Expanding Options for Advanced Bladder Cancer
Urinary tract reconstruction, next-generation tumor sequencing, and targeted adjuvant therapy enhance outcomes for patient with multiple comorbidities
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Advancing Masculinization Surgery
Patient counseling and access to ongoing care proves critical
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Surgery or Surveillance?
A new clinical update provides useful guidance for managing small kidney tumors
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MESSAGE FROM THE CHAIR

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Over the past year, our urology faculty have made great strides in understanding the mechanisms underlying urologic diseases and advancing treatments.

Among our many bench-to-bedside advances, our department is at the forefront of exploring new options for the screening, detection, and treatment of prostate cancer.

Our researchers recently found that exposure to e-cigarette smoke caused mice to develop lung cancer and bladder hyperplasia.

Other advances include innovations in reconstructive surgery, new approaches to managing bladder cancer, as well as guidance on the role of active surveillance for some small kidney tumors.

Read on to learn more about our achievements and their potential impact on patient care.
A 59-year-old, married white male with a history of obesity, Chronic Obstructive Pulmonary Disease (COPD) related to ongoing tobacco smoking, and hypertension was presented for evaluation and referral to NYU Langone Health.

PATIENT PRESENTS WITH MUSCLE-INVASIVE BLADDER CANCER

The patient had been newly diagnosed with muscle-invasive urothelial cancer of the bladder (MIBC), a highly mutated tumor. The patient’s primary risk factor was a long history of smoking. He had no family history of cancer. Gross hematuria in September of 2018 had prompted an evaluation, at an outside institution. Cystoscopy and CT urogram identified significant right-sided hydronephrosis and possible T3 clinical disease, characterized by extension beyond muscle into the perivesical fat. In early October, the patient underwent transurethral resection of the bladder tumor, the initial step in staging evaluation, which revealed muscle-invasive bladder cancer. The preferred treatment is radical cystectomy with resection of the bladder, regional lymph nodes, and adjacent organs. Dr. Balar presented an option for a clinical trial evaluating neoadjuvant cisplatin-based chemotherapy with immunotherapy prior to radical cystectomy, which has been shown to improve survival for patients with MIBC.

SURGEON CREATES NEOBLADDER TO ALLOW FOR URINARY DIVERSION

A month after completing neoadjuvant combined therapy, the patient saw Gary D. Steinberg, MD, in consultation for radical cystectomy and orthotopic continent urinary tract reconstruction. A highly experienced bladder cancer surgeon, advocate, and researcher, Dr. Steinberg, professor of urology, director of the Goldstein Urology Bladder Cancer Program, and a member of Perlmutter Cancer Center at NYU Langone, has developed expertise in continent urinary tract
reconstruction with creation of a neobladder. The procedure allows the patient to live without an ileal conduit, which collects urine in an external bag through a stoma.

The surgery was uneventful. The surgeons did not discover any tumor outside the bladder, and the lymph nodes appeared unremarkable. Surgeons preserved both of the patient’s neurovascular bundles for restoration of erectile function post-surgery.

Postoperative findings were significant for high grade urothelial carcinoma with 3 of 19 nodes positive. Specifically, the cancer was pathologically staged as pT2N2, or tumor invasion into the muscularis propria, with multiple regional lymph node metastasis in the true pelvis. Recovery after surgery was uncomplicated, and the ureteral stents were removed on postoperative day seven, with discharge home.

NEXT-GENERATION TUMOR SEQUENCING EXPANDS OPTIONS

With extensive experience in immunotherapies for bladder cancer, Dr. Steinberg hopes that personalizing treatment will optimize patient care, particularly in cases where the cancer has not responded adequately to initial treatments. In this case, the patient was referred to Dr. Balar for next-generation tumor sequencing and consideration of targeted adjuvant therapy.

On postoperative day 21, the patient’s Foley catheter and suprapubic tube were removed, and by 3 months post-op, he was continent day and night and successfully using sildenafil to achieve erection. We are following the patient with surveillance imaging and reviewing his NGS of the surgically resected tumor and lymph nodes.

Generally, checkpoint inhibitor immunotherapy targeting the protein programmed-cell-death-1 or its ligand is recommended for patients who progress after platinum-based chemotherapy. In this patient, the checkpoint inhibitor atezolizumab was initially used in the combination neoadjuvant regimen. New therapies target tumor-specific genetic alterations and include recently approved erdafitinib for patients with advanced fibroblast growth factor receptor (FGFR) mutated urothelial tumors.

In phase II trials there was a response rate of almost 60 percent for chemotherapy plus immunotherapy in patients who had progression of the disease. Other potential targets include deletions in phosphatase and tensin homolog (PTEN), cyclin 1, and mouse double minute 2 homolog; regulators of the G1-S cell cycle progression; aberrant chromatin remodeling genes; and cell adhesion molecule nectin-4.

Researchers at NYU Langone continue to collaborate in developing and evaluating novel agents for targeted personalized therapy. Current bladder cancer options including clinical trials can be found online.

Disclosures: Gary D. Steinberg, MD, is a member of clinical trial protocol committees for Merck, Bristol-Myers Squibb, Janssen, and Cold Genesys. He is a scientific advisor or consultant for Heat Biologics, Cold Genesys, Photocure, Merck, Roche/Genentech, Ciclomed, TARIS Biomedical, MDxHealth, Fidia Farmaceuticals, UroGen Pharma, Ferring Pharmaceuticals, Adaro Biotec, Boston Scientific, Bristol-Myers Squibb, AstraZeneca, Pfizer, Janssen, EpiVax Oncology, Natera, FJD Therapies Oy, EnGene Bio, and Sesen Bio. Dr. Steinberg has equity or stock options in EpiVax Oncology and UroGen Pharma.
Patient demand for gender affirming surgery—including facial, chest, and genital reconstructive surgery—has increased in recent years and become more accessible due to changes in insurance coverage.

However, only a handful of institutions worldwide offer these complex operations. A recent study led by NYU Langone’s Lee C. Zhao, MD, assistant professor of urology, suggests that many patients receive the initial surgery far from home and seek follow-up care for short-term complications with other surgeons.

**COMPLICATIONS EMERGE SOON AFTER SURGERY**

In a retrospective study published online June 20, 2019, in *Urology*, Dr. Zhao, who is also director of male reconstructive surgery and co-director of transgender reconstructive surgery—part of NYU Langone’s transgender surgery services—and colleagues report on the cases of 55 patients who experienced urethral complications following masculinizing GRS.

All patients, who ranged in age from 17 to 60, sought care with one of the study’s 8 co-authors a median of 4 months following their initial surgery at a different center. Anastomotic stricture was the most common form of urethral complication, occurring in 46 percent of patients. Most patients presented with 2 or more complications, the authors note, and all of those with urethrocutaneous fistula (56 percent) had concurrent urethral stricture.

The findings underscore a scenario that is becoming increasingly common and often challenging for reconstructive urologists—the expectation of managing complications stemming from procedures at other centers. The urologist may lack important details about the original operation, and patients may be surprised or confused about the need for additional interventions.

“Urethral complications after masculinizing genital surgery is very different from urethral strictures occurring in cisgender patients after trauma,” Dr. Zhao says. “The techniques needed to revise these strictures are different, and even when the operative reports are available, there is no substitute for the knowledge that the original surgeon had.”

**Total Healthcare for Individuals Seeking Gender-Affirming Procedures**

NYU Langone Health is at the forefront of research and innovation in performing gender-affirming procedures and conducting studies to improve patient outcomes and satisfaction that contribute to the overall wellness of transgender and gender diverse individuals.

NYU Langone’s multidisciplinary team provides medical services for transgender men, women, and adolescents, including surgery, hormone therapy, reproductive health services, and mental health services. Lee C. Zhao, MD, MS, assistant professor of urology and director of Male Reconstructive Surgery, has pioneered the use of robotic techniques at NYU Langone to make gender-affirming procedures safer, faster, and less invasive. Dr. Zhao often collaborates with Rachel Bluebond-Langner, MD, the Laura and Isaac Perlmutter Associate Professor of Reconstructive Plastic Surgery, at NYU Langone’s Hansjörg Wyss Department of Plastic Surgery. Together, they have established one of the country’s only dual-surgeon, cross-specialty programs that performs robotic “bottom” genital surgery for vaginoplasty and phallasspasty, which many experts agree presents safer and more effective results.

Dr. Zhao and Dr. Bluebond-Langner are part of a growing team of specialists at NYU Langone who care for transgender patients.
NYU Langone Health has been recognized by the Human Rights Campaign Foundation Healthcare Equality Index (HEI) Report, a certification that acknowledges the work of medical facilities that are providing equal healthcare access to LGBTQ+ Americans. We also follow the standards of care guidelines set forth by the World Professional Association for Transgender Health (WPATH).

**Equality in Healthcare**

A BROAD RANGE OF COMPLICATIONS

“Masculinizing genital reconstructive surgery, especially phalloplasty, involves a number of separate operations: vaginectomy, perineoplasty, urethroplasty, scrotoplasty, and radial forearm free flap. Each of these procedures have complications. When all of these procedures are performed simultaneously, it is natural for complications to add up.”

The variety of surgical techniques used by the co-authors highlights the broad range of potential urethral complications following masculinization surgery, and the lack of standardized approaches to address them.

For example, patients who received multiple prior skin grafts for urethral repairs had fewer options for reconstruction. In addition, almost half of the patients presented with vaginal remnant, said Dr. Zhao. This can occur after the primary vaginectomy if the mucosa is incompletely resected, leaving remnants in the urinary tract. Patients may experience symptoms including difficulty voiding, leakage, pain, and recurrent urinary tract infections.

“Treatment of vaginal remnants typically requires complete excision and closure of associated tracts,” says Dr. Zhao. “At NYU Langone, we remove the vaginal remnant via a robotic approach. Since the patients previously had a perineal reconstruction, we are able to avoid making an incision into the perineum to completely remove the vaginal remnant.”

A PROGRAM BUILT ON CONTINUOUS QUALITY IMPROVEMENT

“Due to the complexity of the operation and the unacceptably high rate of complications, it makes sense to have a constant process of quality improvement. At NYU Langone, we perform both revision surgery and primary gender affirming surgery. Taking care of complications from other centers has really informed how we perform the primary operation. We’ve found that complications often lead to other complications, such as urethral strictures causing urethral fistula or wound breakdown. Thus, we perform phalloplasty in stages to prevent one complication from causing others.”

The authors caution that the study is limited by its small size and incomplete details from institutions where the primary surgeries were performed. However, the findings highlight the importance of alerting patients to the signs and symptoms of complications and of having access to long-term follow-up care.

“In addition to reconstructive urologists who are prepared to evaluate and treat patients with complex surgical needs, this study highlights the need for thorough preoperative counseling and long-term local follow-up of transgender patients who undergo masculinizing GRS,” concludes Dr. Zhao.
Incidental detection of small kidney tumors has risen dramatically over the past several decades due to increasing use of diagnostic imaging.

In the past, surgery was the standard approach to managing all of these lesions, but recent research suggests that many small, incidentally discovered tumors frequently do not become aggressive; therefore, in select patients, these small masses can be safely managed through an initial period of observation or active surveillance.

**SMALL KIDNEY TUMORS POSE LOW RISK OF MORTALITY**

A Clinical Update was published in the April 23/30, 2019 issue of JAMA, describing investigations by William C. Huang, MD, associate professor of urology, chief of the Urology Service at Tisch Hospital, and co-director of the Robotic Surgery Center at NYU Langone, and others. According to their research, small tumors measuring 4 centimeters or less—which are often found during imaging for other problems—pose very low risk of mortality from kidney cancer. Dr. Huang, part of Perlmutter Cancer Center at NYU Langone and a pioneer in developing the most effective minimally invasive approaches to managing kidney cancer, along with his colleagues, note that 75 to 80 percent of small lesions ultimately prove to be malignant while the remaining 20 to 25 percent remain benign. Although less than 5 percent of these small malignant tumors will metastasize, we still recommend treatment; imaging and even biopsy give us limited information at this time which of these small tumors will become life-threatening.

**ACTIVE SURVEILLANCE EFFECTIVE AS INITIAL MANAGEMENT STRATEGY**

Dr. Huang and colleagues point to recent evidence supporting active surveillance as an effective initial management strategy for many patients. For example, the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry reported a 100 percent cancer-specific survival rate over five years for patients under active surveillance. Another large review published in Cancer reported metastatic disease rates of only 1 to 2 percent for patients managed with active surveillance for 2–3 years. "The low risk posed by small kidney lesions suggests that these tumors can be managed similarly to low-risk prostate cancer, which also frequently has an indolent or lazy, course," says Dr. Huang.

**INDIVIDUALIZED TREATMENT PLANS AND SHARED DECISION MAKING**

Management of small tumors should be individualized to each patient, advises Dr. Huang. Factors to consider when creating a treatment plan include the risk of mortality from kidney cancer, mortality risk from comorbid conditions, and the potential for treatment-related side effects. The most recent American Urological Association clinical guidelines endorse an initial period of active surveillance instead of surgery as an option for small lesions measuring less than 2 centimeters. The guidelines caution that patients should be fully informed about the low risk of cancer-specific mortality.
for very small lesions, in the absence of comorbid conditions, and also be given the option to pursue biopsy when warranted.

Decisions about whether to pursue surgery versus surveillance should take into account the overall health and anticipated longevity of the patient. In addition, tumor characteristics such as location may also play a role in decision-making as treatment may unnecessarily result in loss of kidney function. In patients with small renal masses and/or significant co-morbid conditions or chronic kidney disease, any surgical treatment including partial may negatively impact their kidney function, their quality of life, or both.

While active surveillance is emerging as a safe and effective option for select patients with very small tumors, evidence from randomized trials is lacking, Dr. Huang notes. As a result, physicians should fully inform patients about the potential risks and benefits of various treatment options and engage them in shared decision-making.

“In the future, we hope to develop new tests so that we can accurately identify tumors which are not safe to observe,” says Dr. Huang. “However, for now, we can help patients fully understand the low mortality risk associated with many of these small tumors so that they are enabled to make an informed decision as to whether they want to pursue treatment for their small renal mass.”

Disclosure: Dr. Huang reported membership on the American Society of Clinical Oncology Guidelines Panel for Small Renal Masses.

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William C. Huang, MD

At Perlmutter Cancer Center, No Two Patients Are Treated Exactly the Same (Not Even Twins)

Urologic oncologist James S. Wysock, MD, and radiation oncologist Jonathan A. Haas, MD, leveraged advanced diagnostics and shared decision-making to help two brothers with prostate cancer navigate the many surgical and nonsurgical options available at Perlmutter Cancer Center. Although one brother required a course of hormonal therapy prior to radiation, ultimately the twins were treated with stereotactic body radiotherapy (SBRT). Their care was coordinated seamlessly between our Manhattan campus and NYU Winthrop Hospital on Long Island.

Disclosure: Dr. Huang reported membership on the American Society of Clinical Oncology Guidelines Panel for Small Renal Masses.

75–80% OF SMALL LESIONS ULTIMATELY PROVE TO BE MALIGNANT

20–25% REMAIN BENIGN

LESS THAN 5% MALIGNANT TUMORS WILL METASTASIZE
"I thought I was doing pretty good."
Aside from getting up to go to the bathroom twice a night—common for men his age—he felt vibrant. So when tests showed that Zuckerman had prostate cancer, his fear was mingled with a sense of disbelief.

**CUTTING THROUGH THE CONFUSION & NAVIGATING HIS TREATMENT OPTIONS WITH CONFIDENCE**

Like many of the more than 174,000 men diagnosed with the disease annually in the United States, he faced an agonizing decision. "For patients with prostate cancer, choosing a course of action can be overwhelming," says Herbert Lepor, MD, the Martin Spatz Chair of the Department of Urology and director of the Smilow Comprehensive Prostate Cancer Center, part of Perlmutter Cancer Center at NYU Langone Health.

A decade ago, the vast majority of patients diagnosed with prostate cancer opted for a radical prostatectomy—surgical removal of the prostate—or radiation therapy. However, today almost half choose active surveillance, in which slow-growing early-stage tumors are monitored through a combination of a blood test that measures a protein known as prostate-specific antigen, or PSA, and biopsies. This trend reflects a raft of recent studies showing that prostate tumors rated 6 or less on the Gleason scale (a 1 to 10 measure of likely aggressiveness) rarely metastasize. Still, many patients are uncomfortable with a watch-and-wait approach, and it’s typically not an option in higher-risk cases like Zuckerman’s. Then, the choices become more complex.

Zuckerman’s MRI scan revealed a gumball-size tumor, and biopsies showed a Gleason score of 7, indicating an intermediate risk that the cancer would spread beyond the prostate. He visited several specialists, each of whom suggested a different type of treatment. He took to the internet, as many patients do, in search of

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**For Prostate Cancer, Many Treatment Options, but No Easy Answers**

At 68, Artie Zuckerman had a 31-inch waist, a 46-inch chest, and could knock out 20 chin-ups. "I was exercising, eating my fish and veggies," recalls Zuckerman, who works as a chauffeur and personal assistant for a corporate CEO.

"I was exercising, eating my fish and veggies," recalls Zuckerman, who works as a chauffeur and personal assistant for a corporate CEO. Like many men, Artie Zuckerman had virtually no symptoms when he was diagnosed with prostate cancer at age 68. A fitness enthusiast who gets plenty of exercise caring for his three Great Danes, he felt blindsided. "I thought I was doing pretty good," he recalls.
information and talked with friends who’d undergone treatment for prostate cancer. But his confusion only intensified; he simply couldn’t find a consensus on which treatment was best. Finally, he consulted Dr. Lepor, whose approach put him at ease. “He spent an hour with me,” Zuckerman recalls. “I was impressed with his experience, his confidence, and his honesty.”

As a leading prostate cancer surgeon, Dr. Lepor has performed more than 5,000 radical prostatectomies. Yet he has also helped pioneer a nonsurgical technique known as focal ablation, in which precisely targeted beams of energy, such as extreme cold or high-intensity ultrasound, destroy diseased tissue while leaving the rest of the prostate intact. Preliminary studies—including some by Dr. Lepor and his colleagues—suggest the method can eradicate tumors with fewer side effects than surgery or radiation. In addition, unlike with radiation, patients can undergo another round of focal therapy or opt for conventional methods in case of recurrence. “I told Artie that this could be a way to control his cancer with less risk of life-altering complications,” Dr. Lepor explains. “But I emphasized that there were no guarantees.”

Zuckerman was willing to take a chance. Because of the position of his tumor, among other factors, Dr. Lepor recommended focal cryotherapy, in which repeated freezing and thawing causes cancer cells to rupture. Last July, while Zuckerman was under anesthesia, Dr. Lepor inserted a thin probe into his prostate, using ultrasound guidance to reach the site of the tumor. He then cycled supercooled argon gas through the probe, chilling the target area to -40 degrees Celsius. The procedure took about two hours, and Zuckerman, like most patients, went home the same day. He returned to work 10 days later. Since then, Zuckerman has experienced no incontinence, and his sexual function, though impacted at first, has returned to near normal. A follow-up PSA test, MRI, and biopsy after six months showed no cancer. (He’ll continue with PSA testing every six months.) “I think I did the right thing,” he says.

But ultimately every man with prostate cancer must make his own choice, notes Dr. Lepor. “This is a visceral decision,” he says. “One patient will insist on the most definitive cure. Another will accept some uncertainty if there’s less impact on quality of life. The doctor’s role is to provide realistic expectations, and help patients process the risks and benefits.”

This article originally appeared in the Fall 2019 Perlmutter Cancer Center Special Report.

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E-Cigarette Smoke Causes Lung Cancer and Bladder Hyperplasia in Mice

Exposure to e-cigarette smoke caused mice to develop lung cancer and bladder hyperplasia, a new study finds.

Published online October 7 in Proceedings of National Academy of Sciences (PNAS), the study found that 9 of 40 mice (22.5 percent) exposed to e-cigarette smoke with nicotine for 54 weeks developed lung adenocarcinomas. None of the 20 mice from the study exposed to the same e-cigarette smoke without nicotine developed cancer.

Led by Moon-Shong Tang, PhD, an NYU School of Medicine researcher, the study also found that 23 of 40 mice (57.5 percent) exposed to e-cigarette smoke developed bladder hyperplasia, genetic changes that make cells more likely to multiply, and a step toward abnormal tissue growth seen in cancer. Only 1 of the 17 mice exposed to the zero-nicotine e-cigarette smoke developed hyperplasia.

Dr. Tang acknowledges the study’s limitations, including that it was conducted in a relatively small number of mice susceptible to developing cancer over their lifetime (a one-year study period designed to offset age-related cancer). The study mice also did not inhale smoke like a human would, but instead, were surrounded by it through whole-body exposure. “Tobacco smoke is among the most dangerous environmental agents to which humans are routinely exposed, but the potential of e-cigarette smoke as a threat to human health is not yet fully understood,” says Dr. Tang, professor of environmental medicine, medicine, and pathology. “Our study results in mice were not meant to be compared to human disease, but instead argue that e-cigarette smoke must be more thoroughly studied before it is deemed safe or marketed that way.”

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PHOTO: DANCHOOALEX/GETTY
For more information about our physicians, services, and locations, visit nyulangone.org

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ABOUT NYU LANGONE HEALTH

Leader in Quality

NYU Langone has achieved top rankings by Vizient, and is the only full-service health system in New York City with an “A” Leapfrog safety grade and a CMS 5-star rating in 2020. These accolades are reflective of a shared culture of quality that permeates our growing network, now inclusive of NYU Winthrop Hospital and its ambulatory sites on Long Island. All of our sites are held to the highest quality standards set at an institutional level.

#9 in the Nation

Ranked ninth by U.S. News and World Report for both Best Hospitals and Best Medical Schools (Research)

Transforming Medical Education

To address some of today’s most pressing issues in medical education such as physician shortages, debt burden, and lack of diversity, we have introduced accelerated pathways to the MD degree and full-tuition scholarships regardless of need or merit at the recently renamed NYU Grossman School of Medicine and the new primary-care focused NYU Long Island School of Medicine.
Our urology faculty continue to make great strides in understanding and advancing treatment for urologic diseases. We are expanding options for treatment for urologic diseases, understanding and advancing active surveillance for some small kidney tumors, minimizing complications of masculinization surgery, and considering the role of active surveillance for some advanced bladder cancer. We are expanding options for masculinization surgery.