NYU Langone Health

Department of Urology
Case of the Month

# Trimodal Therapy for Muscle-Invasive Bladder Cancer

## CASE PRESENTATION

An 82-year-old man with a past medical history significant for hypertension, insulin-dependent diabetes, stroke, and depression presented with gross hematuria in the fall of 2020. His urine cytology was positive for malignant cells, and his CT urogram showed a 4 cm solid bladder mass on the left lateral wall, with no upper tract dilation or filling defects. The patient was taken directly to the operating room for a cystoscopy and transurethral resection of the bladder tumor. Cystoscopy showed a solitary papillary tumor on the left lateral wall (Figure 1). The tumor was completely resected, and the pathology report showed high-grade urothelial carcinoma with squamous differentiation, invasive into the muscularis propria (clinical stage T2).

**Figure 1.** Cystoscopy image showing papillary tumor on the left lateral wall of the bladder.

The patient was initially counseled to undergo neoadjuvant chemotherapy followed by radical cystectomy (RC). He completed 4 cycles of gemcitabine and cisplatin, which he tolerated well. Follow-up office cystoscopy and preoperative imaging showed no evidence of residual disease in his bladder and no metastatic disease.

At this time, the patient began to express an unwillingness to proceed with the previously planned (RC), stating that he was not interested in having a "bag for a bladder" and was unwilling to catheterize and flush a continent diversion. After discussion with our multidisciplinary tumor board, the patient was deemed to be a candidate for trimodal therapy (TMT).

### Cnblinical Data

Cr: 0.9 mg/dL

eGFR: >60 mL/min/1.73 m2

UA: >180 RBCs

Urine cytology: positive for malignant cells

TURBT pathology: muscle-invasive high-grade urothelial carcinoma with squamous differentiation

## MANAGEMENT

The patient was taken to the operating room for a repeat transurethral resection of the previous tumor bed; pathology showed no residual disease in the specimen. The patient was then started on concurrent chemotherapy and radiation therapy. Weekly cisplatin was administered as a radiation-sensitizing agent, and the tumor bed and bladder were treated with 55 Gy intensity-modulated radiation therapy delivered over 20 fractions. The patient tolerated the treatment well, developing only mild urinary hesitancy, which was managed with tamsulosin. His post-treatment cystoscopy showed no evidence of disease, and he has remained disease-free on surveillance cystoscopies and imaging for 9 months since he completed his TMT. He will continue surveillance with cystoscopy, urine cytology, chest imaging, and cross-sectional imaging of the abdomen and pelvis per AUA guidelines.

## COMMENT

RC is the well-established gold standard treatment for non-metastatic muscle-invasive bladder cancer, with 21st-century advances including the addition of neoadjuvant chemotherapy (NAC) and minimally invasive approaches.[1,2] However, RC is a highly morbid procedure with a significant impact on quality of life,[3] leading many patients to pursue bladder-preserving strategies out of either necessity or personal preference.

Unfortunately, the studies supporting bladder-sparing approaches in muscle-invasive bladder cancer are primarily retrospective and highly influenced by selection biases, but multimodal strategies appear to be superior to radiation or chemotherapy alone.[2] Although there has been no successfully completed randomized controlled trial comparing NAC plus RC to TMT (consisting of maximal transurethral resection, radiation-sensitizing chemotherapy, and radiation), existing data suggest that properly selected patients treated with curative-intent TMT may experience similar survival outcomes to patients undergoing NAC plus RC.[4,5] Interestingly, a recent study using the Markov model constructed to simulate a head-to-head comparison of RC vs. TMT showed that age was a strong determinant of the relative life expectancy benefit between the 2 treatments, with older patients having longer unadjusted and quality-adjusted life expectancy with TMT compared to RC.[6]

Appropriate patient selection is critical for TMT with curative intent. Factors that may exclude a patient from this strategy include multifocal tumors, carcinoma in situ, hydronephrosis (suggestive of extravesical extension), and metastatic disease.[7] Another factor to consider is the patient's ability and willingness to comply with the intense treatment schedule, which will likely require daily visits 5 days a week for 4 to 6 weeks during radiation therapy, followed by life-long cystoscopic and radiographic surveillance.

Although a multidisciplinary team is needed, patients undergoing TMT should be managed primarily by the urologist, given that the candidacy for TMT, initial response to treatment, and post-treatment surveillance all require cystoscopies. In addition, the transurethral resection is the most operator-dependent component of TMT; care should be taken to ensure that a maximal resection has occurred prior to chemotherapy and radiation. (There are no consensus recommendations regarding repeat resection, but a repeat resection may be beneficial if there is a delay to chemoradiation initiation or if there is concern for prior incomplete resection.) The urologist will need to coordinate with the medical oncologist and the radiation oncologist to determine whether the patient will undergo split-course chemoradiation (with an interval cystoscopy performed to assess response after two-thirds of the cumulative radiation has been administered) or continuous-course chemoradiation (with cystoscopy deferred until all radiation treatments have been completed).

The management of disease recurrence after TMT should be discussed with patients prior to initiating TMT, as this may influence a patient's treatment decisions.[8] Patients with muscle-invasive recurrence should be offered salvage RC if they are candidates for surgery, with counseling that the options for urinary diversion may be limited and the overall morbidity of the procedure increased compared to patients undergoing primary RC. Non-muscle-invasive recurrences may be managed similarly to primary non-muscle-invasive disease, with resections and intravesical therapy.

Finally, it is worth noting the emerging role of immunotherapy in bladder-sparing approaches. The results of a multicenter phase 2 trial using pembrolizumab added to TMT with gemcitabine for muscle-invasive bladder cancer were promising, demonstrating a 1-year bladder-intact disease-free survival rate of 77% with a pembrolizumab-related toxicity profile similar to monotherapy.

## REFERENCES


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## LAMONT J. BARLOW, MD

Dr. Barlow is assistant professor of urology and pathology at NYU Grossman School of Medicine. He is a fellowship-trained urologic oncologist with a surgical focus on endoscopic and robotic surgery for bladder and prostate cancer. He attended Harvard College and Columbia University College of Physicians and Surgeons, followed by a urology residency at New York-Presbyterian – Columbia University Medical Center and a SUO urologic oncology fellowship at New York-Presbyterian – Weill Cornell Medical Center.

Dr. Barlow has published numerous articles and book chapters on urologic oncology, including several studies of intravesical taxane therapy for Bacillus Calmette-Guerin–unresponsive bladder cancer. He pioneered a method for growing patient-derived bladder tumor cells in 3-dimensional organoid culture. His clinical practice is at the Margaret Cochran Corbin VA Campus of New York Harbor Health Healthcare System in Manhattan, where he established the region's first VA robotic cystectomy program. Dr. Barlow also runs a translational research laboratory that focuses on using patient-derived organoids to study novel intravesical therapeutic strategies and resistance pathways.

# Department of Urology

NYU Langone Health

Our renowned urologic specialists have pioneered numerous advances in the surgical and pharmacological treatment of urologic disease.

*For questions and/or patient referrals, please contact us by phone or by e-mail.*

| Faculty | Specialty | Phone Number/Email |
|---|---|---|
| **James Borin, MD** | Kidney stones, Kidney Cancer, Ureteral Stricture, UPJ obstruction, Endourology, Robotic Renal Surgery, Partial Nephrectomy, Ablation of Renal Tumors, PCNL | 646-825-6387<br>james.borin@nyulangone.org |
| **Benjamin Brucker, MD** | Female Pelvic Medicine and Reconstructive Surgery, Pelvic Organ Prolapse-Vaginal and Robotic Surgery, Voiding Dysfunction, Male and Female Incontinence, Benign Prostate Surgery, Neurourology | 646-754-2404<br>benjamin.brucker@nyulangone.org |
| **Seth Cohen, MD** | Female Sexual Dysfunction, Male Sexual Dysfunction, General Urology, Benign Disease Prostate, Post-Prostatectomy Incontinence, Erectile Dysfunction, Hypogonadism | 646-825-6318<br>seth.cohen@nyulangone.org |
| **Frederick Gulmi, MD*** | Robotic and Minimally Invasive Urology, BPH and Prostatic Diseases, Male and Female Voiding Dysfunction, Kidney Stone Disease, Lasers in Urologic Surgery, and Male Sexual Dysfunction | 718-630-8600<br>frederick.gulmi@nyulangone.org |
| **Mohit Gupta, MD†** | Urologic Oncology, Open, Laparoscopic, or Robot-Assisted Approaches to Surgery, Surgical Management of Genitourinary Malignancies including Kidney, Bladder, Prostate, Adrenal, Penile, and Testis Cancers | 646-825-6325<br>Mohit.Gupta2@nyulangone.org |
| **William Huang, MD** | Urologic Oncology (Open and Robotic) – for Kidney Cancer (Partial and Complex Radical), Urothelial Cancers (Bladder and Upper Tract), Prostate and Testicular Cancer | 646-744-1503<br>william.huang@nyulangone.org |
| **Grace Hyun, MD** | Pediatric Urology including Hydronephrosis, Hypospadias, Varicoceles, Undescended Testicles, Hernias, Vesicoureteral Reflux, Urinary Obstruction, Kidney Stones, Minimally Invasive Procedures, Congenital Anomalies | 212-263-6420<br>grace.hyun@nyulangone.org |
| **Christopher Kelly, MD** | Male and Female Voiding Dysfunction, Neurourology, Incontinence, Pelvic Pain, Benign Prostate Disease | 646-825-6322<br>chris.kelly@nyulangone.org |
| **Herbert Lepor, MD** | Prostate Cancer: Elevated PSA, 3D MRI/Ultrasound Co-registration Prostate Biopsy, Focal (Ablation) of Prostate Cancer, Open Radical Retropubic Prostatectomy | 646-825-6327<br>herbert.lepor@nyulangone.org |
| **Stacy Loeb, MD, MSc**** | Urologic Oncology, Prostate Cancer, Benign Prostatic Disease, Men's Health, General Urology | 718-261-9100<br>stacy.loeb@nyulangone.org |
| **Danil Makarov, MD, MHS***** | Benign Prostatic Hyperplasia, Erectile Dysfunction, Urinary Tract Infection, Elevated Prostate-specific Antigen, Testicular Cancer, Bladder Cancer, Prostate Cancer | 718-376-1004<br>danil.makarov@nyulangone.org |
| **Nnenaya Mmonu, MD, MS** | Urethral Strictures, Robotic and Open Reconstructive Surgery for Ureteral Obstruction/Stricture, Fistulas, Bladder Neck Obstruction, Penile Prosthesis, Post Prostatectomy and Radiation Urinary Incontinence | 646-754-2419<br>nnenaya.mmonu@nyulangone.org |
| **Bobby Najari, MD** | Male Infertility, Vasectomy Reversal, Varicocele, Post-Prostatectomy, Erectile Dysfunction, Male Sexual Health, Hypogonadism, Oncofertility | 646-825-6348<br>bobby.najari@nyulangone.org |
| **Nirit Rosenblum, MD** | Female Pelvic Medicine and Reconstructive Surgery, Voiding Dysfunction, Neurourology, Incontinence, Female Sexual Dysfunction, Pelvic Organ Prolapse and Robotic Surgery | 646-825-6311<br>nirit.rosenblum@nyulangone.org |
| **Ellen Shapiro, MD** | Pediatric Urology including: Urinary Tract Obstruction (ureteropelvic junction obstruction), Vesicoureteral Reflux, Hypospadias, Undescended Testis, Hernia, Varicocele, and Complex Genitourinary Reconstruction. | 646-825-6326<br>ellen.shapiro@nyulangone.org |
| **Mark Silva, MD*** | Kidney stones, PCNL, Kidney Cancer, UPJ obstruction, Endourology, Robotic Renal Surgery, Ablation of Renal Tumors | 718-630-8600<br>mark.silva@nyulangone.org |
| **Gary D. Steinberg, MD** | Muscle-Invasive Bladder Cancer, Non-Invasive Bladder Cancer, Radical Cystectomy, Urinary Tract Reconstruction After Bladder Removal Surgery | 646-825-6327<br>gary.steinberg@nyulangone.org |
| **Lauren Stewart, MD** | Female Pelvic Medicine and Reconstructive Surgery, Pelvic Organ Prolapse, Incontinence in Women, Female Voiding Dysfunction | 646-825-6324<br>lauren.stewart@nyulangone.org |
| **Samir Taneja, MD** | Urologic Oncology – Prostate Cancer (MRI-Guided Biopsy, Robotic Prostatectomy, Focal Therapy, Surveillance), Kidney Cancer (Robotic Partial Nephrectomy, Complex Open Surgery), Urothelial Cancers | 646-825-6321<br>samir.taneja@nyulangone.org |
| **James Wysock, MD, MS** | Urologic Oncology – Prostate Cancer, MRI-Guided Biopsy, Kidney and Prostate Cancer Surgery, Robotic Urological Cancer Surgery, Prostate Cancer Image-guided Focal Therapy (Ablation, HIFU), and Testicular Cancer | 646-754-2470<br>james.wysock@nyulangone.org |
| **Lee Zhao, MD** | Robotic and Open Reconstructive Surgery for Ureteral Obstruction, Fistulas, Urinary Diversions, Urethral Strictures, Peyronie's Disease, Penile Prosthesis, and Transgender Surgery | 646-754-2419<br>lee.zhao@nyulangone.org |
| **Philip Zhao, MD** | Kidney Stone Disease, Upper Tract Urothelial Carcinoma, Ureteral Stricture Disease, and BPH/Benign Prostate Disease | 646-754-2434<br>philip.zhao@nyulangone.org |

*at NYU Langone Hospital – Brooklyn ** NYU Langone Ambulatory Care Rego Park ***NYU Langone Levit Medical †222 East 41st street; NYU Langone Ambulatory Care Bay Ridge, and NYU Langone Levit Medical