Oncological Control Following Partial Gland Ablation for Intermediate-Risk Prostate Cancer

CASE PRESENTATION
A 75-year-old Caucasian male was referred to our urology department in October 2017 with an elevated PSA of 8.7 ng/mL. His PSA had been very slowly rising over the prior 3 years. On digital rectal exam (DRE), the prostate gland was 50 g and benign.

EVALUATION
Multiparametric magnetic resonance imaging (mpMRI) showed an 18 x 14 mm PIRADS 4 region of interest left anterior mid, with a prostate volume of 68 cc (Figure 1). An MRI ultrasound fusion-targeted biopsy (MRFTB) and 12 systematic biopsies (SBs) were performed using the Artemis platform:

- 4 biopsies of the MRI target: 3 of 4 cores Gleason grade group (GGG) 2
- 12 SBs: right mid medial core 5% GGG 1

![Figure 1. Pre-treatment mpMRI showing 18 x 14 mm PIRADS 4 region of interest in the left anterior mid TZ.](image)

TREATMENT AND MANAGEMENT
All treatment options were discussed with the patient, including active surveillance, radical prostatectomy, radiation therapy, and partial gland ablation (PGA). The MRFTB showed that there was an anterior TZ cancer and an incidental contralateral GGG 1 cancer. The patient required a phosphodiesterase type 5 (PDE5) inhibitor in order to achieve erections adequate for penetration, and preserving potency was a high priority. In light of the location and the GGG of the index lesion and the patient’s age and high priority to preserve sexual function, the patient elected PGA. Based on the size of the gland and the location of the cancer, cryoaulation, which uses extreme cold to destroy tissue, was considered the optimal ablation energy source.
CASE OF THE MONTH

Cryoablation was performed under general anesthesia using 4 anterior-directed freezing probes, achieving temperatures of ~70°C within the ablation zone. The patient was discharged 3 hours after arriving in the recovery room. A Foley catheter was left indwelling for 3 days. He returned to work the day the urinary catheter was removed and to unrestricted activities 1 week following the PGA.

At 3 months post-PGA, the patient’s PSA was 0.8 ng/mL. He never wore a pad for urinary incontinence, his International Prostate Symptom Scores (IPSSs) pre- and post-PGA were 1, and his Sexual Health Inventory for Men (SHIM) scores pre- and post-PGA were 10 and 12, respectively. The sensation of orgasm was unchanged and the semen volume was reduced by 50%.

At 6 months post-PGA, an MRI and biopsy were performed. The MRI showed a 22 x 15 mm non-enhancing area concordant with the pre-treatment PIRADS 4 lesion and the planned ablation zone (Figure 2). Six biopsies were targeted to the ablation zone together with 6 SBs targeted to the left peripheral zone. All biopsies of the target zone showed treatment effect and all SBs were benign.

At 24 months post-PGA, the patient’s PSA was 0.6 ng/mL and his MRI was unchanged from the 6-month post-PGA study (Figure 3, left). The patient signed informed consent to participate in a clinical trial evaluating the ability of PET/MRI using fluciclovine F 18 (Axumin) to predict biopsy outcomes. The Axumin study showed no activity within the prostate ablation field and physiological uptake in the remaining right prostate (Figure 3, right). The 24-month biopsies of the ablation zone and the 12 SBs showed treatment effect in the ablation zone and a 1 mm GGG 1 cancer in the right medial mid tissue core.

![Figure 2. 6-month post-PGA mpMRI contrast-enhanced sequence showing no uptake within the ablation zone.](image)

![Figure 3. 24-month Axumin PET/MRI showing no contrast enhancement in the ablation zone (left) and physiological uptake of 18F-fluciclovine in the untreated prostate and no signal in the ablation zone (right).](image)
Comment
Over the last decade, there has been increasing interest in PGA for the treatment of low- and intermediate-risk prostate cancer. Historically, the primary objections to PGA for management of prostate cancer have been disease multifocality\(^1,2\) and inability to localize clinically significant disease.\(^3\) Today, the primary barrier to adopting PGA is its unknown oncological outcomes.\(^4\)

Oncological Rationale for PGA for Management of Prostate Cancer
The evolving acceptance of PGA is based on the observation that in the majority of cases of radical prostatectomy (RP), there is a single index lesion that drives the biology of the disease\(^1\) and that mpMRI reliably identifies this index lesion.\(^5,6\)

The most compelling study validating that mpMRI fusion-targeted biopsy and systematic biopsy SB identify appropriate candidates for PGA was a study reported by Kenigsberg et al.\(^7\) In this report, RP surgical specimens from 59 men meeting institutional criteria for PGA (single mpMRI lesion concordant with GGG 1-3 disease, no contralateral disease >5 mm or GGG >1 disease, and no extracapsular extension) were step-sectioned and all cancers were identified and characterized. Only 24% and 19% of cases exhibited GGG 2 in the RP surgical specimen outside of a hypothetical ablation template defined by lesion + 10 mm margin or hemiablation, respectively. All of these GGG 2 cancers exhibited <1 mm of Gleason pattern 4 disease.

Definition of Oncological Outcomes
There is no consensus on how to assess or define oncological outcomes following PGA. We do believe that until surrogate predictors of both in-field and out-of-field disease are identified, reflex biopsy is mandatory at various time points throughout follow-up. Ideally, clinically significant prostate cancer (csPCa) should be defined by both the disease and life expectancy. In general, clinically insignificant vs. significant prostate cancer is defined as GGG 1 vs. GGG >1.

Do PSA and mpMRI Predict Oncological Outcomes Following PGA?
There are only 3 studies reported in the literature where the inclusion criteria specified pre-treatment mpMRI in predominantly >GGG 1 disease and where reflex mpMRI fusion-guided prostate biopsy was performed within 1 year of PGA.\(^8-10\) These reports provide insights into the utility of PSA and mpMRI as “early” predictors of persistent disease following PGA. They provide consensus on the lack of predictive value of PSA, but they are discordant on mpMRI. Unfortunately, there is only 1 report of reflex biopsy at 2 years\(^11\) and there are no studies beyond 2 years for intermediate-risk disease mandating reflex biopsy.

Becher, Wysock, Gogaj, Velazquez, and Lepor\(^12\) reported on a cohort of 73 consecutive men who underwent partial gland cryoablation at NYU Langone Health who met the following baseline characteristics: single mpMRI lesion concordant with GGG >1 disease, no contralateral cancer >5 mm or GGG >1, and no extracapsular extension. Median baseline age and PSA were 64 years and 6.2 ng/mL, respectively. The GGG 1, 2, and 3 distribution was 12%, 57%, and 30%, respectively. Of these men, 60 (83%) underwent PSA testing, DRE, mpMRI, and mpMRI targeted biopsy 6 months following PGA with cryotherapy. A suspicious mpMRI was defined by contrast enhancement within or around the ablation cavity. The biopsy protocol included 4 targeted biopsies in and around the ablation cavity and 6 SB cores ipsilateral to the ablation. Overall, 5 (9%) in-field biopsies were
positive for any cancer and only 1 was GGG 2 and 4 were GGG 1. Since there was only a single case of csPCa, we examined the utility of mpMRI to detect any prostate cancer 6 months after PGA with cryotherapy. The ability of mpMRI to predict any cancer was disappointing based on an AUC of 0.551. Of the 7 suspicious mpMRI scans, only 1 targeted biopsy was found to be positive on biopsy (positive predictive value [PPV] of 14%). Of the 53 negative mpMRI scans, 49 lesions exhibited no cancer (negative predictive value [NPV] of 88%). The median decrease in PSA level was 67%. The rate of any in-field cancer detection was not significantly different for cases with PSA changes above or below the median change. The AUC of the PSA nadir was 0.66.

Additional studies are required to clarify the utility of PSA, PSA velocity, and mpMRI to predict in-field and out-of-field disease following PGA. These studies will require subjecting participants to prostate biopsy independent of the test results. A summary of the limited literature suggests that mpMRI becomes a useful predictor of csPCa when the incidence of csPCa is high.8-10 In appropriately selected patients operated on by experienced surgeons, the risk of early persistent disease (within <1 year of PGA) is too low to justify routine in-field biopsy. Therefore, we no longer routinely perform prostate biopsy at 6 months. The risk of persistent in-field and out-of-field disease is likely to increase with increasing time following treatment. It is imperative that the predictive utility of both PSA velocity and mpMRI be elucidated before these tests are used as proxies for oncological control.

CONCLUSION

PGA is routinely performed as an outpatient procedure with minimal treatment-related complications and minimal impact on quality of life.13 Rigorous oncological outcomes data are lacking, and so the intermediate- and long-term oncological control following PGA is unknown. Therefore, the primary barrier for adopting PGA is its unknown oncological outcomes.4 There is no consensus on how to assess or define oncological outcomes following PGA. There are very limited data on oncological outcomes mandating reflex biopsy testing in men with baseline csPCa beyond 1 year of treatment. Identifying predictors of both in-field and out-of-field disease following PGA requires that all men undergoing PGA follow up with reflex testing and biopsy at predefined time points.

I believe that the rational for PGA in selected cases of intermediate-risk prostate cancer is compelling and that the early oncological studies are reassuring. For those who are embracing PGA today, it is imperative to select candidates for treatment judiciously, disclose the unknown oncological outcomes, plan the treatment thoughtfully, follow patients rigorously, and be prepared to offer salvage treatment. If these measures are followed, oncological control is unlikely to be compromised and many men will avoid or defer the significant adverse effects of whole-gland treatment.
REFERENCES


Herbert Lepor, MD, received his undergraduate degree from the University of California Los Angeles in 1975 and his medical degree from The Johns Hopkins University School of Medicine in 1979. Dr. Lepor completed his surgery and urology residency training at The Johns Hopkins Hospital.

In 1993, Dr. Lepor was appointed professor and chair of the Department of Urology, NYU Grossman School of Medicine, and professor of pharmacology at NYU Grossman School of Medicine. Dr. Lepor is currently Chief Urologist at NYU Langone Medical Center and the Martin Spatz Chair of the Department of Urology. Dr. Lepor’s primary clinical and basic research interests are related to the prostate.

Dr. Lepor has served on the editorial boards of four major urological journals and has written more than 400 peer-reviewed articles, 50 book chapters, and 12 books related to prostate cancer, benign prostatic hyperplasia, and the pharmacology of the prostate. He is the co-founder and editor of Reviews in Urology. Dr. Lepor has been a visiting professor at 30 institutions. Some of Dr. Lepor’s landmark scientific contributions have focused on the identification of the autonomic intervention regulating male sexual function, development of the nerve sparing radical prostatectomy, improving outcomes following radical retro-pubic prostatectomy, outcomes following focal ablation of prostate cancer, characterization of the prostate alpha-1 adrenoceptor, and the medical and surgical management of benign prostatic hyperplasia.

In 1995, Dr. Lepor was awarded the Gold Cystoscope Award by The American Urological Association. Dr. Lepor is a member of the American Association of Genitourinary Surgeons, the Clinical Society of the American Association of Genitourinary Surgeons, the American Surgical Association, and the Johns Hopkins University Society of Scholars.
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