wound infection and wound dehiscence.

Perioperative complications occurred in 12.4% of the procedures and led to 38 (2%) secondary surgical interventions. These interventions included exploratory laparotomy (1.1%), ureteral stent placement (0.5%), renal embolization (0.2%), and lower limb fasciotomy.

Postoperative complications occurred in 8.9% of the patients. The most common of these were hemorrhage in 52 (2.7%), and acute renal failure in 16 (0.8%). Intraoperative and postoperative hemorrhage accounted for 40% of all perioperative complications.

Logistic regression analysis identified risk factors for perioperative complications. Among these were radical cystectomy (adj. OR 4.9, 95% CI 1.3 - 8.0), partial nephrectomy (OR 2.4, 95%
Despite the significantly increased technical complexity of the procedures, the complication rate actually decreased somewhat (17.3% vs. 12.5%) although this did not achieve statistical significance ($p = 0.302$).

The strengths of this study are its size and design. It includes a large and varied number of surgeries conducted over several years in what is generally considered to be a high-risk oncologic population. Conversely, its weaknesses are that it is a retrospective study from a single institution where the definitions of complications may not be exactly the same as those being reported by other institutions.

For references, please e-mail the editor.
Augmented Reality: Its Initial Application in Urology

Inderbir S. Gill, M.D., Osamu Ukimura, M.D., Monish Aron, M.D., Georges-Pascal Haber, M.D., Jihad H. Kaouk, M.D., and Mihir M. Desai, M.D.

The ability to clearly visualize target tissues and surrounding anatomy in an unobstructed operating field contributes significantly to improved outcomes. It is a circumstance always desired but not always reached. One of the advantages of laparoscopy is that it allows procedures to be conducted in a relatively bloodless field. But even bloodless fields and magnification do not reveal the characteristics of defects or tumors hidden beneath layers of tissue. Augmented reality may change this.

Augmented reality superimposes the 3-D image of otherwise hidden structures onto anatomic features to allow the laparoscopic surgeon to see tumors, defects and other aspects of anatomy that would otherwise remain hidden. The technology accomplishes this by drawing on real-time ultrasound, computed tomography and/or magnetic resonance images, and processing the data to create 3-D images that are then oriented to the surgeon’s perspective and projected as a video image that shows structures that lay beneath tissues and beyond normal vision.

For example, images of a tumor are acquired by ultrasound, CT and/or MRI. These are analyzed and cast into a 3-D image by a computer that is also monitoring the position and movement of various laparoscopic instruments in real time. The computer then projects the image onto the laparoscopic image captured by standard laparoscopic videography. The surgeon sees both the organ and tumor oriented to instrumentation.

To date, surgeons at Cleveland Clinic have employed the technology in 8 laparoscopic partial nephrectomies, 2 laparoscopic radical nephrectomies, 13 laparoscopic radical prostatectomies, and one laparoscopic radical cystectomy.

Negative surgical margins were achieved in all renal tumors and in all but one prostatic tumor. One patient with pT3b prostate cancer had a vocal positive margin at the site of seminal vesicle involvement. Postoperative serum creatinine values demonstrated well-preserved renal functions in all nephron-sparing surgeries at the time of discharge on postoperative day 1 or 2. Eight prostatectomy patients were followed with the Sexual Health Inventory for Men (SHIM) and urinary incontinence questionnaires. Of these, four reported postoperative full-time continence at one month, and 2 of 6 patients reported excellent potency (SHIM > 22) at one month postop.

These procedures illustrate the system’s advantages. It opens new opportunities for surgical planning. Its color-coded navigation system provides a 3-D “road map” that extends beyond the surgeon’s view. Just as a GPS device in an automobile shows the twists and turns a road might take hundreds of yards beyond the driver’s view, the augmented reality system can project the anatomy of structures covered by surrounding fat and viscera. In prostatectomy, the technology can display the often obscured location of the neurovascular bundle.

In laparoscopic partial nephrectomies – highly challenging laparoscopic procedures – the technology images the tumor and paints color-coded margins around it. A margin marked as a “yellow zone” describes a perimeter 0 – 5 mm around the tumor, and a “green zone” margin is 5 – 10 mm from the tumor. By staying within the “green zone,” a surgeon can remove the tumor and be assured of negative margins while preserving a maximum amount of kidney function.

Determining a surgeon’s ability to remain within these margins may be difficult in a clinical setting, but in animal experiments we have found that the system can be accurate to less than 3 mm under ideal conditions.

There are few laparoscopic procedures that would not benefit from the advantages provided by augmented reality imaging. The Cleveland Clinic team is continuing to explore the limits of technology, its ability to make invasive procedures more precise and efficacious, and to apply it to an ever-widening range of presentations.
Robotic-assisted laparoscopic pyeloplasty (RALP) is an evolving approach in the pediatric population for the treatment of ureteropelvic junction (UPJ) obstruction. Available robotic systems provide precision afforded by 3-D visualization and articulating instruments. At the Cleveland Clinic Glickman Urologic and Kidney Institute, we have refined and introduced innovative RALP techniques in the pediatric population.

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

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

**Key Points**

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

We are developing additional innovative techniques to further enhance the robotic-assisted surgical treatment of ureteropelvic junction obstruction.
Cytoreductive Nephrectomy: Studying New Paradigms for Integrating Surgery and Systemic Therapy for Patients with Metastatic RCC

Michael Gong, M.D., Ph.D., Venkatesh Krishnamurthi, M.D., David Goldfarb, M.D., Amr Fergany, M.D., and Steven Campbell, M.D., Ph.D.

Cytoreductive nephrectomy has become a mainstay in the multimodal treatment of patients with metastatic renal cell carcinoma (RCC). Approximately one-third of patients with RCC will present with metastatic disease. Historically, surgical treatment of metastatic RCC was primarily palliative. With the advent of more effective systemic therapies, the role of debulking nephrectomy was revisited. Two widely quoted prospective randomized trials comparing patients undergoing cytoreductive nephrectomy plus interferon alpha versus immediate interferon alpha alone demonstrated a survival benefit to those undergoing cytoreductive nephrectomy (median survival 13.6 months versus 7.8 months). In addition, morbidity from the nephrectomy was low in that 94% of the patients undergoing nephrectomy were able to continue the study to receive subsequent interferon alpha therapy, with a median time to initiation of interferon therapy of 19 days after nephrectomy. These publications led to the widespread acceptance of cytoreductive nephrectomy for select patients with metastatic RCC.

**Defining patient selection criteria and surgical approach**

Patient selection criteria and prognostic factors remain controversial. Patients with good performance status (ECOG performance status of 0 or 1) and those with minimal co-morbid diseases have been considered suitable candidates. Multiple prognostic factors have been evaluated but none have been definitively used as selection criteria. Sites of metastasis and burden of disease have been correlated with outcomes. The best outcomes are achieved with patients with low-volume pulmonary metastasis and good performance status. Presence of visceral metastasis, including bone, liver and brain, typically portends a worse prognosis. Indeed, in a retrospective review of the author’s personal experience of 66 patients undergoing cytoreductive nephrectomy over the past few years, the overall median survival was 16.1 months. Twenty-seven patients (41%) presented with bone metastasis. The median survival of those with bone metastasis was 12.6 months versus 19.2 months for those without bone metastasis (see Figure 1). Histology is also prognostic; sarcomatoid features are associated with poor outcome, while predominance of clear cell subtype is associated with better outcome. Finally, lymph node involvement has also been associated with worse outcomes. All of these criteria are utilized in patient selection, but none have been demonstrated as definitive exclusion or inclusion criteria. These parameters are now under study in a larger retrospective review of more than 300 patients treated with cytoreductive nephrectomy at Cleveland Clinic since 1995.

![Image](https://via.placeholder.com/150)

**Key Points**

Cleveland Clinic recently initiated a study in which patients with locally advanced and unresectable renal cell carcinoma (RCC) will receive targeted molecular therapy first (Sutent®) followed by surgery.

Cytoreductive nephrectomy remains a standard of care for select patients with metastatic RCC but will require continued reassessment in the new era of molecular targeted therapy.

The surgical approach utilized is also controversial and is highly selective. Generally, incision and approach are primarily determined by surgeon preference based on experience and expertise. As laparoscopic techniques have become more advanced and more widely utilized, there has been an increase in the proportion of laparoscopic cytoreductive nephrectomies. Typical selection criteria at Cleveland Clinic for laparoscopic approach for this procedure are: 1) tumor size less than 15 cm; 2) absence of local invasion or bulky lymphadenopathy; 3) lack of high level IVC thrombus. Retrospective comparisons of laparoscopic versus open cytoreductive nephrectomy have been previously reported. There appears to be a shorter hospital stay, less operative blood loss and shorter interval to receive systemic immunotherapy with laparoscopic approaches. Inclusion of lymphadenectomy and extent of lymphadenectomy remains controversial. There are data suggesting that there is no benefit of resecting clinically negative lymph nodes, however, there may be a survival benefit for resecting clinically positive lymph nodes. It is unclear whether resection of microscopically positive lymph nodes results in improved outcomes in the cytoreductive setting. In the author’s experience, laparoscopic lymphadenectomy can be performed with no significant additional morbidity, and a mean laparoscopic lymph node yield of 23 was obtained in the cytoreductive nephrectomy series. At this point in time, about half of the cytoreductive nephrectomies at Cleveland Clinic are performed laparoscopically. Careful patient selection is the key to the safe and effective performance of this procedure.

In the current era of molecular targeted therapy, the above described paradigms and outcomes will need to be reevaluated. The previous data in favor of cytoreductive nephrectomy was accumulated in an era when immunotherapy was the only available systemic therapy. Two oral drugs, sorafenib (Nexavar®) and sunitinib (Sutent®), have recently been approved by the FDA (January 2006) for the treatment of advanced RCC. Sorafenib and sunitinib are tyrosine kinase inhibitors targeting the vascular endothelial growth factor (VEGF) pathway. A third molecular targeted agent, temsirolimus (CCI-779 or Torisel®), an
inhibitor of mammalian target of rapamycin (mTOR) was the most recently approved drug by the FDA (May 2007). Temsirolimus is an inhibitor of cell proliferation and also may inhibit angiogenesis. These medications provide improved progression-free survival, and the response rates are improved over immunotherapy in most studies. Our current practice is to perform cytoreduction prior to the use of these agents whenever sensible and feasible, translating the cytoreductive paradigm into this era. However, this will require continued reassessment.

Studying the integration of surgery and systemic therapies

To explore new approaches and in an attempt to improve the management of patients with locally advanced and unresectable RCC, we recently initiated a study in which patients will receive targeted molecular therapy first (Sutent®) followed by surgery. Downsizing of the tumor to allow for safe surgical resection will be the main outcome parameter. Two cohorts of patients will be included—those with and without metastatic disease. Eligibility is defined by consideration of: 1) large tumor size; 2) high level IVC thrombus; 3) bulky lymphadenopathy; 4) encasement of the hilum; or 5) proximity to vital structures. Unresectability refers to some combination of the above factors that substantially increases the risk of morbidity. This trial will allow us to begin to explore novel and rational ways to integrate surgery and systemic therapies for the management of patients with metastatic RCC.

Since the discovery of the VHL gene and the hypoxia-induced pathway, molecular targeting of RCC has become a reality where reported response rates are unprecedented. Cytoreductive nephrectomy remains a standard of care for select patients with metastatic RCC but will require continued reassessment in this era.

Sunitinib (Sutent®) as Neoadjuvant Treatment for Unresectable Renal Cell Carcinoma

Brian I. Rini, M.D.

The management of metastatic renal cell carcinoma (RCC) has undergone a revolution over the last decade. A survival advantage of debulking radical nephrectomy in patients with metastatic RCC has been validated in two prospective, randomized trials. More recently, systemic therapy targeted at vascular endothelial growth factor (VEGF) has produced robust clinical effects in metastatic RCC, leading to regulatory approval of two agents, sorafenib (Nexavar®) and sunitinib (Sutent®). Given the emerging role of VEGF-targeted systemic therapy, an examination of the utility of VEGF-targeted therapy in patients with large primary renal tumors is warranted.

VEGF-targeted therapy in RCC

Metastatic RCC is a disease historically unresponsive to conventional treatment strategies, with a limited subset of patients experiencing clinically meaningful benefit from immunotherapy. Response rates average 15-20%, and substantial responses in the primary tumor are decidedly uncommon. A growing understanding of the underlying molecular biology of RCC has identified a number of pathways pertinent to the pathophysiology of clear cell RCC. Inactivating mutations or methylation in the VHL gene have been observed in the majority of sporadic clear cell RCC tumors. Resulting constitutive activation of the hypoxia-response pathway leads to upregulated expression of multiple genes important in tumor angiogenesis, including VEGF and platelet-derived growth factor (PDGF). A variety of strategies have been developed to block these pathways, including sorafenib and sunitinib.
Debulking nephrectomy in metastatic RCC
Debulking nephrectomy has become a standard of care in selected patients on the basis of two identically designed, prospective randomized trials. Eligibility for both trials included metastatic RCC with a primary tumor amenable to resection, ECOG performance status 0 or 1, no prior radiotherapy or systemic treatment and adequate end-organ function. Eligible patients were randomized to radical nephrectomy followed within one month by interferon alpha or to immediate interferon without preceding nephrectomy. A combined analysis demonstrated an overall survival advantage for the surgery group (13.6 months mean survival versus 7.8 months for the interferon alone arm). The combined results in 253 patients with measurable disease revealed a 6.9% response rate in the nephrectomy arm versus a 5.7% response rate in the interferon only arm. Surgical morbidity and mortality were acceptable and did not prevent subsequent administration of interferon in 95% of patients at a median of 19 days after surgery. These trials have established cytoreductive nephrectomy followed by systemic therapy as a standard of care in this field. However, cytoreductive nephrectomy should not be performed indiscriminately – proper patient selection is essential. The optimal candidates include those with: 1) good performance status; 2) a resectable primary tumor representing the majority of tumor burden; 3) no evidence of rapidly progressing extra-renal disease; and 4) no prohibitive medical comorbidities.

Debulking nephrectomy in the era of VEGF-targeted therapy
It is clear both that debulking nephrectomy is beneficial in select patients, and that VEGF-targeted therapy has robust clinical effects in metastatic RCC. The lack of insight into the biologic alterations of nephrectomy precludes definitive statements about how to integrate these modalities. Our current standard is to perform debulking nephrectomy in appropriately selected patients followed by systemic therapy, including cytokines or VEGF-targeted therapy. Delayed nephrectomy after systemic therapy could also be considered as a strategy, allowing assessment of response to systemic therapy and overall disease pace, and permitting more appropriate patient selection for surgery and potential downstaging.

Neoadjuvant therapy
The impact of VEGF-targeted therapy on primary renal tumors and, thus, the role of neoadjuvant therapy in RCC patients with unresectable or locally advanced primary tumors has not been defined. The vast majority of patients in the sorafenib and sunitinib trials had undergone prior nephrectomy. Anecdotally, however, primary tumor shrinkage has been observed with these agents, a relatively rare finding with conventional cytokine therapy. We have recently applied sunitinib in such patients with an effect on the primary tumor observed (Figures 1 and 2).

The Cleveland Clinic Taussig Cancer Institute and Glickman Urological and Kidney Institute have recently opened a collaborative protocol to prospectively test this treatment approach. Sunitinib 50 mg daily for 4 of 6 weeks in repeated cycles will be given to patients with unresectable primary RCC tumors, including patient cohorts both with and without distant metastases. The primary endpoint is the percentage of patients for which the primary tumor becomes resectable after sunitinib therapy. Further, the safety of sunitinib in this setting and objective response rate will be established. Blood and tissue collected at baseline and throughout treatment will also be studied for biomarkers of response and resistance in this setting.

For references, please e-mail the editor.

Sunitinib (Sutent®) as Neoadjuvant Treatment continued from page 27

![Figure 1](image1.png)
Pre-sunitinib

![Figure 2](image2.png)
Post-sunitinib
Laparoscopic partial nephrectomy (LPN) has been developed recently as a minimally invasive form of nephron-sparing surgery, incorporating the fundamental principles of open partial nephrectomy (OPN). While LPN currently is offered at an increasing number of centers, few have achieved sufficient experience to permit comparison of a large number of patients undergoing LPN and OPN.

In a recent multi-center study, data regarding 1,800 consecutive OPN or LPN operations were collected prospectively or retrospectively in tumor registries at three large referral centers. These centers comprised Cleveland Clinic, Mayo Clinic and Johns Hopkins University. Michael Blute, M.D., was the primary co-investigator from the Mayo Clinic and Louis Kavoussi, M.D., was the primary co-investigator from Johns Hopkins University. Inclusion criteria for this study comprised patients with a single, localized, suspected sporadic renal cell carcinoma ≤ 7 cm in size who were treated with LPN or OPN between January 1998 and September 2005. The primary focus of the study was on perioperative and early renal functional outcomes with the two techniques.

OPN was performed in 1,029 patients, and LPN was performed in 771 patients. Patients undergoing OPN were a higher risk group as defined by a greater percentage presenting symptomatically with reduced performance status, impaired renal function and tumor in a solitary kidney (p < 0.0001). More tumors in the OPN group were > 4 cm and centrally located (p < 0.0001), and more proved to be malignant (84% vs. 72%, p = 0.0003).

Based on multivariable analysis, LPN was associated with shorter operative time (201 vs. 266 minutes, p < 0.0001) and shorter hospital stay (3.3 vs. 5.8 days, p < 0.0001). However, LPN was also associated with longer warm ischemia time (31 vs. 20 minutes, p < 0.0001) and more postoperative renal/urologic complications (9.2% vs. 5.0%, p = 0.0006), particularly postoperative hemorrhage (4.7% vs. 1.6%, p = 0.0001). More patients in the LPN group required a subsequent procedure compared with the OPN group (6.9% vs. 3.5%, p < 0.0001). The odds of a postoperative renal/urologic complication, hemorrhage or a subsequent procedure were 2.14, 3.52 and 3.05 times higher after LPN compared to OPN, respectively.

Renal functional outcomes were similar three months after LPN and OPN, with 97% and 99% of renal units retaining function. Loss of function in the operated kidney occurred in 16 patients from the LPN group (2.1%) and four patients from the OPN group (0.4%), which was not statistically significant.

3-year cancer-specific survival for patients with a single cT1N0M0 renal cell carcinoma was 99.3% and 99.2% after LPN and OPN, respectively; however the median follow-up interval was only 1.4 years for patients in the LPN group.

The investigators conclude from these data that LPN can achieve early renal functional outcome comparable to OPN when applied to select patients with a single renal tumor ≤ 7 cm in size. This technique, however, is associated with longer ischemia time, more postoperative complications and more frequent need for a subsequent procedure. Open partial nephrectomy remains the preferred approach for more complicated renal tumors such as those which are larger, hilar/intrarenal in location and multi-centric.
Management of long segment ureteral pathology including benign disease, such as stricture, or malignant disease, such as tumor, is a significant challenge for any urologist. Patients are often faced with the decision of undergoing a major reconstructive salvage procedure such as ileal ureteral interposition or renal autotransplantation with potential for significant morbidity.

Although there have been no direct comparisons of ileal ureter replacement and autotransplantation, ileal ureter substitution has demonstrated excellent short- and long-term functional efficacy with minimal metabolic sequelae. Nevertheless, both ileal ureter and autotransplantation have been historically performed through large open incisions with associated perioperative morbidity and extended recovery times.

Over the last several years, various groups have reported their experience with laparoscopic ureteral reimplantation with psoas hitch or boari flap as well as ureteroureterostomy. Outcomes have been favorable as our group has recently reported decreased hospital stay and blood loss compared to similar procedures through an open incision.

In 2000, we reported the initial laparoscopic ileal interposition for ureteral TCC in a solitary kidney. Since that time, 5 additional cases have been performed with excellent results and several modifications in technique.

### Laparoscopic Ileal Ureteral Replacement

Robert J. Stein, M.D., Amr F. Fergany, M.D., Burak Turna, M.D., Christopher J. Weight, M.D., Mihir M. Desai, M.D.

<table>
<thead>
<tr>
<th>Key Points</th>
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<tbody>
<tr>
<td>In 2000, we reported the initial laparoscopic ileal interposition for ureteral TCC in a solitary kidney. Since that time, 5 additional cases have been performed with excellent results and several modifications in technique.</td>
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<tr>
<td>Benefit in terms of post-procedural analgesic use and recovery parameters highlight the advantages of a minimally invasive approach for these procedures.</td>
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</table>

### Key Points

- In 2000, we reported the initial laparoscopic ileal interposition for ureteral TCC in a solitary kidney. Since that time, 5 additional cases have been performed with excellent results and several modifications in technique.
- Benefit in terms of post-procedural analgesic use and recovery parameters highlight the advantages of a minimally invasive approach for these procedures.

### Table 1. Perioperative data comparing laparoscopic with open ileal substitution

<table>
<thead>
<tr>
<th></th>
<th>Laparoscopic ileal ureter</th>
<th>Open ileal ureter</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>68.8±12.7 (50-87)</td>
<td>39±12 (22-55)</td>
<td>0.0043</td>
</tr>
<tr>
<td>Operative time (minutes) Median</td>
<td>470</td>
<td>383</td>
<td>0.475</td>
</tr>
<tr>
<td>Hospital stay (days) Median</td>
<td>6</td>
<td>8</td>
<td>0.475</td>
</tr>
<tr>
<td>Narcotic analgesic use (mg) (morphine equivalent) Median</td>
<td>108.55</td>
<td>322.2</td>
<td>0.199</td>
</tr>
<tr>
<td>No. of complications (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>2 (33.3)</td>
<td>2 (28.6)</td>
<td>0.592</td>
</tr>
<tr>
<td>Major</td>
<td>1 (16.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Convalescence (weeks) Median</td>
<td>3.5</td>
<td>5.5</td>
<td>0.053</td>
</tr>
<tr>
<td>No. successful procedures (%)</td>
<td>6/6 (100)</td>
<td>7/7 (100)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

1 patient developed recurrence for upper tract TCC subsequently underwent nephrectomy.
the laparoscopic cases were compared with 7 ileal interposition cases completed through an open incision. Table 1 presents comparative perioperative results.

Age was significantly higher for laparoscopic cases while analgesic use and total time to convalescence were decreased for the laparoscopic group (approaching statistical significance).

One major complication of anastomotic bowel leak occurred after the second procedure and required open revision. All bowel manipulation during this case had been performed intracorporeally. Therefore all bowel work is now completed through a small abdominal incision.

Our experience with laparoscopic ileal interposition demonstrates the feasibility of performing highly complex reconstructive procedures laparoscopically. Furthermore, benefit in terms of post-procedural analgesic use and recovery parameters highlight the advantages of a minimally invasive approach for these procedures. ■

Expanding Indications for Laparoscopic Pyeloplasty

Mihir M. Desai, M.D., Robert J. Stein, M.D., Hadley M. Wood, M.D., Burak Turna, M.D., Jihad H. Kaouk, M.D., Inderbir S. Gill, M.D.

Since initially reported in 1993 by Schuessler, experience with laparoscopic pyeloplasty has steadily grown. After documenting excellent success in patients with primary ureteropelvic junction obstruction (UPJO), the laparoscopic approach has been carefully expanded to patients with more complex problems such as solitary kidney status, prior failed endopyelotomy or pyeloplasty, long segment strictures, concomitant stones, or anatomic anomalies such as ectopic kidney or horseshoe kidney.

Key points of our standard laparoscopic pyeloplasty technique include pre-placement of a 4.7 Fr x 28 cm double-J stent just prior to starting the laparoscopic operation, laparoscopic dissection of the proximal ureter and renal pelvis, dismemberment of the UPJ, and running sutured anastomosis using 4-0 vicryl suture with tailoring of the pelvis if redundant. The decision to transpose a crossing vessel is made on an individual basis and primarily depends on the operating surgeon’s impression of the obstructing nature of the vessel.

189 adult patients were identified who had undergone laparoscopic (n=154) or robotic pyeloplasty (n=35) at Cleveland Clinic since 2003. All procedures were performed

continued on next page
Laparoscopic Pyeloplasty continued from page 31

using an Anderson-Hynes dismembered technique, and 29 were performed retroperitoneoscopically. One patient required elective open conversion due to adhesions.

Twenty-three patients (12.2%) had undergone prior endopyelotomy or pyeloplasty, and 5 of these patients (2.6%) were considered extremely complicated with prior history of multiple UPJ procedures or long proximal ureteral strictures. One patient required a renal pelvic flap procedure for additional length to create a tension-free anastomosis.

Eight patients (4.2%) underwent laparoscopic pyeloplasty of a solitary kidney. Table 1 details renal functional outcomes of these eight patients compared to 6 who underwent open pyeloplasty of a solitary kidney. Fifteen patients (7.9%) underwent concomitant pyelolithotomy for ipsilateral renal calculi at the time of laparoscopic pyeloplasty. Figure 1 demonstrates the technique used for pyelolithotomy, and Figure 2 depicts the use of spoon graspers for removal of calculi. Three patients (1.6%) had an ASA score of 4 or greater and 1 patient (0.5%) had a duplicated collecting system. Four patients (2.1%) had a congenitally abnormal kidney with 2 patients having a pelvic kidney and 2 patients having a horseshoe kidney, 1 of which had a previous endopyelotomy.

<table>
<thead>
<tr>
<th></th>
<th>LP (N=8)</th>
<th>OP (N=6)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop CrCl (mL/min)</td>
<td>82 (40-172)</td>
<td>55 (26-104)</td>
<td>NS</td>
</tr>
<tr>
<td>Postop CrCl (mL/min)</td>
<td>70 (50-103)</td>
<td>62 (38-104)</td>
<td>NS</td>
</tr>
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</table>

Comparison of creatinine clearance preoperatively and postoperatively between laparoscopic and open pyeloplasty.

The overall success rate for all pyeloplasty procedures was 96.4%. Stone-free rate for concomitant pyelolithotomy procedures was 80%. No patient who underwent laparoscopic pyeloplasty of a solitary kidney progressed to end stage renal disease after a mean of 21 months followup.

As experience with advanced laparoscopic reconstruction grows, more complicated situations associated with UPJO can be successfully managed using a minimally invasive approach. Benefits of this minimally invasive approach include improved cosmesis, decreased analgesic requirement, shorter hospitalization and shorter recovery time.

Figure 1: Distribution of techniques used for pyelolithotomy during 15 total cases of laparoscopic pyeloplasty.

Figure 2: Laparoscopic spoon grasper used for pyelolithotomy.
Small Renal Masses: Predicting Benign vs. Malignant

Steven Campbell, M.D., Ph.D., Brian Lane, M.D., Christopher Weight, M.D., Denise Babineau, Ph.D., Michael Kattan, Ph.D., Inderbir Gill, M.D., and Andrew C. Novick, M.D.

Small renal masses, or SRMs, are an increasingly common clinical challenge due to the prevalent use of ultrasound and CT for the evaluation of nonspecific abdominal symptoms. Most of these masses are discovered incidentally and their malignant potential is highly variable, ranging from benign to highly aggressive. Management options also vary greatly, including active surveillance, thermal ablation and surgical excision. Unfortunately, renal mass biopsy is not reliable for assessing the malignant potential of SRMs, or even for differentiating benign and malignant. Counseling about the management of SRMs thus continues to be challenging and complex.

We hypothesized that clinical parameters such as age, sex, tumor size, smoking history and presence of symptoms could be used in nomograms to predict the likelihood of benign vs. malignant for SRMs, and for malignant tumors, indolent vs. potentially aggressive. Our study population consisted of all 862 patients managed with partial nephrectomy for a single, solid, enhancing clinical T1 (7 cm or less) tumor at our institution between 1999 and 2005.

Overall, 173 (20%) tumors were benign and 678 (80%) were malignant. Of the RCCs, 202 (30% of RCCs, 24% of all SRMs) showed potentially aggressive features defined as grade 3 clear cell histology, grade 4 of any histologic type, or locally invasive characteristics (invasion of the fat, venous system or collecting system). Great variance in malignant potential was thus observed. All 11 patients with systemic symptoms were confirmed to have RCC and were excluded from further analysis.

Our nomogram for predicting benign vs. malignant histology for SRMs proved to be robust with strong predictive power provided by patient age, sex and tumor size. The interaction between age and sex was particularly interesting, as illustrated in the figure, which shows the probability that a 3-cm SRM will be malignant in men vs. women. Our analysis showed that young women are more likely to have a benign SRM, suggesting that they should be strongly considered for partial nephrectomy. Hormonally dependent benign tumors that are more common in young or middle aged women likely account for these differences. In contrast, our data demonstrate that the risk of malignancy falls in men as they get older, providing increased rationale for a less aggressive approach in some subgroups of older men with substantial comorbidities or decline in performance status.

Prediction of indolent vs. potentially aggressive RCC was much less powerful in this population of patients with SRMs.

Only advanced age and tumor size provided predictive power, but even for these parameters the prognostic capability was limited. As shown in the table, the predicted likelihood of having a potentially aggressive SRM did not vary greatly (13-28%) among the various subgroups of patients.

In summary, our study demonstrates that clinical factors can provide substantial prognostication to predict benign vs. malignant for SRMs amenable to partial nephrectomy, and can be used for clinical decision making and patient counseling. Although most of these SRMs are benign or indolent, our ability to predict potentially aggressive cancer remains limited, and most patients should still be managed in a proactive manner. Surgical excision with partial nephrectomy remains the gold standard in this patient population.

For references, please e-mail the editor.

<table>
<thead>
<tr>
<th>Age-Sex</th>
<th>% Benign</th>
<th>% Cancer</th>
<th>% Potentially Aggressive Cancer</th>
</tr>
</thead>
<tbody>
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<td>40-M</td>
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Predicted pathologic outcomes for a 2.5-cm incidentally discovered SRM, according to age and gender.

![Predicted Probability of Cancer](image)

Predicted probability that a SRM amenable to partial nephrectomy is cancer in men vs. women with an incidentally detected 3.0-cm solid tumor. Note that the likelihood of cancer increases with age in females and decreases with age in males.

Key Points

Our study demonstrates that clinical factors can provide substantial prognostication to predict benign vs. malignant for small renal masses amenable to partial nephrectomy, and can be used for clinical decision making and patient counseling.

Partial nephrectomy remains the gold standard in patients with small renal masses.
Female sexual dysfunction (FSD) is defined as a disorder of sexual desire, arousal, orgasm and/or pain, which results in personal distress and has an impact on quality of life and interpersonal relationships. FSD is a highly prevalent problem affecting 4 out of 10 women in the United States. Yet unlike male sexual dysfunction, our knowledge and treatment of FSD are rudimentary. In order to further our understanding of female sexual function and the impact of overactive bladder on female sexual health, we are currently conducting two clinical trials at Cleveland Clinic.

The first study, “Current Perception Thresholds of the Female Genitalia in Sexually Active Women,” is aimed at establishing normative current perception threshold (CPT) values with neuroselective sine wave currents in the external genitalia of healthy, sexually active pre-menopausal women. Several studies have suggested that alterations in tactile sensitivity of the female genitalia are linked with FSD, particularly arousal, orgasmic and pain disorders. Interestingly, little is known about normal sensory nerve thresholds in female genitalia. We do know, however, that the female genitalia are richly innervated. The inner two-thirds of the vagina is innervated only by pain receptors. The outer third is innervated by touch receptors, Merkel tactile discs, which respond to steady pressure. Given that different areas of the female genitalia are innervated by different receptors, different areas of the genitalia respond to different types of stimulation and have different sensory nerve thresholds.

Most of the studies focusing on alterations in tactile sensation between women with and without sexual dysfunction have used von Frey and Semmes-Weinstein monofilaments. However, these monofilaments give limited sensory information. While they can detect gross alterations in tactile sensation they cannot detect alterations among the three types of afferent fibers, A-β, A-δ and C fibers. A-β fibers are large, myelinated fibers that respond to touch and pressure sensation. A-δ fibers are small, myelinated fibers that conduct temperature, pressure and fast pain. C fibers are large, unmyelinated fibers that conduct temperature and slow pain. C fibers are normally quiescent and only active in various pathologic states. Unlike the von Frey and Semmes-Weinstein monofilaments, the Neurometer® CPT (current perception threshold) (Neurotron, Inc., Baltimore), a sine-wave electrical stimulator, can detect alterations in the 3 types of afferent fibers. The Neurometer® CPT is an electrical stimulator that uses painless, automated sensory nerve conduction threshold (sNCT®) evaluation through application of constant current neuroselective electrical stimuli. This electro-diagnostic procedure has been used in various clinical settings to establish normative painless, CPT values for various cutaneous sites. The Neurometer® CPT also has been used to detect axonal and demyelinating peripheral neuropathies in patients with diabetes mellitus. Studies have demonstrated the neuroselectivity of the Neurometer® CPT in evaluating large unmyelinated and small myelinated fiber function. This device also can detect small fiber pathology with associated symptomatology, including autonomic dysfunction. The Neurometer® CPT has been used to assess afferent autonomic sensation of the bladder. Studies using the Neurometer® CPT in the human bladder suggest that CPT may be a useful method in identifying the subselective disturbances of the autonomic neuropathy in the lower genitourinary tract. Therefore, we are using the Neurometer® CPT to establish normative female genital sensory thresholds in sexually active women.

The second study is a prospective, randomized, double-blind study to evaluate the effect of anticholinergic medications and topical vaginal estrogen cream on bladder and sexual function in postmenopausal women with overactive bladder (OAB). While several studies have shown urinary incontinence to negatively impact female sexual function, few studies have focused primarily on the effects of OAB on female sexual health. Recently, Coyne et al. conducted a study looking at the impact of OAB on 34 sexually
active women. This study found that both OAB dry and OAB wet had a negative impact on women’s sexual health by reducing sexual desire and the ability to achieve orgasm.

Anticholinergic agents and estrogen therapy have independently been shown to alleviate the symptoms associated with urinary incontinence by eliminating urinary leakage during sexual activity. Topical estrogen therapy has also been shown to improve vaginal atrophy, a condition associated with sexual dysfunction. It is important to note, however, that no data exist on the combined efficacy of topical estrogen therapy and oral anticholinergic drugs in postmenopausal women. Therefore, our study is aimed at determining whether combination therapy (anticholinergic medications and topical estrogen replacement) is better than either individual therapy alone in the treatment of postmenopausal women with OAB.

The last 15 years have seen a tremendous increase in our understanding of female sexual function. Yet despite our advancements, our understanding of the complexities of female sexual function and how different conditions impact female sexual health remains rudimentary. As researchers in this field we hope that these two studies will further our knowledge and advance the field of female sexual function.

For references, please e-mail the editor.
Update on Complications of Vaginal Surgery

Sandip Vasavada, M.D., Howard Goldman, M.D., and Raymond Rackley, M.D.

As a tertiary care referral center, we have seen and treated many of the complications that result from vaginal surgery. While overall success rates of both stress incontinence and prolapse surgery may be at all-time highs, the innovative surgical techniques currently in use have led to new types of complications. This is not to suggest that one should not innovate or try new approved therapies, but rather that one should be comfortable with the problems that can arise in the context of these new therapies.

Key Points

- Cleveland Clinic urologists have studied complications resulting from the placement of slings via a transobturator approach and found that when a groin abscess develops, these cases required aggressive debridement and opening of the medial thigh to adequately expose and drain the abscesses.

- Chronic pain in the groin crease or vaginal fornix requires incision or removal of the offending sling segment.

- Our technique for removal of mesh extrusion that does not resolve with hormonal cream treatment includes excising all visible mesh along with an additional 1-cm border. This allows for healthy vaginal skin edges, which allow for uncomplicated healing.

Sling Surgery

Retropubic mid-urethral synthetic slings have become firmly established as first-line therapy for the management of stress urinary incontinence. Recently, many have started placing these slings via a transobturator approach in an effort to avoid potential bladder and intra-vesical complications associated with the retropubic approach, as well as to decrease the rate of iatrogenic obstruction below that noted with the traditional TVT. A recent prospective, randomized trial of the TVT versus TOT slings at Cleveland Clinic and Good Samaritan Hospital in Cincinnati, in collaboration with the Section of Urogynecology, has borne out these concepts by demonstrating a 3% retention rate in the TOT arm vs. 5% in the TVT arm. However, as we gain experience with transobturator slings it is evident that they, too, can have potential complications despite their more favorable safety compared with retropubic slings.

During the last few years we have seen and managed several cases of thigh and groin abscesses from these slings placed via an obturator approach (see Figure 1). These cases required aggressive debridement and opening of the medial thigh to adequately expose and drain the abscesses. While these cases were more common with ObTape® (Mentor Corp., Santa Barbara, Calif.) slings, they have been seen with other types of slings as well.

Chronic pain in the groin crease or vaginal fornix has been seen too. It appears that the slings have been placed under too much tension and/or too close to the vaginal fornix, thus causing pulling in the vagina with each movement. Most of these patients have been referred in as they failed conservative treatments such as trigger point injections or physical therapy. Most have required incision or removal of the offending sling segment and have responded well to this intervention.
**Prolapse Surgery**

In an effort to reduce what many feel to be unacceptably high rates of recurrence of prolapse, there has been a move toward the use of synthetic mesh to help augment prolapse repairs. While early data support the use of mesh, its use has resulted in unique complications. The most common ones seen are extrusion of mesh into the vagina, reported to occur in 3-15% of cases, and pain syndromes frequently resulting from tension at mesh arm sites where the arms enter the pelvic side walls. The complication rates are suggested to vary based on surgical technique and surgeon experience.

During the last 2 years we have had an increasing number of patients referred to us with these problems. We have thus gained experience at managing these complications successfully and minimizing patient morbidity. While some cases of mesh extrusion resolve with local treatment with hormonal cream, others require surgical excision. Our technique for removal involves excising all visible mesh along with an additional 1-cm border in order to give adequate healthy vaginal skin edges that will allow for uncomplicated healing. Often, the removal of mesh off of the underlying bladder or rectum can be challenging, but with good surgical technique can be accomplished (see Figure 2). For those with pain localized to the site of mesh arm insertion into the pelvic side wall, conservative therapies can be initially employed, but many will ultimately require release of those arms. We have generally approached these with an incision through the vaginal fornix directly over the offending mesh arm and then dissected out and incised the mesh. Most patients have had immediate resolution of much of their pain.

Every new technology comes with its own unique set of complications. While overall the benefits of these new approaches appear to outweigh the risks, it is important to develop strategies for dealing with patients who may develop some of these complications. At the Glickman Urological and Kidney Institute, our large referral base has allowed us to gain extensive experience with dealing with these complications and restoring these patients back to a full active lifestyle.
Much anatomic information is available regarding the neuroanatomy of the penis. However, until recently, little research has been performed to evaluate the pertinent neuroanatomy of the clitoris. With the advent of new sling techniques for the treatment of stress incontinence as well as increasing interest in the use of neuromodulation for patients with overactive bladder and other types of lower urinary tract dysfunction, knowledge of the course of the clitoral nerves has become important. Whether as something to avoid (in sling procedures) for fear of causing diminished sexual sensation or something to find (as a route for neuromodulation) the importance of a clear understanding of the location of these nerves cannot be understated.

Using a collaborative multidisciplinary approach, members of the Glickman Urological and Kidney Institute (Howard B. Goldman, M.D., J. Stephen Jones, M.D., Raymond Rackley, M.D., and Sandip Vasavada, M.D.) and their colleagues (Ashwin Vaze, M.D., and Ken Gustafson, Ph.D.) embarked on a series of cadaveric studies to define the course of these nerves. After careful dissection of multiple female cadavers, the course of the clitoral nerves was revealed. Essentially, these nerves, which are thought to play a primarily sensory role and ultimately join and become a component of the pudendal nerves, were noted to travel in a consistent manner across all of the specimens examined. Traveling from the pudendal nerve, the clitoral nerve pierced the perineal membrane 2.7 cm lateral to the external urethral meatus. It then traversed 1.9 cm along the bulbospongiosus muscle before traversing posterior to the crura. It then reappeared, hooking over the crura, to run for 2.3 cm on the anterolateral surface of the body of the clitoris, before dividing into two cords 0.5 cm long and terminating 1 cm short of the tip of the glans clitoris (see Figure).

This unique course – particularly the transition from running on the lateral surface of the clitoral body to hooking medially and running in a triangular area between the diverging clitoral bodies and the pubic symphysis – opens the door to a possible site for stimulation of the nerves and neuromodulation of bladder function. Prior studies have demonstrated that stimulation of the genital nerve can lead to inhibition of bladder activity. Knowledge of a relatively superficial site where both nerves can be stimulated simultaneously with one electrical lead opens up new avenues for the treatment of overactive bladder syndromes. In addition, knowledge of the location of these nerves should help prevent iatrogenic surgical injury and potential diminution of sexual function resulting from newer sling and other reconstructive vaginal surgery techniques.

Ultimately, these neuroanatomic insights have the potential to improve the quality of life of patients with lower urinary tract dysfunction as well as to maintain sexual function in women undergoing pelvic reconstructive surgery.
Innovative Surgical Techniques and a Multidisciplinary Approach Lead to Success in Treating Pediatric Urinary Stones

Jeffrey S. Palmer, M.D., F.A.C.S., F.A.A.P.

Our experience at the Glickman Urological and Kidney Institute with pediatric urinary stones has led to several innovative surgical techniques that are now used by urologists worldwide to improve surgical care and safety in this area. First, semirigid ureteroscopy in adults and children is traditionally reserved only for distal ureteral procedures due to the proposed risk of injury associated with proximal ureteroscopy. However, the potential advantages of semirigid compared to flexible ureteroscopes include enhanced optics and larger working channels. We evaluated all children 12 years of age and younger who underwent attempted semirigid proximal ureteroscopy and pyeloscopy with the newer advanced endoscopes. Our results demonstrate that this technique can be successfully performed in a high percentage (85%) of prepubertal children to treat proximal ureteral and renal pelvis calculi as well as to perform diagnostic ureteroscopy.

Second, active dilation (e.g., balloon or rigid dilation) of the ureteral orifice is commonly performed to access the ureteral orifice in the adult and pediatric population prior to ureteroscopy. We evaluated all children less than 18 years of age undergoing a ureteroscopic procedure who were not able to have the ureteral orifice endoscopically accessed by a ureteroscope. All children then underwent double J stent insertion rather than active dilation of the ureteral orifice. We found that passive dilation of the ureteral orifice in preparation for ureteroscopy in the pediatric population is a straightforward, successful (100%), and beneficial technique.

Third, ungated extracorporeal shock wave lithotripsy (ESWL) is unsynchronized to the patient’s electrocardiogram. Although ungated ESWL in adults has been associated with arrhythmias, its safety in children is not well established. We evaluated all children less than 18 years of age undergoing ungated ESWL of renal calculi. Our results demonstrate that ungated ESWL of renal calculi is safe (100%) and efficacious (92%). Also, the arrhythmias associated with ungated ESWL in adults do not appear to occur in children.

The Glickman Urological and Kidney Institute has taken a multidisciplinary approach to the care of children with urinary stones. We believe that this approach maximizes the care of the child. A pediatric urologist experienced in endoscopy and lithotripsy performs all surgical interventions with the most advanced pediatric endoscopic and lithotripsy equipment. Experienced interventional radiologists and anesthesiologists provide access for percutaneous procedures and safe pediatric anesthesia. Pediatric nephrologists perform a complete metabolic evaluation and provide medical management.

Figure 1: Semirigid ureteroscopy of proximal ureter
Figure 2: Semirigid ureteroscopic view of proximal ureteral stones
Figure 3: Stone fragments after extracorporeal sound wave lithotripsy
Outpatient Ureteral Reimplantation: Definitive Results and Improved Quality of Life

Jeffrey S. Palmer, M.D., F.A.C.S., F.A.A.P.

Ureteral reimplantation is the gold standard for the surgical treatment of vesicoureteral reflux (VUR) in the pediatric population. There are two surgical approaches, intravesical and extravesical, which typically have a 98-100% success rate thereby making the postoperative VCUG a parental prerogative. The intravesical approach (e.g., Cohen cross-trigonal) is the preferred technique by the majority of urologists. It involves opening the bladder and then mobilizing and reimplanting the ureter. The extravesical approach involves splitting the detrusor muscle (i.e. detrusorrhaphy), creating detrusor flaps, advancing the ureter, and then closing the flaps over the ureter. The popularity of the intravesical techniques is due in part to the beliefs that the extravesical approach results in a high incidence of postoperative urinary retention after bilateral surgery, and cannot be used for more complicated reimplantations (e.g., diverticulectomy, ureterocelectomy and ureteral tapering).

The intravesical procedures have associated morbidity including postoperative hematuria and bladder spasm. Also, the cross-trigonal technique places the ureter in a deviated course, resulting in difficult access for future retrograde procedures (e.g., ureteroscopy or stent placement). On the contrary, the extravesical approach has less morbidity, including no postoperative hematuria or bladder spasms, and places the ureter in a normal anatomic course. More recently, endoscopic treatment has been promoted as an outpatient, non-invasive technique with low morbidity. However, the success rate of this technique is significantly lower than the intravesical or extravesical operations, is contraindicated for several associated ureteral/bladder anomalies, and still requires a general anesthetic and postoperative voiding cystourethrogram (VCUG). Therefore, an ideal operation would be an outpatient ureteral reimplantation even for associated anomalies.

Key Points
We at the Glickman Urological and Kidney Institute have performed more than 70 consecutive bilateral extravesical reimplantations in toilet-trained children. All were discharged on the day after surgery without any cases of urinary retention, acute urinary tract infections or hospitalization after discharge.

We further refined the extravesical surgical technique and postoperative critical pathway in order to consistently have same-day discharge of unilateral, bilateral and complicated reimplantations without urinary retention or increased morbidity while having high parental and patient satisfaction. This was accomplished in 50 patients.

This modified surgical approach, preoperative and postoperative education, and implementation of the critical pathway have markedly changed the way vesicoureteral reflux is surgically treated and has led to enhanced parental and patient satisfaction.

Figure 1: Dissection of the ureter to the bladder hiatus keeping the bladder mucose intact.

Figure 2: Two ureteral advancing/fixation sutures are placed in a horizontal mattress fashion between the distal detrusor muscle tunnel then to the corresponding position of the distal ureter extra-mucosally, and then back to detrusor muscle. Traction on these two sutures brings the distal edge of the ureter under the lip of the detrusor muscle.
ureteral/bladder anomalies, without postoperative urinary retention even after bilateral surgery, and have high parental and patient satisfaction.

The Glickman Urological and Kidney Institute has accomplished these goals. We first modified the extravesical ureteral reimplantation technique and developed a critical pathway to prevent urinary retention in toilet-trained children undergoing bilateral surgery. The modified surgical technique limits ureteral dissection and mobilization, and detrusor dissection to as distally as possible. No surgical dissection occurs in proximity to the obliterated umbilical artery, nor is the artery ligated. Patients follow a strict postoperative critical pathway, and parents receive extensive preoperative and postoperative education. A child is required to fulfill strict criteria in order to be discharged including parents feeling comfortable taking the child home.

More than 70 consecutive bilateral extravesical reimplantations in toilet-trained children have been performed with all patients discharged on the day after surgery without any cases of urinary retention, acute urinary tract infections or hospitalization after discharge. All patients tested had radiographic resolution of the vesicoureteral reflux on postoperative VCUG. Parents and patients expressed high satisfaction with their experience.

We then further refined the extravesical surgical technique and postoperative critical pathway in order to consistently have same-day discharge of unilateral, bilateral and complicated reimplantations without urinary retention or increased morbidity while having high parental and patient satisfaction. Implementing this technique and protocol in 50 unilateral and bilateral extravesical reimplantations has resulted in patients being uniformly discharged on the same day of surgery. None of the children has had any significant complications or hospitalization after discharge. All patients tested postoperatively have had radiographic resolution of the vesicoureteral reflux. Again, parents and patients expressed high satisfaction with their experience, especially the ability of the child to return home the same day as surgery.

This modified surgical approach, preoperative and postoperative education, and implementation of the critical pathway have markedly changed the way VUR is surgically treated and has led to enhanced parental and patient satisfaction. These advances have allowed out-of-state patients to come to Cleveland the evening before or day of surgery and return home the same day. Therefore, the ureteral reimplantation cannot only cure the patient of VUR, but have them sleeping in their own bed the same day.
Examination of a Series of Non-Schistosomal Squamous Cell Carcinomas of the Bladder

Donna E. Hansel, M.D., Ph.D.

Bladder cancer ranks 5th in cancer incidence in the Western Hemisphere, and the vast majority of bladder cancers that occur in the United States are urothelial carcinomas. However, other less common forms of bladder cancer, such as squamous cell carcinoma and adenocarcinoma, exist. Of these less common forms, squamous cell carcinoma of the bladder has not been well characterized in Western populations where infection with *schistosoma hematobium* – a major risk factor in the development of this neoplasm worldwide – is exceedingly uncommon. Although other risk factors, such as neurogenic bladder, chronic catheterization and urinary tract calculi, may precede the development of squamous cell carcinoma, little is known regarding the pathologic or molecular alterations commonly associated with these lesions. In addition, the outcomes associated with squamous cell carcinoma on radical cystectomy have remained somewhat controversial.

Several studies have been performed in the past 30 to 40 years, that address outcomes for patients with squamous cell carcinoma of the bladder. Although well-performed, several challenges existed in the interpretation of long-term outcomes. First, several studies were based primarily on biopsy and TUR material in which neither the entire tumor could be surveyed for mixed morphologies nor associated lesions in other sites of the bladder assessed. Second, patients in several studies underwent radiation treatment rather than surgery, with poor subsequent outcomes. Finally, many studies incorporated some patients with schistosomal-based cancers, although the molecular mechanisms underlying the development of these cancers may be different than non-schistosomal cancers. Recently, however, one study that examined progression rates for squamous cell carcinoma on radical cystectomy identified outcomes similar to those of invasive urothelial carcinoma.

**Patient demographics and clinical findings**

To further address the clinical and histologic findings of this uncommon bladder neoplasm, we examined 45 cases of non-schistosomal squamous cell carcinoma of the bladder on cystectomy. Although our study examined patients who were surgical candidates, approximately 15% of all patients initially identified with squamous cell carcinoma of the bladder on biopsy or transurethral resection were ultimately unresectable. Patient age ranged from 46 to 83 years (average 68 years) and the male to female ratio was 3:2. No patient had a prior history of schistosomal infection and only one patient demonstrated extensive vaginal condylomata. The most common clinical signs and symptoms included hematuria (n=29), dysuria (n=6) and flank or suprapubic pain (n=5).

**Histopathologic findings**

Tumors were predominantly unifocal and ranged in size from 0.8 to 6.4 cm (average 3.8 cm). Invasion was identified into the lamina propria (pT1; 2%), muscularis propria (pT2; 31%), perivesical fat (pT3; 60%) or adjacent organs (pT4; 7%). Concurrent metastases were present in 24% of cases, most commonly to the pelvic lymph nodes, and consisted of keratinizing squamous cell carcinoma. Most tumors were moderately (64%) to poorly (29%) differentiated and many tumors demonstrated perineural (24%) or angiolymphatic (16%) invasion.

In addition to examining findings of relevance to the invasive component, we were also in the unique position of reviewing superficial mucosal findings present throughout the bladder, as cystectomy specimens are - in general - extensively sampled. A variety of lesions were present on the bladder surface, including keratinizing squamous metaplasia, verrucous squamous hyperplasia, and condylomata. Some small separate foci of flat urothelial carcinoma in situ were also identified, which were often identified in conjunction with keratinizing squamous metaplasia and dysplasia in other regions of the bladder.
Clinical outcomes

Long-term outcomes indicated that approximately 29% of patients ultimately died of progressive disease. The most important factor that influenced progression on multivariable Cox regression analysis was the presence of invasion into the perivesical fat or beyond (pT3/pT4).

Squamous cell carcinoma of the bladder often presents at an advanced stage, although surgical resection appears to be of value in a subset of patients. Following cystectomy, the long-term survival of patients with this disease does not appear as dismal as that historically reported and further studies that examine this specific patient population may be of interest in determining best management strategies for this disease.

For references, please e-mail the editor.

Narrow-Band Imaging for Detection of Bladder Cancer

J. Stephen Jones, M.D., F.A.C.S.

Researchers at the Glickman Urological and Kidney Institute have investigated a new imaging technology for the past four years in conjunction with engineers from Olympus America, Inc. Narrow-Band Imaging, or NBI, is an endoscopic system that allows enhanced visualization of changes in tissues in order to better understand the difference between benign and malignant tissues. The result has been improvement in the ability to rapidly detect subtle mucosal lesions.

NBI works by altering the standard white light source to consist of specific wavelength bands, which take advantage of the scattering and absorption properties of human tissues. The narrow-band light is composed of two specific wavelengths that are strongly absorbed by hemoglobin. Filters limit entry of other wavelengths that might overwhelm the bands of greatest interest, which enhances visualization of the target wavelengths. The short wavelengths of light consist of 415 nm light, which penetrates only the superficial layers of the mucosa, so these wavelengths are absorbed by capillaries in the surface layer of the mucosa.

The longer 540 nm wavelengths of light penetrate deeper compared to 415 nm light and are absorbed by blood vessels, such as veins, which are located deeper than capillary vessels in the surface layer of the mucosa. As a result, under narrow-band illumination, capillaries on the mucosal surface are displayed in brown and veins in submucosa are displayed in cyan on the monitor. The use of digital camera chip technology with high-definition television monitors further improves the image and allows accurate recognition and quantification of mucosal abnormalities. The improved visibility provided by NBI may improve examination efficiency by helping to reduce examination time through enhancement of subtle lesions. It also may facilitate more accurate biopsies by clarifying which tissues appear to have abnormal vasculature.

Combining cutting-edge optics with NBI, researchers from the Glickman Urological and Kidney Institute continue to work with Olympus engineers to optimize visualization of the urinary tract and to improve detection and surveillance techniques for bladder cancer.

Subtle lesion identified using white light cystoscopy (fig 1) near right ureteral orifice becomes easily visible with sharply demarcated borders using Narrow-Band Imaging (fig 2). Biopsy confirmed carcinoma-in-situ with high-grade papillary features.
Long-Term Results Following Buccal Mucosa Graft Urethroplasty

Kenneth Angermeier, M.D.

A variety of tissues and materials have been used for the reconstruction of urethral strictures; more are being studied now and yet more, no doubt, will be studied in the future. Today, buccal mucosa is the tissue of choice for such reconstructions. As such, it is to be considered the gold standard to which all other materials must be compared, and given that, it is worthwhile to examine the long-term attributes of that standard.

The ideal material for substitution urethroplasty should be readily incorporated with rapid healing, resist complications such as infection or calculus formation, minimize scarring, and should be readily available and easy to handle. Buccal mucosa meets these criteria. It resists infection and is compatible with a moist environment, which may have implications for long-term success. It has a thick epithelium and a thin lamina propria, allowing for relatively efficient inosculation.

Buccal mucosa actually has a long history. Its potential for urethral repairs was identified in 1941 by Humby, but fell from use for a variety of reasons. It was rediscovered in 1992 by Burger who applied it in hypospadias repair, and it is now favored over other grafts such as those derived from the skin and bladder as well as genital skin flaps. Tissue engineering is now being studied in an attempt to grow larger sheets of buccal mucosa and, if successful, such engineered tissue would overcome the only downside to buccal mucosa, which is limitations on the amount of tissue available during extensive urethral repair.

In order to evaluate the long-term results with buccal mucosa graft urethroplasty, we conducted a retrospective study of 39 men who had undergone surgery for refractory urethral strictures between 1997 and 2001. Although we had short-term chart review for all patients, we were able to contact 26 (67%) of the patients for long-term data that provide one of the few five-year follow-up studies of the success and durability of the procedure.

The men were ages 20 to 72 with the mean being 42.4 years. The majority had previously undergone multiple dilations and urethrotoomies for recurrent bulbar urethral strictures. Six had prior skin flap or graft urethroplasties and four had panurethral stricture disease. Twenty-five men had a ventral onlay repair, and one had the graft placed dorsally. When doing a ventral buccal mucosa graft only it is critical to close the corpus spongiosum over the graft (spongioplasty) to aid take and minimize the potential for sacculation. In the dorsal approach, the buccal mucosa is spread and fixed to the underlying corpora cavernosa before being sutured to the urethra.

The overall success rate in this series was 85%. The success rate for the 26 patients in whom direct long-term contact was possible was 85%, which is comparable to the rate seen in the report by Andrich, the only other 5-year study we were able to find in the literature. The mean AUA score in these patients was 5.0 (range 0 - 27). The appearance of a buccal mucosa graft in place for longer than 8 years is seen in the accompanying figure. Four patients did have focal recurrent strictures defined as the inability to pass a standard flexible cystoscope through the area, and three of these required dilation and/or optical urethrotomy. One patient was completely asymptomatic with a wide caliber recurrence and refused additional intervention.

Although more long-term studies need to be conducted, we feel that our study shows that buccal mucosal graft urethroplasty is a procedure that provides very good success rates to at least five years and probably longer, based on the long-term visual appearance of the grafts.

For references, please e-mail the editor.
Chronic PDE-5 Inhibitors Can Help Prevent Erectile Dysfunction Following Prostate Brachytherapy

Craig D. Zippe, M.D., and Geetu Pahlajani, M.D.

Definitive treatment of localized prostate cancer, whether by surgery or external beam radiation or prostate brachytherapy, is a significant comorbidity in the sexual longevity of our younger patients. It is not any different than having a diagnosis of diabetes mellitus, severe hypertension or hyperlipidemia requiring daily medication.

In exploring the feasibility of a chronic therapy or dosing model, we chose to investigate a pharmacologic stimulus in a subset of patients who underwent prostate brachytherapy. We hypothesized that beginning a daily oral dose of a PDE-5 inhibitor (sildenafil) at the time of radioactive seed placement may mitigate the subsequent radiation damage and fibrosis. Between December 2002 and January 2004, data on 44 sexually active patients (mean age 68.6) was collected. Group 1 (24 patients) received a daily maintenance dose of sildenafil (50mg/day for 12 months, then prn). The PDE-5 inhibitor was started immediately following brachytherapy [mean-3 days (1-5)]. Group 2 (20 patients) did not receive any early treatment. All patients were assessed after a minimum follow up of 12 months using the International Index of Erectile Function (IIEF-5). In Group 1, IIEF-5 scores were totally preserved at 12 months follow-up (pre-brachy IIEF score: 24 + 3.0 vs. post-brachy IIEF-5: 21+ 3.6). In Group 2, there was a significant decline in IIEF-5 scores (pre-brachy IIEF-5: 22.4 +2.67 vs. post-brachy IIEF-5: 10.6 + 6.86 (Table). This pilot study is one of the first models in the radiation literature to demonstrate that early intervention and perhaps chronic therapy may impact subsequent potency rate.

With the evidence that patients with brachytherapy-induced erectile dysfunction respond favorably to sildenafil, we need to focus on prevention of erectile dysfunction. Promising results with early PDE-5 inhibitors make it necessary to explore chronic maintenance therapy to help preserve sexual activity in our younger patients.

It may be possible to convince patients to use a daily medicine for a period of neuropraxia (0-12 months) following definitive prostate cancer treatments, and then use oral therapy as adjuvant treatment on an as needed basis to augment erectile performance.

For references, please e-mail the editor.

### Key Point
Promising results with early PDE-5 inhibitors following prostate brachytherapy make it necessary to explore chronic maintenance therapy to help preserve sexual activity in our younger patients.

### Response to IIEF-5 Questionnaire by Patients on Chronic Sildenafil Dosing Following Prostate Brachytherapy

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<td>4.5+1.0</td>
<td>3.75+0.96</td>
</tr>
<tr>
<td>Maintenance ability</td>
<td>4.1+1.01</td>
<td>3.65+0.87</td>
</tr>
<tr>
<td>Maintenance frequency</td>
<td>4.5+1.03</td>
<td>3.79+1.9</td>
</tr>
<tr>
<td>Intercourse satisfaction</td>
<td>4.5+1.04</td>
<td>4.0+1.1</td>
</tr>
<tr>
<td>Total</td>
<td>24+3.0</td>
<td>21+3.6</td>
</tr>
</tbody>
</table>

p<0.05, SD-Standard deviation
Beyond the Semen Analysis: New Tests in Male Infertility

Edmund Sabanegh, M.D., and Ashok Agarwal, Ph.D.

Sophisticated new tests that evaluate sperm function and genetics are taking male infertility evaluation to a new level.

While the semen analysis remains the cornerstone for a male fertility evaluation, it has limitations that mean it does not always accurately predict fertility. With the availability of tests that provide more in-depth information regarding sperm quality, Cleveland Clinic reproductive medicine specialists now can provide better diagnostic information for patients allowing more effective therapy.

The reactive oxygen species (ROS) test, one of the newest resources available, detects the presence of free radicals in the sperm. This is significant because polyunsaturated fatty acids in the plasma membrane of sperm cells are highly susceptible to damage by reactive oxygen species such as the superoxide anion, hydroxyl radical and hypochlorite radical. Oxidative stress results due to an imbalance in the amount of oxidants and antioxidants. This can degrade sperm quality by affecting sperm morphology and motility, cause fragmentation of the DNA or affect the sperm’s ability to fertilize an egg.

Approximately 5 to 10 percent of infertile males will have normal semen analysis testing and no obvious etiology for their infertility. The ROS test is particularly useful in these men to detect the presence of oxidative stress in the sperm as a potential cause of infertility. The test is also appropriate in men with varicoceles, infections or occupational exposure to toxins such as lead or cadmium, all of which are linked to excessive ROS production.

Published studies have reported that oxidative stress may play a role in as high as 40 percent of male infertility. When the problem of ROS is identified through testing, supplementation with antioxidants and other treatments may help resolve the problem and improve fertility.

New genetic tests have furthered our understanding of male infertility and allow targeted therapy. These tests detect abnormalities in the number of chromosomes,
microdeletions or translocations in the Y chromosome, or the presence of specific gene mutations such as the cystic fibrosis gene mutation. The latter is associated with obstruction of or lack of the vas deferens.

DNA defects in sperm inhibit male fertility and can also affect the success of assisted reproductive techniques. For this reason, sperm DNA testing has assumed a very important role in a selected group of infertile men.

The sperm chromatin structure assay is one of the few techniques for evaluating DNA integrity within the sperm cells. At Cleveland Clinic, we recommend this assay in women who have had repeated miscarriages as well as men whose semen analysis reveals marked morphological abnormalities or whose semen is normal but fertilization is unsuccessful.

These tests should be applied selectively, based on semen analysis results, the couple’s history of infertility and the family medical history. Used appropriately, these novel tests now allow for evaluation of the functional quality of sperm when semen analysis alone is insufficient for predicting fertility. This information allows us to tailor therapy, thus expanding a couple’s reproductive options and increasing their chances for success.

Penile Prosthesis Implantation after Radical Prostatectomy

Drogo Montague, M.D.

In the era of PSA screening for the early detection of prostate cancer, radical prostatectomy has become commonplace. Nerve sparing is not always advisable and, when indicated, it is not always successful; hence erectile dysfunction (ED) following radical prostatectomy frequently occurs. ED occurring after radical prostatectomy responds less often to systemic therapy (PDE5 inhibitors) than does ED from other causes. In this setting penile prosthesis implantation is frequently considered.

The ideal penile prosthesis would result in a penis that appears as closely as possible to normal in both the flaccid and erect states. To do this, a large volume of fluid needs to be transferred into penile cylinders that expand to produce the erection. This same volume of fluid must be able to leave the penis to permit penile flaccidity. To accomplish this, the large-volume fluid reservoir of a three-piece inflatable penile prosthesis is necessary. The most common location for this reservoir is the prevesicle space, and entry into this space is achieved by blindly puncturing the lower abdominal fascia through the single penoscrotal incision.

Because this fascia is scarred following radical retropubic prostatectomy, many avoid considering three-piece inflatable prosthesis implantation for this indication. A recent review of our experience with 942 consecutive patients undergoing penile prosthesis implantation in our institute revealed that 115 had ED following radical retropubic prostatectomy. In each of these patients the fascia could be blindly penetrated through the penoscrotal incision allowing successful reservoir implantation into the prevesicle space without injury to surrounding structures. Comparison of outcomes between this post radical prostatectomy cohort and the remainder of the implant recipients showed no significant differences.

Key Points

- When men face penile prosthesis implantation after radical prostatectomy, the three-piece inflatable penile prosthesis can be safely implanted and need not be avoided.
Vacuum Constriction Device (VCD) Revisited: Its Emerging Role in Preventing Erectile Dysfunction

Craig D. Zippe, M.D., and Geetu Pahlajani, M.D.

There is considerable interest in early intervention protocols in the use of VCD to encourage corporal rehabilitation and prevention of post radical prostatectomy veno-occlusive dysfunction. Early penile rehabilitation after radical prostatectomy enhances earlier recovery of nocturnal erections by enhancing oxygenation of the corpora cavernosa and preventing formation of collagen and fibrosis, a cofactor in smooth muscle relaxation and erectile function. Clinically, this is evident by the preservation of penile length and girth that is seen with early use of the VCD following radical prostatectomy.

Several years ago our group completed a prospective, but non-randomized study on the use of early VCD after retropubic prostatectomy at Cleveland Clinic. This study included 109 patients who underwent radical prostatectomy between August 1999 and October 2001. Of the 109 patients, 74 (Group 1) patients used early VCD daily for 9 months and 35 were observed without any early maintenance erectogenic treatment (Group 2). Patients in Group 2 occasionally used oral PDE-5 inhibitors on a prn basis. Treatment efficacy was analyzed at baseline and subsequently by responses to the International Index of Erectile Function (IIEF-5) or Sexual Health Inventory for Males (SHIM). Patient outcomes regarding compliance, changes in the penile length and circumference, return of natural erection, and ability for vaginal intercourse were also assessed. With the minimum follow-up of 9 months, 80% (60/74) in Group 1 successfully used their VCD with a constriction ring for vaginal intercourse at a frequency of twice/week with an overall spousal satisfaction rate of 55% (33/60) (Table). Nineteen of these 60 patients (32%) reported return of natural erections at 9 months with 10/60 (17%) having erections sufficient for sexual intercourse. After a mean use of 3 months, 14/74 (18%) discontinued treatment. Overall in the early VCD group, 17% (10/60) had natural erections sufficient for sexual intercourse. In Group 2, 37% (13/35) of patients regained spontaneous erections at a minimum follow-up of 9 months after surgery. However, only 4/35 of these patients (11%) had erections sufficient for successful vaginal intercourse or potency, with the remaining patients (26%) seeking adjuvant therapy.

Radical prostatectomy has a significant effect on penile length and girth. Munding et al in 2001 reported that 71% men had a decrease in penile stretched length. Similarly Savoie and colleagues in 2003 reported a decrease in penile length in 68% of their patients after radical retropubic prostatectomy. In our study, when assessing the penile length and girth in the observation group (no VCD) 63% reported a decrease in penile length and girth. In contrast in the 60 compliant VCD patients, only 14 (23%) reported a decrease in penile length and girth at 9 months (range 4 to 8 months).

Our study has been confirmed recently that early use of VCD preserves penile length and girth. Dalkin et al presented an abstract at the Society of Urologic Oncology in 2007 demonstrating that early use of VCD 10 minutes per daily session reduced the likelihood of penile shortening from 48% in historical control to 3.5% in his study.

Evolving data suggests that the early use of the VCD facilitates early sexual intercourse, early patient/spousal sexual satisfaction and preservation of penile length and girth. These benefits of early VCD therapy are significant because of the length of nerve praxia that occurs following radical prostatectomy. VCD therapy carries a high patient compliance and is affordable, as it is covered by most insurance plans. Our current early intervention program following radical prostatectomy includes daily VCD therapy, 5 minutes twice a day, and maximum use of oral PDE-5 inhibitors. Due to lack of insurance coverage for PDE-5 inhibitors, VCD therapy has emerged as the dominant therapy in our intervention strategies.

For references, please e-mail the editor.
Cell Phone Use Causes Decline in Semen Quality

Ashok Agarwal, Ph.D., and Edmund Sabanegh, M.D.

Worldwide more than 700 million cell phones are in use and the number is expected to increase to 1.6 billion very soon. The question of whether mobile phone radiation causes any adverse effects on fertilization potential of males has raised a significant public concern. Sufficient studies have been published documenting the effects of electromagnetic waves on blood pressure, melatonin, concentration, sleep and headaches to validate the question of their potential effects on semen quality.

An observational study recently completed by researchers in the Cleveland Clinic’s Reproductive Research Center, the Glickman Urological and Kidney Institute and the Department of Obstetrics-Gynecology is the first to demonstrate that cell phone usage has adverse effects on multiple semen parameters. Results were presented at the fall 2006 meeting of the American Society for Reproductive Medicine in New Orleans.

Researchers stratified 361 men attending an infertility clinic into four cell phone usage groups: no use (Group A, n=40), < 2 hr/day (Group B, n=107), 2 to 4 hr/day (Group C, n=100) and >4 hr/day (Group D, n=114). Semen analysis was performed to evaluate sperm for volume, liquefaction time, pH, viscosity, sperm count, motility, viability and percentage normal morphology.

Four sperm parameters – sperm count, motility, viability and percent of normal morphology differed significantly among the cell phone use groups. We found a strong correlation between reduction in these parameters and the highest rates of cell phone use among the 361 men studied.

Electromagnetic waves potentially exert their deleterious effects on sperm through thermal and nonthermal effects or a combination. The exact mechanism is still unknown, and is one of the critical questions to be answered.

The values of these parameters were lowest in Group D (> 4 hr/day of use). As an example, average sperm count among the subjects in Group D was 50.30 x 10⁶/mL ± 41.92, compared with 58.87 ± 51.92 in Group C, 69.05 ± 40.25 in Group B and 85.89 ± 35.56 in Group A. Similar declines in motility, viability and percent of normal morphology were reported across all four cell phone usage groups. These four sperm parameters also showed significant positive correlation with each other.

When subjects were divided by sperm count into normospermic and oligospermic, motility and morphology still were significantly lower in those men who used cell phones for >4 hr/day. This suggests that the effects of cell phone use on sperm parameters are independent of the subject’s initial sperm quality.

The study results were sufficiently dramatic to attract extensive media attention, but additional research is necessary. Electromagnetic waves potentially exert their deleterious effects on sperm through thermal and nonthermal effects or a combination. The exact mechanism is still unknown, and is one of the critical questions to be answered.

Given the vulnerability of spermatozoa to radiofrequency damage, and the clinical significance of this damage in terms of fertility, pregnancy and childhood health, human studies with a careful design are urgently needed to know the impact of RF waves from cell phones on testicular tissue and male germ line. Research is being conducted in our center utilizing better study designs (by eliminating possible bias due to patient demographics, lifestyle issues and environment) in order to verify our own results and explore the pathophysiology of damage caused by EMW emitted from cell phones on the male reproductive system.

Key Points

An observational study recently completed by researchers in the Cleveland Clinic’s Reproductive Research Center, the Glickman Urological and Kidney Institute and the Department of Obstetrics-Gynecology is the first to demonstrate that cell phone usage has adverse effects on multiple semen parameters.

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Electromagnetic waves potentially exert their deleterious effects on sperm through thermal and nonthermal effects or a combination. The exact mechanism is still unknown, and is one of the critical questions to be answered.
A new protocol for the recovery of organs from non-heart-beating donors has been introduced in the county in which Cleveland Clinic is located (Cuyahoga). This protocol allows the option of organ donation for individuals who have sustained irreversible and irrecoverable brain injuries but do not fit the strict criteria for brain death.

There are currently more than 90,000 patients in the United States waiting for an organ transplant; about 2,800 are in Ohio. A minority of patients awaiting either a kidney or liver transplant have a suitable living donor, while the majority of patients are awaiting organs from deceased donors. Traditionally, organs for donation have been recovered from donors who meet strict criteria for brain death. However, since only a small percentage of suitable donors actually meet the strict brain-death criteria, protocols have been adopted in the United States and worldwide to expand the donor pool by using organs from donors who have sustained irrecoverable brain injury.

Organ donation now is an option for ventilator-dependent individuals who have sustained devastating brain injuries and have not yet progressed to brain death. Only after the patient’s family has decided to withdraw life-sustaining support will organ donation be discussed. Once the family’s consent for donation is obtained, the patient is removed from respiratory support in either the operating room or in the recovery room to facilitate organ recovery. It remains the responsibility of the patient’s primary medical team to make the declaration of death as the transplant team has no role in the patient’s care until the declaration of death. Organ recovery will commence after a period of at least five minutes after the cessation of cardiac and respiratory activity and the declaration of death.

Several large studies have demonstrated that organs from DCD donors yield similar graft survival to those from brain-dead donors. A recent review of the UNOS database showed a similar 81% five-year patient survival and 67% graft survival for recipients of DCD or brain-dead kidney donors. Similarly, a 70% five-year pancreas graft survival was seen for simultaneous pancreas-kidney recipients from DCD or brain-dead donors.
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