NYU Langone Health

Department of Urology
Case of the Month

Management of Recurrent Prostate Cancer After Radical Prostatectomy

CASE PRESENTATION AND EVALUATION

A 40-year-old African American man presented in 2005 with a PSA of 10.6 ng/mL. Biopsy demonstrated Gleason 4+3 prostate cancer in 4 of 12 cores.

TREATMENT AND MANAGEMENT

The patient underwent an uncomplicated open radical retropubic prostatectomy in February 2006, which demonstrated Gleason 4+3, pT3b, N0, Mx prostate cancer with negative surgical margins. In first-year postoperative follow-up, he recovered total continence without use of pads and erectile function adequate for penetrative intercourse. His first post-operative PSA was 0.03 ng/mL in May 2006 (Table 1).

The patient's PSA continued to rise to a level of 0.37 by December 2006. He was advised to consider salvage radiotherapy, and in April 2007, he completed 6660 cGy external beam radiotherapy to the pelvis, with a boost to the prostate bed. Following radiotherapy, his PSA declined to 0.07 ng/mL in June 2007 and eventually to 0.03 ng/mL in June 2009. His PSA then remained stable at around 0.02 ng/mL until 2013, when it started to rise slighty.

The patient's PSA remained below 0.1 ng/mL until January 2017, when it began to rise rapidly, to a level of 4.217 by January 2018. A bone scan showed nonspecific foci in the pelvis and the humerus, not suspicious for prostate cancer. An 18F-fluciclovine (Axumin) PET scan demonstrated isolated uptake in a right internal iliac lymph node (Figure 1) and an incidental 4.6 cm left renal mass.

After discussion of options and given the rapidly rising PSA, the patient elected to proceed with a robot-assisted laparoscopic salvage right pelvic lymph node dissection, which was performed on April 17, 2018. Final pathology demonstrated metastatic prostate cancer in 3 of 16 resected lymph nodes. The patient recovered uneventfully. His PSA level was undetectable (<0.02 ng/mL) by August 2018. A left robot-assisted laparoscopic partial nephrectomy on August 3, 2018, revealed a pT1b, Nx, Mx clear cell renal cell carcinoma with negative surgical margins. In follow-up, the patient's PSA has remained undetectable (Table 2).

Table 1. PSA scores and treatments: 2005 to January 2018

2005	10.6	
2/2006		T3b, N0, Mx Gleason 4+3, negative margins
5/2006	0.03	
6/2006	0.20	
12/2006	0.37	
4/2007		EBRT, 6660 cGy
6/2007	0.07	
6/2009	0.03	
9/2010	0.02	
4/2011	0.02	
10/2011	0.02	
3/26/2012	0.02	
10/2012	0.02	
4/3/2013	0.05	
12/2/2013	0.03	
4/12/2014	0.02	
11/25/2014	0.04	
5/27/2015	0.06	
11/27/2015	0.09	
1/6/2017	0.18	
8/2017	0.70	
1/19/2018	2.71	
1/26/2018	4.217	
2/13/2018		Bone scan shows no metastasis
2/25/2018		Axumin PET/MRI demonstrates suspicious uptake in right internal iliac lymph node

Figure 1A. Annotated_PET_MIP (Maximum Intensity Projection)

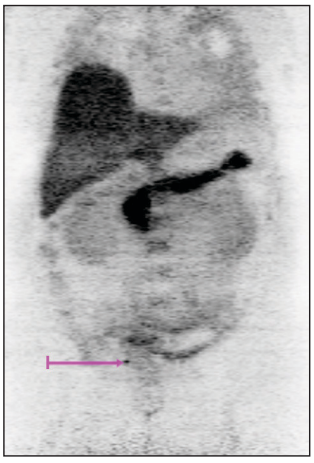

Figure 1B. Annotated right internal iliac node_SUV8

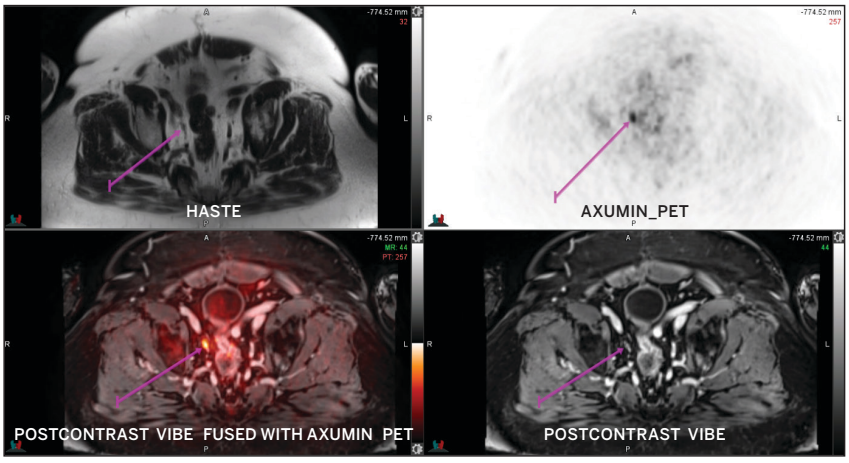

Figure 1. 18F-fluciclovine (Axumin) positron emission tomography(PET)/MRI.
A) Annotated PET maximum intensity projection demonstrating intense uptake in a right internal iliac lymph node (arrow);
B) MRI (left upper panel and right lower panel) and Axumin PET (right upper panel) demonstrating a minimally enlarged right internal iliac lymph node, just beneath the common iliac bifurcation, with intense PET uptake (SUV 8). Fused images localize the PET uptake to the lymph node (left lower panel).

Table 2. PSA scores and treatments: April 2018 to August 2020

Date	PSA (ng/mL)	Treatment
4/17/2018		Robot-assisted salvage lymph node dissection shows metastatic prostate cancer in 3/16 lymph nodes
8/3/2018	<0.02	Partial nephrectomy shows pT1b, Nx, Mx clear cell renal cell carcinoma with negative surgical margins
11/24/2018	<0.02	
2/2020	<0.02	
8/2020	<0.02	

COMMENT

The management of recurrent prostate cancer after radical prostatectomy has evolved substantially over the past 25 years, in part owing to the availability of new imaging modalities, which have enhanced surgical techniques, and in part owing to a growing body of evidence supporting the role of salvage management techniques, rather than adjuvant, to allow selective therapeutic intervention and to mitigate the risk of secondary side effects.

Despite this patient's apparent negative margins and benign lymph node dissection, his PSA never declined to an undetectable level on ultrasensitive assay, and this predicted a higher likelihood of recurrence in follow-up, regardless of pathology. Previously published outcomes from NYU Langone Health have demonstrated that men who do not achieve an undetectable PSA level (<0.02 ng/mL) are at a markedly increased risk of relapse in follow-up within 3 years as compared to those with undetectable PSA levels.[1] Nonetheless, a measurable PSA immediately after surgery, that falls below the accepted threshold of recurrent disease (0.02 ng/mL to 0.2 ng/mL) can be attributed to a number of causes, ranging from residual benign tissue to occult metastasis. For this reason, our practice at NYU Langone has generally been to observe PSA levels until a time that the kinetics can be established and true evidence of recurrence is demonstrated.

Historically, there have been data that supported the use of empiric adjuvant radiotherapy in men with high-risk pathology at the time of prostatectomy. Two large trials, conducted by SWOG[2] and by EORTC,[3] respectively, demonstrated improved recurrence-free survival among men receiving adjuvant radiation for locally advanced disease and/or positive margins in the absence of nodal metastasis.[2,3] The SWOG trial also demonstrated improved overall survival among the adjuvant radiation group.[2] Despite these results, routine use of adjuvant therapy was sparse, and this may largely be explained by the fact that in these trials the observation arm was not uniformly treated with early salvage radiotherapy at the first sign of relapse. In fact, a number of men in the adjuvant treatment arms had measurable PSA levels, further confusing the meaning of the findings. Retrospective data further supported the use of early salvage radiotherapy, with demonstration of comparable efficacy when it was administered below a PSA of 0.4 ng/mL.[4] In general, we at NYU Langone, along with most practitioners, believed that immediate adjuvant radiotherapy would benefit some but would likely overtreat many as well.

This patient's PSA began to rise relatively soon after surgery, making it highly likely that the PSA was attributable to relapse. Even though the relatively rapid doubling time might have suggested occult metastatic disease rather than local recurrence, empiric salvage radiotherapy was administered because of the patient's high-risk local pathology. Three large trials published in 2020 evaluated the question that has lingered since the time of the SWOG and EORTC trials, that is, whether early salvage radiotherapy in men with biochemical relapse is inferior to empiric adjuvant radiotherapy for high-risk pathology. The GETUG-AFU 17 trial, the RADICALS-RT trial, and the TROG 08.03/ANZUP-RAVES trial randomized men with high-risk pathology to immediate adjuvant radiotherapy or early salvage therapy at time of relapse.[5-7] Collectively, the trials demonstrated similar results: (1) adjuvant radiotherapy did not improve event-free, relapse-free, or overall survival, (2) adjuvant radiotherapy increased the risk of genitourinary and gastrointestinal toxicity, and (3) salvage radiotherapy was most effective when delivered in a timely manner at the earliest signs of relapse (typically, PSA <0.5 ng/mL).[8] This recent literature has supported long-term practices at NYU Langone and to some extent nullified the observations of earlier trials.

In this patient, salvage radiotherapy did result in a biochemical response but did not bring the PSA to undetectable levels. Durable control of disease after salvage radiotherapy is generally considered to be predicted at 2 years of follow-up, but the absence of an undetectable nadir may have hinted at the possibility of residual disease. The presentation is a bit unusual given the prolonged biochemical stability after treatment, followed by a rapid rise suggestive of occult metastatic disease. In general, men with early relapse and rapid PSA kinetics are most likely to harbor occult metastases.[9]

The final intervention in this patient was a salvage node dissection, empowered by the observation of metastasis in minimally enlarged lymph nodes in the right pelvis. Using robotic surgical techniques at NYU Langone, we have been able to employ surgical approaches for recurrent disease in lymph nodes, seminal vesicles (after radiotherapy), and even in the surgical bed. Such approaches have yet to be shown to improve survival, and while they are rarely curative, early data suggest the possibility of delaying time to androgen-deprivation therapy in a larger subset of men.[10,11] In this patient, thus far a durable complete response appears to have been achieved.

The use of metastasis-directed salvage therapies for prostate cancer recurrence has recently gained traction in the global urology community, largely because of the ability to recognize sites of limited metastatic disease at an early stage using novel molecular imaging agents such as Axumin and a number of labeled prostate-specific membrane antigen (PSMA) ligands. While PSMA PET has largely been considered to be more sensitive than Axumin, the wide availability of Axumin in the United States has increased its relative utilization. At NYU Langone, we are fortunate to have a PET/MRI facility that enables simultaneous evaluation with PET and MRI, further improving the specificity of the test. In general, Axumin PET is most informative at a minimum PSA of 0.5 ng/mL, and because this coincides with an acceptable PSA for salvage radiotherapy per recent studies, the use of PET may ultimately lead to a new paradigm in the management of men with recurrent disease in which men are observed until PSA 0.5 ng/mL, undergo PET imaging followed by empiric pelvic radiotherapy for those with no evidence of disease, and metastasis-directed therapy for those with discernible sites of disease. Such an approach is investigational and, as of yet, remains to be validated.

REFERENCES

1. Shen S, Lepor H, Yaffee R, Taneja SS. Ultrasensitive serum prostate specific antigen nadir accurately predicts the risk of early relapse after radical prostatectomy. *J Urol.* 2005;173(3):777-780.
2. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological t3n0m0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol.* 2009;181(3):956-962.
3. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet.* 2012;380(9858):2018-2027.
4. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA.* 2004;291(11):1325-1332.
5. Sargos P, Chabaud S, Latorzeff I, et al. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. *Lancet Oncol.* 2020;21(10):1341-1352.
6. Parker CC, Clarke NW, Cook AD, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet.* 2020;396(10260):1413-1421.
7. Kneebone A, Fraser-Browne C, Duchesne GM, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *Lancet Oncol.* 2020;21(10):1331-1340.
8. Vale CL, Fisher D, Kneebone A, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet.* 2020;396(10260):1422-1431.
9. Patel R, Lepor H, Thiel RP, Taneja SS. Prostate-specific antigen velocity accurately predicts response to salvage radiotherapy in men with biochemical relapse after radical prostatectomy. *Urology.* 2005;65(5):942-946.
10. Suardi N, Gandaglia G, Gallina A, Di Trapani E, et al. Long-term outcomes of salvage lymph node dissection for clinically recurrent prostate cancer: results of a single-institution series with a minimum follow-up of 5 years. *Eur Urol.* 2015;67(2):299-309.
11. Zattoni F, Nehra A, Murphy CR, et al. Mid-term outcomes following salvage lymph node dissection for prostate cancer nodal recurrence status post-radical prostatectomy. *Eur Urol Focus.* 2016;2(5):522-531.

SAMIR TANEJA, MD

Samir S. Taneja, MD, is the James M. and Janet Riha Neissa Professor of Urologic Oncology; professor of urology, radiology, and biomedical engineering; GU Program Leader in the Perlmutter Cancer Center; director of the Division of Urologic Oncology, and vice chair in the Department of Urology at NYU Langone Health. Dr. Taneja is nationally renowned as a key opinion leader in the treatment and research of prostate cancer. Over the past decade, his clinical research interest has been in prostate cancer diagnostics, with particular focus on the application of imaging in the detection, risk stratification, and surgical therapy of prostate cancer. He has pioneered the clinical application of pre-biopsy prostate MRI and techniques of MRI-targeted biopsy, and is widely recognized as an innovator in the emerging field of prostate cancer focal therapy. He is an oral examiner for the American Board of Urology, a member of the Society of Urologic Oncology Board of Directors, and is an elected member of the American Association of Genitourinary Surgeons. He has authored over 250 articles, 25 book chapters, and 5 textbooks. He has an h-index of 59. He is the and current Prostate Cancer Urology Surveys contributor for the Journal of Urology, and editor of the 3rd, 4th, and 5th, editions of Taneja's *Complications of Urologic Surgery: Prevention and Diagnosis*, one of the most widely read textbooks in American urology.

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 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 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 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 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 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 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 grace.hyun@nyulangone.org
Christopher Kelly, MD	Male and Female Voiding Dysfunction, Neurourology, Incontinence, Pelvic Pain, Benign Prostate Disease	646-825-6322 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 herbert.lepor@nyulangone.org
Stacy Loeb, MD, MSc**	Urologic Oncology, Prostate Cancer, Benign Prostatic Disease, Men's Health, General Urology	718-261-9100 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 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 nnenaya.mmonu@nyulangone.org
Bobby Najari, MD	Male Infertility, Vasectomy Reversal, Varicocele, Post-Prostatectomy, Erectile Dysfunction, Male Sexual Health, Hypogonadism, Oncofertility	646-825-6348 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 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 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 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 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 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 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 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 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 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