Expanding the Use of Robotic-Assisted Radical Cystectomy

According to data from the National Cancer Institute, by the time 2013 comes to a close, more than 72,000 people in the United States will be diagnosed with bladder cancer. The average age for a patient diagnosed with bladder cancer is 68. Demographics show a higher incidence of bladder cancer among men than women — about 4-to-1. Mortality rates have been stable in men since 1998 and slowly declining in women. In general, however, incidence and mortality rates have changed very little over the past 20 years. But, with increased longevity and a growing baby boomer population, the incidence of bladder cancer is expected to rise over the next decade.

The classical standard of care for patients with invasive bladder cancer is open radical cystectomy. But another surgical technique, robotic-assisted radical cystectomy (RARC), is emerging as a less invasive approach for the treatment of invasive bladder cancer. According to Healthcare Cost and Utilization Project’s (HCUP’s) Nationwide Inpatient Sample (NIS), there were 10,529 radical cystectomies performed in 2010. Mayo Clinic continues to be on the cutting edge of treating patients with invasive bladder cancer, having been one of the early adopters of robotic-assisted radical cystectomy. In 2007, a Mayo Clinic team, led by Erik P. Castle, M.D., a Mayo Clinic urologist who helped pioneer the robotic technique as a fellowship-trained specialist, conducted the first RARC at Mayo Clinic. Since 2007, this less invasive approach has been performed by Mayo Clinic surgeons on more than 175 patients, and today is available at all three Mayo campuses.

Because of the complexity of a radical cystectomy with urinary reconstruction, adoption of

Figure. Intracorporeal urinary diversion. A) Bowel anastomosis. B) Ureteroileal anastomosis.
Robotic-assisted technology has a steep learning curve. “Early on, people were skeptical because it is a complex operation (done) open, let alone doing robotically,” explains Dr. Castle. But seen as a natural evolution of technology developed from robotic radical prostatectomy, RARC is one of the last frontiers of robotic urologic surgery.

**Urinary diversion**

When robotic technology was first adopted, the urinary diversion portion of the procedure — the ileal conduit or neobladder — was conducted extracorporeally. Now Mayo Clinic surgeons at the Arizona campus also perform the urinary diversion portion of the procedure intracorporeally. From start to finish, the entire operation can be completed with laparoscopic incisions. In female patients, the bladder is removed through the vagina. In male patients, a 7- to 10-centimeter incision below the bellybutton allows for the removal of the bladder and creation of the ileal conduit. Mayo Clinic surgeons have performed numerous intracorporeal urinary diversion procedures since the advent of the technology in 2007. This is just one way Mayo Clinic continues to be on the cutting edge of bladder cancer treatment. “The experience and protocols in place at Mayo Clinic are enhancing recovery following surgery as well as improving outcomes and making the surgery safer every day,” notes Mayo Clinic urologist Matthew K. Tollefson, M.D.

**Oncologic equivalent?**

Because RARC is still a relatively new procedure, long-term studies on patient oncologic outcomes comparing the RARC with radical open cystectomy are lacking. To date, Mayo Clinic data on patient outcomes over a seven-year period show an oncologic equivalency for the two procedures, with RARC demonstrating decreased transfusion rates, shorter hospital stays and fewer complications.

Absent long-term published data comparing outcomes of patients of equal health status, debate continues within the urologic community as to whether or not patients undergoing RARC have an equivalent oncologic outcome to those undergoing the radical open cystectomy, says Dr. Castle. To provide this long-term data, Mayo Clinic is currently involved in the first multi-institutional randomized trial sponsored by the National Institutes of Health — *Open Vs. Robotic-Assisted Radical Cystectomy: A Randomized Trial*. Measured by two-year progression-free survival, the trial will evaluate oncologic, perioperative and functional outcomes of patients undergoing the two procedures to determine if RARC delivers the same oncologic result as open radical cystectomy.

Dr. Tollefson explains the significance of the study, “Once we get the results of these studies, I believe we will see more and more patients with bladder cancer treated with RARC.” Dr. Castle agrees, “Hopefully this will settle the debate. So far the data supports and suggests they are equivalent.”

**Reduced complications**

Paul R. Young, M.D., also an urologist at Mayo Clinic, has spent a significant portion of his career performing open radical cystectomies as a treatment for patients who have invasive bladder cancer. In the past three-plus years, he has incorporated robotic-assisted radical cystectomy, the less invasive technique, into his practice. It is clear to him that patients’ lose less blood during that surgery, resulting in a reduced need for postoperative transfusions. And while the data are not yet conclusive, Dr. Young is hopeful that the long-term studies will confirm oncologic outcomes to be comparable, and the number of postoperative complications to be reduced.

“Postoperative complications following cystectomies are very high. Since these patients tend to be older and the risk of complications is 20 to 30 percent no matter how you do it, where or who does it, my big hope is that we can decrease the complication rate and it will not be as big a project of managing these patients,” says Dr. Young. Incorporating robotic technology into his arsenal of bladder cancer treatment allows Dr. Young to offer his patients an additional course of treatment —“one he hopes will meet his goal of decreased post-surgical complications, resulting in decreased length of stay and faster postoperative recovery.”

Like his fellow Mayo Clinic urologists, Dr. Young sees the future in bladder cancer surgery moving toward RARC. “The beauty of the RARC is it is essentially the same space, the same operation, just done with different instruments. So if it’s in the best interest of the patient to convert to open, it is an easy transition,” explains Dr. Young. “This approach helped significantly during my learning curve and helped with the transition from open to robotic cystectomy.” He anticipates that in the near future, when consulting patients on treatment options, he will tell patients they have the two surgical options. But based on his experience, RARC will be the preferred one. “It will be an equivalent way to do this, and it might become the new standard of care,” he emphasizes.
Renal cell carcinoma is often discovered incidentally — oftentimes when patients are being evaluated for other unrelated medical conditions, such as kidney stones or elevated blood pressure. Typically, small renal masses (< 7 centimeters) are found during abdominal CT scans. In the U.S., approximately 60,000 new cases of renal cell carcinoma are identified annually, with about a third of those patients exhibiting metastatic disease. The incidence of renal cell carcinoma is rising, although reasons are not clear. Unfortunately, the increase includes not only small renal masses, but advanced cases as well.

Mayo Clinic urologists have valuable data right at their fingertips. Mayo Clinic urologist Bradley C. Leibovich, M.D., explains, “We have one of the largest patient registries, which allows us to understand our patients’ treatment results in extreme detail. This facilitates our excellent clinical outcomes and allows us to conduct research to continually improve our care, to assure we always provide our patients with the most optimal management.” The nephrectomy registry maintained by Mayo Clinic provides 30-plus years of renal cancer surgery outcomes from more than 7,000 patients. This registry contains vital data on patient demographics, disease attributes, diagnostic test results, treatment methods, pathology and clinical reviews, complications, outcomes, and survival.

**Surgical options**

In many circumstances urologists will surgically remove the primary tumor in the setting of metastatic renal cell carcinoma. Mayo Clinic subspecialty urologists have extensive experience and training in such complex procedures. In selected cases surgical teams inclusive of other specialties at Mayo Clinic will collaborate with urologists to eradicate all renal cell carcinoma tumors including those that have metastasized outside the kidney. Numerous studies have shown a survival advantage for surgical metastectomy in selected patients with solitary or limited metastatic disease. In a Mayo registry-based study of 888 renal cell carcinoma patients who had complete removal of all tumors, patients had a median cancer-specific survival (CSS) rate of almost five years. Patients who did not have any metastatic tumors removed had a median CSS rate of only 1.1 years. Dr. Leibovich explains that appropriately selected patients may experience better outcomes if all metastases are removed. “We are strong advocates, if feasible, for removing the cancer where it has metastasized.”

“We have a group of urologists dedicated to treating kidney cancer who work with multiple surgical specialties and in close collaboration with medical oncology and interventional radiology, says Dr. Leibovich. This collaboration provides patients with comprehensive and diverse therapy options, as well as with experienced surgeons who are able to provide advanced surgical management of metastasized tumors. Our colleagues in other specialties have expertise in helping manage these complex patients including systemic therapy options, clinical trials, radiation therapy, image-guided ablation, and complementary and alternative medicine.”

**Research**

Mayo Clinic is a research leader in the advancement of new treatment options for patients with metastatic renal cell carcinoma. In part because of a commitment to research, the National Cancer Institute designates the Mayo Clinic Cancer Center as a comprehensive cancer center. Groundbreaking research provides viable treatment options that were previously unavailable to patients with metastatic renal cell carcinoma whose cancer has spread outside the kidney.

**Systemic therapy treatment options**

Patients with metastatic renal cell carcinoma historically have had particularly limited treatment options outside of surgery, as this type of cancer does not respond well to conventional cytotoxic
chemotherapy. In fact, prior to 1992, an FDA-approved drug for the indication of advanced renal cell carcinoma was unavailable. Immunotherapy options approved after 1992 worked on a limited subset of patients, with many patients unable to tolerate drug toxicity. With several new drug approvals in 2005, patients have new treatment options. Fortunately, these drugs have been able to significantly extend survival of patients with metastatic renal cell carcinoma, although they have not been associated with complete responses or cures, with rare exceptions. “These drugs stabilize the disease or shrink the disease burden, but they are not a long-term solution because, in most cases, they only work for a limited period of time before the patient needs to switch to a different drug,” explains Dr. Leibovich.

Mayo urologists are working on multiple new ways to utilize new biologic and immunologic therapies to provide better treatment options. Mayo lab research combined with the power of the Nephrectomy Registry have identified a family of immune inactivating “co-regulatory molecules” that are critical for the ability of renal cell carcinoma to avoid destruction by the immune system. Mayo Clinic’s discovery of the role of these molecules has resulted in new opportunities for renal cell carcinoma prognostication and treatment. In fact, new treatments based on these molecules are now in clinical trials. Other current research includes investigating factors involved in the spread of renal cell cancer and identifying combination therapies that target genes involved in renal cell cancer. “We have had dramatic changes in just the past few years, and a large part of that story can be told by our labs here at Mayo Clinic. I am very optimistic that in the future we will have an even brighter picture to offer our patients,” emphasizes Dr. Leibovich.

Novel Treatments For Recurrent Prostate Cancer

Most men who are diagnosed with prostate cancer and who undergo curative treatment will not have a biochemical recurrence of the disease. However, a considerable number of men will notice a rise in prostate-specific antigen (PSA) following primary treatment, suggesting a treatment failure and a recurrence of the disease. Lance A. Mynderse, M.D., a urologist at Mayo Clinic, explains that regardless of the type of treatment a patient undergoes, whether radiation, cryoablation or surgical removal of the prostate, the rate of primary treatment failure is significant. Historical data mined from the Mayo Clinic prostatectomy registry of more than 20,000 men indicates 26 to 30 percent of men who have the procedure will have a rise in their PSA following surgery, ultimately indicating a biochemical recurrence of the disease. The percent is even higher for those who undergo radiation. “Because of the wide variety of protocols for patients undergoing radiation, the number of patients who experience a biochemical recurrence of the disease is higher and more variable — between 38 and 50 percent, says Dr. Mynderse.

For patients who experience a recurrence, traditional treatment options have been historically limited to either radiation or hormonal therapy. Mayo Clinic urologists, however, offer patients advanced clinical options, including novel treatments specifically for recurrent prostate cancer. A multidisciplinary team of radiologists, oncologists, cancer researchers, pathologists and surgeons is dedicated to specifically meeting the needs of this growing patient population. At the heart of this approach is a prostate cancer clinic, headed by urologist and cancer researcher Eugene D. Kwon, M.D. The clinic is designed specifically to evaluate suspected recurrences of the disease, and to ensure that those patients have the opportunity to take part in any appropriate novel treatment. “This clinic is set up for the patient whose cancer has metastasized or not. We are offering something more than what has been done for years for these patients, whether it is a clinical trial, a novel application of radiation, a novel application of ablative technology or state-of-the-art imaging,” says R. Jeffrey Karnes, M.D., another Mayo Clinic urologist.

Imaging — Early detection of the recurrence

When prostate cancer does recur, Mayo Clinic urologists utilize imaging modalities to detect the disease at its earliest stage — even at very low PSA levels — as low as < 0.58. “Imaging capabilities are often unable to detect the disease in patients with low PSAs, even in centers that have...
a lot of expertise in imaging modalities. It requires building a program that really does tell you a lot more with the imaging,” says Dr. Mynderse.

Because of its high level of sensitivity, endorectal coil magnetic resonance imaging (MRI) can often identify cases of local recurrence, allowing for the precise pinpointing of the suspected area to be biopsied. This imaging modality is used in the evaluation of biochemical recurrence to help guide prostate fossa biopsies under transrectal ultrasound (TRUS), thus identifying patients suitable for localized salvage therapy. The MRI followed by the biopsy allows for the early detection of prostate cancer recurrence, a cancer that is often not detected with typical imaging modalities.

In a Mayo Clinic study, Dr. Mynderse and his colleagues Brian J. Linder, M.D., and Akira Kawashima, M.D., Ph.D., studied 188 patients with a biochemical prostate cancer recurrence following radical prostatectomy. These patients underwent endorectal coil MRI with dynamic gadolinium-contrast enhancement to determine the possible recurrence of prostate cancer in the surgical bed. The MRI followed by TRUS-guided biopsy of the prostatic fossa confirmed local recurrence in 138 of the 188 patients. Dr. Mynderse explains further, “Use of the MRI to start and then the biopsy technique, which proves the spot on the MRI, is a critical part of finding the cancer recurrence.” He explains that the technology also enables clinicians to look at the lymph nodes in and around the rectum, a potential hiding place that is very hard to detect with other types of imaging.

For those patients whose next treatment course requires radiation, use of the endorectal coil MRI followed by TRUS-guided biopsy

Figure. Example of a C11 choline PET-CT scan demonstrating avidity in a left pelvic lymph node and the added performance of PET over the “normal” CT image
provides Mayo Clinic radiologists with a valuable tool. Putting markers at the site of the positive biopsy allows the radiation oncologist to pinpoint the radiation and design specific targeted treatment. Dr. Mynderse explains that when the tumor can be identified and located, large regions do not have to be radiated. “If we can tell the clinician precisely where the tumor is with this imaging, he or she has a better target on which to focus the radiation,” he emphasizes.

Immunotherapy
Dr. Kwon, a Mayo Clinic urologist and cancer researcher, is a pioneer in prostate tumor cell immunotherapy studies. Along with his laboratory colleagues, he is tackling recurrent prostate cancer with immunotherapy. Development of a two-step immunotherapy for prostate cancer provides a treatment option previously unavailable to men with widespread disease or inoperable prostate cancers. Dr. Kwon is optimistic that a two-step approach — a combination of hormonal and anti-CTLA treatment strategies — will provoke a stronger, more focused immune response against prostate tumors.

Step one in this two-step immunotherapy approach begins with hormone therapy to initiate an immune response that activates T cells and guides them to the tumor site. In the second step, the T cell fighting capability is prolonged by using the anti-CTLA-2 antibody. The anti-CTLA-4 antibody works by blocking the T cell off-switch receptor.

Two developments in Dr. Kwon’s research lab led to the development of the two-step immunotherapy. First, a new mouse model that spontaneously develops prostate cancer provided a deepened understanding of how to use the immune system to destroy tumor cells. Second, one of Dr. Kwon’s collaborators identified new strategies for activating T cells, a central component to his research. Dr. Kwon explains that T cells can recognize and kill tumor cells. So when the T cell is manipulated appropriately, it can find and destroy the prostate tumor without destroying other normal cells in the body.

Researchers also discovered that T cells are self-regulating. Once activated, they make receptors that work as off-switches to stop the attack.

C-11 choline imaging
“C-11 choline positron emission tomography and -computerized tomography (PET-CT) scans are a more advanced way in which Mayo Clinic clinicians are better able to detect the recurrence of the disease beyond the capabilities of conventional imaging,” explains Dr. Karnes. Mayo Clinic is the only medical center in North America that is able to use the C-11 choline PET-CT scans to detect the recurrence of prostate cancer.

In two retrospective studies of prostate cancer patients at Mayo Clinic who underwent C-11 choline PET-CT imaging between September 2007 and November 2010, Dr. Karnes validated the use of the C-11 choline PET-CT scans as an evaluation tool. These studies found the C-11 choline PET-CT scans to be important staging and potentially therapeutic tools.

The first study evaluated 176 patients with a biochemical recurrence after primary treatment failure. The study sought to assess the capability of the C-11 choline PET-CT scans’ ability to delineate prostate cancer distribution and extent after primary treatment failure. Results of the study found use of the C-11 choline PET-CT scans to be clinically useful in detecting treatable lesions not identified by conventional imaging in 32 percent of patients. The study results concluded that the optimal value for lesion detection is approximately 2.0 ng/ml. Use of the scans improves the staging and treatment of the cancer by finding the lesions earlier in the course of disease progression, offering patients a more timely course of treatment, rather than further systemic treatment, explains Dr. Karnes. “The big advantage of this technology is it gives you a big decision point because it is capable of seeing things that CT and bone scan are not able to do. So this scan is really critical,” concurs Dr. Mynderse.

The second study evaluated the accuracy of the C-11 choline PET-CT scans in the diagnosis of consolidated prostate cancer recurrence in men with biochemical failure after primary treatment. This study also found the scans to be valuable. Dr. Karnes analyzed data for 36 patients who underwent salvage prostatectomy. At the time of the PET scans, the mean and median PSA levels were 5.3 mg/ml and 2.8 ng/ml respectively. C-11 choline PET-CT scans delivered a sensitivity of 88 percent and a positive predictive value of 94 percent. The results show that the C-11 choline PET-CT scans are an accurate diagnostic tool for detecting localized disease recurrences, and in select cases they can be treated with salvage surgical resection.

MR-guided cryoablation
Yet another novel treatment available to Mayo Clinic patients with recurrent prostate cancer is MR-guided cryoablation. Exclusive to Mayo Clinic, a customized freezing unit adapted to an MRI compatible device allows an ablative team to freeze and destroy prostate tumors. The procedure, performed under anesthesia and MRI guidance, targets 2 to 5 cryotherapy probes
Because of the high volumes, Mayo Clinic urologists have the opportunity to tap into a burgeoning database of valuable prostate cancer information. Clinical data, tissue and serum samples, and treatment follow-up data are included in an extensive database. This gives urologists the data to help develop markers on prostate cancer, diagnostic tests and novel treatments for the diagnosis and treatment of those with low-risk prostate cancer.

For those patients whose prostate cancer is considered to be low risk, about 50 percent per year, or 100,000 men, most might not require aggressive treatment. PSA screening identifies most prostate cancers, but does not always delineate between high-risk and low-risk tumors, in particular for PSAs less than 10 ng/ml. The majority of men with low-risk prostate cancer choose active treatment (radiation or radical prostatectomy) rather than active surveillance. Urologist R. Jeffery Karnes, M.D., explains, “With active surveillance, there are still a lot of unknowns as to what the potential of the cancer might be.”

To solve this conundrum, Mayo Clinic is working on a gene-based prostate diagnostic test to distinguish indolent tumors from aggressive ones. “We are looking at the DNA of these cancers and trying to sort out the differences between an insignificant cancer and a significant one, even when on the surface they all appear to be low risk,” says Dr. Karnes. A multidisciplinary group of Mayo Clinic scientists have joined forces in the development of this gene-based prostate diagnostic test. Researchers are analyzing DNA alterations of prostate tumor cells to weed out significant cancers from insignificant ones.

To develop this gene-based test, Mayo Clinic researchers utilized a combination of technologies to analyze DNA alterations of four groups of tumors — indolent, large volume Gleason 6, both patterns of Gleason 7 (4+3 and 3+4) and a group of Gleason 8 cancers. Laser capture microdissection (LCM) was utilized to capture cells, followed by DNA amplification techniques. DNA changes were analyzed using high-throughput generation sequencing, which provided a revolutionary platform to unravel the precise DNA aberrations concealed within subgroups of tumor cells. The researchers found that this novel methodology aids in the derivation of genomic aberrations that initiate cancer and drive cancer progression. In the future, we hope this test or similar ones will be a valuable tool in guiding treatment decisions. Dr. Karnes explains it this way, “Patients who have a genetic profile of their prostate cancer at Mayo Clinic might better be able to tell if the cancer is an indolent one or a more significant one.”

What Mayo Clinic Is Doing To Better Manage Low-Risk Prostate Cancer

Figure. FISH analysis of a genetic marker in prostate cancer.

R. Jeffrey Karnes, M.D.
Announcing

Mayo Clinic Testicular Cancer Clinic
Mayo Clinic is proud to announce the formation of a Testicular Cancer Clinic. Testicular cancer has been treated by Mayo Clinic staff for many years, and the formation of this clinic creates an even more integrated and multidisciplinary approach. It brings together experts from urology, medical oncology, radiation oncology, radiology and other specialties, all collaborating to do what’s best for each individual patient.

New Staff

Landon W. Trost, M.D.
In January of 2014, Mayo Clinic will proudly welcome Dr. Trost, who will be returning to the Urology Department in Rochester, Minn., after completing additional training. Dr. Trost received his medical degree from Tulane University in New Orleans and did his residency at Mayo Clinic. He recently completed fellowships in male sexual function, microsurgery and infertility at Tulane University in New Orleans, University of Florida in Winter Haven, Fla., and Memorial Sloan-Kettering in New York. His clinical and research interests include male infertility, male sexual and erectile dysfunction, Peyronie’s disease, and testosterone deficiency. Dr. Trost’s surgical background includes experience with traditional microscopic and robotic-assisted varicocelectomy, sperm retrieval, and vasectomy reversal as well as the surgical correction of Peyronie’s disease and penile prosthesis implantation.

Candace F. Granberg M.D.
Mayo Clinic is pleased to announce the addition of Dr. Granberg, a urologist specializing in pediatric urology.

Dr. Granberg earned her medical degree from the University of North Dakota School of Medicine & Health Sciences in Grand Forks, N.D. She then completed her urology residency at Mayo School of Graduate Medical Education in Rochester, Minn. She has recently returned to Mayo Clinic after completing a fellowship in pediatric urology at Children’s Medical Center, University of Texas Southwestern Medical Center in Dallas, Texas.

Dr. Granberg has a special interest in robotic and laparoscopic surgery, primary and reoperative hypospadias repair, pediatric urologic tumors and malignancies, urologic management in spina bifida patients, pediatric stone disease, and other urologic disorders found in children.

Education Opportunities

Mayo Clinic Urology Review
Feb. 3-7, 2014, Hapuna Beach Prince Hotel, Kohala Coast, Hawaii
This weeklong postgraduate course, which will incorporate interactive discussion throughout, will provide a comprehensive update on urology by Mayo Clinic faculty from all three campuses and a distinguished group of invited colleagues. Register at: www.wjweiser.com/upcomingMeeting.aspx