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Biopsy Assessment of Oncologic Control 3 Years Following Primary Partial Gland Cryoablation: A Prospective Cohort Study of Men With Intermediate-risk Prostate Cancer

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Study Need and Importance: There is increasing adoption of focal therapy (FT) for managing select cases of prostate cancer. We have a 10-year experience using a multitude of ablative energy sources and prefer cryoablation due to superior delivery of confluent cytotoxic energy to a predefined treatment zone. There is a paucity of FT studies performing protocol biopsies at predetermined intervals beyond the first year of treatment. The ultimate role of FT awaits compelling evidence demonstrating intermediate- and long-term oncologic disease control. The present study reports disease recurrence following primary partial gland cryoablation for men with intermediate-risk disease enrolled in an institutional review board-approved prospective outcomes registry undergoing protocol biopsies during the third year after treatment.

What We Found: Our oncologic assessment stipulated protocol biopsy of the pretreatment MRI lesion, any new MRI lesion, and 12-core random systematic biopsy in all subjects during the third year of follow-up. At 36 months, model-estimated rates of freedom from recurrence of in-field, out-of-field, and overall clinically significant cancer were 97% (95% CI: 92-100), 87% (95% CI: 80-94), and 86% (95% CI: 78-93), respectively (see Figure). The model-estimated proportion with freedom from failure at 36 months was 97% (95% CI: 93-100).

Limitations: Compliance with protocol biopsy of 76% may introduce unrecognized reporting bias. These very encouraging observations may not be generalizable to patient populations at other medical centers and less experienced surgeons. Additionally, there are limitations inherent in the statistical analyses, particularly as they pertain to our multiparametric



Figure. Nonparametric maximum likelihood estimators for freedom from in-field recurrence (A), freedom from out-of-field recurrence (B), freedom from any recurrence (C), and freedom from failure of treatment (D). Recurrence was defined as Gleason grade group ≥ 2 cancer on biopsy, and failure of treatment was defined as whole-gland salvage treatment, metastatic prostate cancer, or prostate cancer mortality. Solid lines indicate nonparametric maximum likelihood estimators. Gray rectangles represent regions of nonunique nonparametric maximum likelihood estimators. Dashed lines represent 95% confidence intervals.

MRI test characteristics and the structure of our survival models/analyses.

Interpretation for Patient Care: The very low infield cancer detection rate at 3 years indicates successful ablation of localized cancers. Conversely, our observed out-of-field detection rate highlights the need for continued surveillance following primary partial gland cryoablation. The overwhelming majority of clinically significant recurrences were low volume and managed with active surveillance or salvage partial gland cryoablation.

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Biopsy Assessment of Oncologic Control 3 Years Following Primary Partial Gland Cryoablation: A Prospective Cohort Study of Men With Intermediate-risk Prostate Cancer

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Purpose: We evaluated 3-year oncologic outcomes following primary partial gland cryoablation.

Materials and Methods: Men with unilateral intermediate-risk prostate cancer undergoing primary partial gland cryoablation since March 2017 enrolled in a prospective outcome registry. The postablation protocol for all men included surveillance prostate biopsy at 2 years postablation and reflex prostate biopsy for cases with high suspicion of recurrence (eg, progressive rise in PSA). Recurrence of clinically significant prostate cancer was defined as any Gleason grade group ≥ 2 disease on postablation biopsy. Freedom from failure represented no whole gland salvage treatment, metastatic prostate cancer, or prostate cancer mortality. Freedom from recurrence and freedom from failure were characterized using nonparametric maximum likelihood estimators.

Results: A total of 132 men had at least 24 months of follow-up data. Biopsies identified clinically significant prostate cancer in 12 men. At 36 months, model-estimated rates of freedom from recurrence of in-field, out-of-field, and overall clinically significant cancer were 97% (95% CI: 92-100), 87% (95% CI: 80-94), and 86% (95% CI: 78-93), respectively. The model-estimated proportion with freedom from failure at 36 months was 97% (95% CI: 93-100).

Conclusions: The low in-field cancer detection rate at 3 years indicates successful ablation of localized cancers. Conversely, our observed out-of-field detection rate highlights the need for continued surveillance following partial gland cryoablation. Many of these recurrences exhibited very low volume of clinically significant disease below the detection threshold of multiparametric MRI, suggesting a limited role for multiparametric MRI in detecting clinically significant recurrences at 2 years. These findings emphasize the need for long-term surveillance and identification of predictors of clinically significant prostate cancer recurrences to guide biopsy timing.

Key Words: prostatic neoplasms, cryosurgery, patient outcome assessment

MRI disease localization coupled with targeted biopsy has enabled identification of candidates with clinically significant prostate cancers (csPCas) amenable to image-guided partial gland ablation (PGA).¹ As with many organ-sparing oncologic strategies, PGA aims to achieve cancer control while limiting adverse effects and functional impairment.² Literature reviews and consensus

statements reflect an increasing acceptance of PGA.^{3,4} Further validation of PGA requires improved definition of patient selection, treatment parameters, and posttreatment evaluation.

The primary potential limitation of PGA is failure to totally ablate the localized (in-field) disease or the development of csPCa in the untreated (outof-field) prostate. There is no current

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Correspondence: Department of Urology, NYU Grossman School of Medicine, 222 East 41st St, 12th Floor, New York, NY 10017 (telephone: 646-825-6340; email: Herbert.Lepor@nyulangone.org). consensus regarding optimal disease monitoring or indications for surveillance biopsies following PGA.^{5,6} Cryoablation represents the primary energy source utilized at our institution for PGA since it reliably achieves confluence of energy in the ablated field.⁷ Several single institution retrospective studies report oncologic outcomes following primary partial gland cryoablation (PPGCA) without specific protocols for disease monitoring or tissue sampling.⁸⁻¹¹ Consequently, the true rate of csPCa recurrence following PPGCA remains inadequately defined. While oncologic outcomes such as prevention of whole gland or androgen deprivation interventions offer meaningful clinical end points, earlier surveillance biopsy and detection of csPCa provides more immediate feedback on patient selection, ablation technique, and treatment efficacy, and allows more timely initiation of salvage treatment.¹²

Beginning in March 2017, we initiated an Institutional Review Board–approved prospective cohort evaluation of men with csPCa undergoing PPGCA. The protocol stipulated uniform pretreatment disease assessment, selection criteria, and timing of oncologic monitoring and posttreatment surveillance biopsy at 2 years independent of PSA kinetics or MRI findings. Since oncologic outcomes following PGA are highly dependent on baseline risk of disease,^{9,10} the present study included only men with unilateral favorable and unfavorable intermediaterisk prostate cancers.

MATERIALS AND METHODS

Subjects

Our prospective Institutional Review Board-approved outcomes registry was initiated in March 2017 and is currently enrolling men undergoing PPGCA (IRB No. 17-00354). Patient selection required prebiopsy multiparametric MRI (mpMRI). All observed magnetic resonance regions of interest categorized using PI-RADS (Prostate Imaging Reporting & Data System) v2 between 2 and 5 were segmented by radiologists in preparation for biopsy.¹³ Both targeted biopsy (4 cores) of all segmented regions of interest and 12-core systematic biopsy were performed using the Artemis biopsy platform as previously described.¹⁴ The present analysis included subjects meeting the following eligibility criteria: an mpMRI region of interest (ROI) PI-RADS 2-5 concordant with unilateral intermediate-risk disease (Gleason grade group (GGG) 2 or 3 disease), no gross extraprostatic extension on mpMRI, no GGG \geq 2 contralateral to the ROI, no very distal apical disease on mpMRI, and at least 24 months of follow-up data as of October 10, 2022.

Treatment

All PPGCAs were performed under general anesthesia in the dorsal lithotomy position as previously described.⁷ The treatment plan was designed to achieve a 10-mm margin beyond the ROI when technically feasible. Six temperature probes were positioned to maximize safety and treatment margins. A urethral warming catheter was passed over a guidewire under US guidance prior to initiating the first freezing cycle. A minimum of 2 freeze/thaw cycles were carried out. PPGCA was performed using the Cryocare CS system. A Foley catheter was left indwelling between 3 to 5 days depending on baseline International Prostate Symptom Score, size of the gland, and location of ablation.

Surveillance Protocol

The surveillance protocol for men enrolled in the study between March 2017 and August 2020 was PSA testing at 3 and 6 months following PPGCA and every 6 months thereafter, an mpMRI at 6 months, 2 years, 3.5 years, and 5 years, and a surveillance prostate biopsy at 6 months, 2 years, and 5 years. Additionally, men with high suspicion of recurrence (eg, digital rectal examination or rise in PSA concerning for recurrence, symptoms consistent with metastasis, etc) underwent mpMRI and prostate biopsy outside the surveillance schedule at the discretion of their provider. Surveillance biopsy at 6 months was abandoned following an interim analysis in August 2020 demonstrating very low rates of csPCa.⁷ The presence of contrast enhancement or diffusion abnormalities within, or adjacent to, the ablation zone (AZ) or any new ipsilateral PI-RADS >2 ROI was considered suspicious for in-field disease recurrence. The development of any contralateral new PI-RADS >2 ROI was considered suspicious for out-offield recurrence. The 2-year prostate biopsy protocol included 4 cores directed into the AZ even if the ablation cavity atrophied, 4 cores directed into any suspicious in- or out-of-field new MRI targets, and a 12-core computergenerated systematic biopsy consisting of 6 ipsilateral and 6 contralateral tissue cores. When planning the biopsies, the pretreatment ROI of the index lesion was superimposed onto the ablation cavity using Profuse software. In addition, targeted tissue cores were directed into any in-field sites demonstrating contrast enhancement or diffusion abnormality or any new in- or out-of-field PI-RADS >2 ROI.

Statistical Analyses

Recurrence of csPCa was defined as any GGG ≥ 2 disease, and was assessed separately for in-field, out-of-field, and overall recurrences. Failure of treatment was defined as whole gland salvage treatment, metastatic prostate cancer, or prostate cancer mortality. Patients who underwent surveillance biopsy between 18 and 36 months after their PPGCA successfully adhered to the 2-year surveillance protocol. Participants with less than 36 months of follow-up data were still eligible to complete the 2-year surveillance biopsy. Participants who did not undergo biopsy by 36 months were noncompliant with the 2-year surveillance protocol. Among these patients, some underwent mpMRI without a biopsy. Those who recurred with csPCa prior to 2-year surveillance were also considered to have adhered to surveillance biopsy protocol. Associations between surveillance protocol adherence and demographic/oncologic characteristics were investigated using χ^2 tests, Wilcoxon rank-sum tests, and t tests (for categorical, ordinal, and continuous measures, respectively).

Given that recurrence was identified exclusively through prostate biopsy, the exact moment of recurrence could not be known, and patient data were therefore treated as interval censored. The lower bound of the interval for recurrence was defined as the most recent time that a patient was known to be free from csPCa. For patients who were nonadherent to



Figure 1. Participant flow diagram. Inclusion criteria were a multiparametric MRI region of interest (ROI) PI-RADS 2-5 concordant with unilateral intermediate-risk disease (Gleason grade group [GGG] 2 or 3 disease), no gross extraprostatic extension (EPE) on multiparametric MRI, no GGG ≥2 contralateral to the ROI, no very distal apical disease on multiparametric MRI, and at least 24 months of follow-up data after primary partial gland cryoablation (PPGCA). Per-protocol biopsy entailed undergoing biopsy between 18 and 36 months after cryoablation. csPCA indicates clinically significant prostate cancer.

surveillance protocol and never underwent biopsy, this was defined as time of PPGCA. For those who underwent biopsy but were not fully adherent to surveillance protocol, this was defined as time of most recent negative biopsy. Finally, among patients adherent to the 2-year surveillance protocol, the lower bound was set at the time of their most recent known negative workup (ie, negative surveillance/for-cause biopsy and subsequent adherence to the study protocol without trigger for for-cause biopsy). The upper bound of the recurrence interval was defined as the time of detection of csPCa on biopsy. For analyses examining failure of treatment, patients who received whole gland salvage treatment or died of prostate cancer—related causes did not need to be censored since the specific date of treatment/ death was known. However, metastasis of prostate cancer was treated as interval-censored data with a lower bound of last date known not to have metastases and upper bound of date of diagnosis of metastatic prostate cancer. Patients who died of nonprostatic causes without recurrence/failure of treatment were censored at time of death.

To accommodate the interval-censored data structure, nonparametric maximum likelihood estimators

Table 1. Demographics and Baseline Characteristics of Men
With Clinically Significant Prostate Cancer Undergoing
Cryoablation $(n=132)$

D N- (0/)â		
Race, No. (%)	40	(0.0)
Black	13	(9.8)
White	104	(79)
Other/multiracial	12	(9.1)
Ethnicity, No. (%) ^a		
Hispanic	9	(6.8)
Non-Hispanic	122	(92)
PI-RADS, No. (%)		
2	11	(8.3)
3	46	(35)
4	58	(44)
Б	17	(13)
Index lesion location No. (%)	17	(10)
Perinheral zone	103	(78)
Transition zono	24	(70)
	24	(10)
	1	(0.70)
Anterior fibromuscular stroma	4	(3.0)
Clinical stage, No. (%)		(0.0)
11c	117	(89)
T2	15	(11)
GGG, No. (%)		
2	96	(73)
3	36	(27)
Out-of-field GGG1 lesion, No. (%)	36	(27)
Age, median (IQR), y	64.7	(59.5, 68.9)
PSA, median (IOR), ng/mL	6.4	(4.6, 8.5)
PSA density median (IOR) ng/ml^2	0.15	(0.092 0.21)
Prostate volume median (IOR) ml	43	(31 58)
Maximum dimension of index lesion median (IOR) mm	11 5	(80 140)
	11.0	,0.0, 11.0/

Abbreviations: GGG, Gleason grade group; IQR, interquartile range; PI-RADS, Prostate Imaging Reporting & Data System; PSA, prostate-specific antigen. ^a Missing 3 responses for race and 1 response for ethnicity.

were calculated for freedom from recurrence of csPCa (in-field, out-of-field, and overall) and freedom from failure of treatment.^{15,16} The 95% confidence intervals for these nonparametric maximum likelihood estimators were estimated through 36-month post-PPGCA using 1,000 bootstrap replications.

Biopsy results for men who recurred were stratified by salvage treatment and highest GGG, the total number of positive cores, and the total linear length of Gleason pattern (GP) 4 described. To determine whether the presence of an out-of-field GGG1 lesion at baseline was predictive of out-offield recurrence, comparison of the survival distributions for freedom from recurrence of out-of-field csPCa between those who had a baseline out-of-field GGG1 lesion and those who did not was conducted using an asymptotic weighted logrank test that generalizes the Wilcoxon rank-sum test to interval-censored data.¹⁶ Additionally, the performance of 2-year surveillance mpMRI for detecting csPCa was characterized using likelihood ratios and positive and negative predictive values. All statistical testing used 2-sided confidence intervals and an α of .05. All analyses were conducted using R (version 4.0.5) and package *interval* (version 1.1-0.8) from October 2022 to April 2023.

Data Availability

The data sets generated and/or analyzed during the current study are not publicly available to maintain participant privacy, but are available in deidentified form from the corresponding author on reasonable request.

RESULTS

A total of 132 men with at least 24 months of followup data met inclusion criteria and were eligible for analysis (Figure 1). Sample demographics and baseline oncologic characteristics are shown in Table 1.

Surveillance Protocol Adherence

Of the 132 men who contributed to the survival analysis, 125 were eligible to undergo mpMRI and biopsy at 2 years since 2 patients died of nonprostatic causes prior to 2-year surveillance and 5 men were enrolled prior to August 2020, underwent 6-month surveillance, and were found to have recurred at that time. Of these men, 27 are awaiting per-protocol 2-year surveillance biopsy. Of the remaining 98 men, 74 underwent a perprotocol 2-year surveillance biopsy. Of the 24 men who were nonadherent to the 2-year surveillance protocol, 10 had a negative 2-year surveillance MRI and stable PSA. No statistically significant associations were identified between surveillance protocol adherence and patient age, race, or ethnicity, or any baseline oncologic characteristics (ie, PSA, PSA density, PI-RADS, highest GGG, and presence of contralateral GGG1 lesion; all P > .05).

Recurrence and Freedom From Failure

All 132 men who met inclusion criteria contributed to the survival analyses for freedom from recurrence and freedom from failure. Overall, 12 men recurred with csPCa by the end of the surveillance period. At 36 months, model-estimated probabilities of freedom from recurrence of in-field, out-of-field, and overall csPCa were 97% (95% CI: 92-100), 87% (95% CI: 80-94), and 86% (95% CI: 78-93), respectively (Figure 2). Notably, 2 patients had both in- and out-of-field recurrence and were thus included as events in both the in- and out-offield csPCa analyses.

Of the 12 men who recurred throughout the surveillance period, 4 were managed with active surveillance, 4 with repeat cryoablation, and 2 with radical prostatectomy (RP). Two patients were found to have csPCa on routine surveillance yet refused recommended treatment. The model-estimated probability of freedom from failure at 36 months was 97% (95% CI: 93-100; Figure 2).

Characteristics of Recurrence

Baseline out-of-field GGG1 disease was predictive of earlier out-of-field recurrence (P = .04); at 36 months, model-predicted freedom from recurrence of out-of-field csPCa was 92% among those without baseline out-of-field GGG1 disease and 77% among those with baseline out-of-field GGG1 disease (Figure 3). Biopsy results for men who recurred, stratified by treatment type, are summarized in Table 2. Notably, none of the participants who recurred exhibited GP5. All patients with csPCa managed with active surveillance had only a single



Figure 2. Nonparametric maximum likelihood estimators for freedom from in-field recurrence (A), freedom from out-of-field recurrence (B), freedom from any recurrence (C), and freedom from failure-of-treatment (D). Recurrence was defined as Gleason grade group \geq 2 cancer on biopsy, and failure of treatment was defined as whole gland salvage treatment, metastatic prostate cancer, or prostate cancer mortality. Solid line represents nonparametric maximum likelihood estimators. Gray rectangles represent regions of nonunique nonparametric maximum likelihood estimators. Dashed lines represent 95% confidence intervals.

core of GGG ≥ 2 disease and linear length of GP4 less than or equal to 0.1 mm. All of the men undergoing salvage RP and the majority of men undergoing salvage partial gland cryoablation (PGCA) had multiple cores showing GGG ≥ 2 disease. Of the 4 men undergoing salvage PGCA, 2 had a single core showing GGG ≥ 2 disease.

Characteristics of MRI

Of the men who completed 2-year surveillance mpMRI and biopsy and who had not recurred prior to 2-year surveillance, 13 had a positive mpMRI, of whom 2 were found to have csPCa. Sixty-one had a negative mpMRI, of whom 5 were found to have csPCa. Two-year surveillance mpMRI had a positive likelihood ratio of 1.7 and negative likelihood ratio of 0.9; given the study's model-estimated prevalence of recurrence of 14% through the study period, this yields a positive predictive value of 22% and negative predictive value of 88%.

DISCUSSION

Oncologic outcomes in men with localized prostate cancer undergoing RP and PGA are dependent on baseline GGG.^{9,10,17} Therefore, it is imperative to report oncologic outcomes according to baseline GGG. Thus, the present study reports only on those men in our prospective registry with intermediate-risk disease in accordance with an emerging consensus that this cohort represents the ideal candidates for PGA.^{3,5,6}

There is no consensus on how to define csPCa preor posttreatment following PGA. In the PROMIS trial,¹⁸ the presence of any GP4 represented one of several definitions of csPCa disease. In the present study, csPCa was defined as any GP4 disease on biopsy. Since selected cases of low-volume GGG2 disease are guideline-supported candidates for active surveillance.^{19,20} Cases with a single biopsy core exhibiting submillimeter length of GP4 not associated with an MRI lesion were categorized as csPCa even though salvage treatment was not recommended.



Figure 3. Nonparametric maximum likelihood estimators for freedom from out-of-field recurrence of clinically significant prostate cancer (Gleason grade group [GGG] \geq 2 disease), stratified by presence of out-of-field GGG1 lesion at baseline prior to cryoablation. Solid lines represent subset without GGG1 lesion at baseline. Dashed lines represent subset with GGG1 lesion at baseline. Black lines represent nonparametric maximum likelihood estimators. Gray rectangles represent regions of nonunique nonparametric maximum likelihood estimators. Gray lines represent subset with 95% confidence intervals.

There is no consensus on who should undergo repeat biopsy following PGA.³⁻⁶ In several studies reporting on intermediate-term oncologic outcomes following PPGCA, only 59% and 65% underwent a posttreatment biopsy.^{9,10} The percentage of men undergoing a biopsy beyond 1 year was not reported. While some may speculate that men with a stable PSA velocity and negative mpMRI may not require biopsy, there are no studies where routine biopsy at predefined time points validated this practice.

Given the critical need to establish clinical parameters supporting efficacy of PGA, routine biopsy assessment of both the AZ and the untreated prostate is necessary until proven otherwise. Rigorous outcome measurement with tissue evaluation improves guidance on patient selection, treatment parameters (eg, energy type, margin), and oncologic efficacy. We no longer perform a surveillance biopsy at 6 months based on our reported low rate of clinically significant disease at this time point.⁷ Based on the results of the current study, we no longer routinely perform surveillance biopsies at 2 years. Two-year biopsies are performed only on those men with progressively rising PSA levels, new in- or out-of-field mpMRI regions of interest, or concerning digital rectal examination. Furthermore, the current report strengthens the rationale for the application of a 1-cm treatment margin to the index lesion as well as providing convincing evidence that PPGCA

Salvage management	Highest N GGG witi		Linear length GP4, mm ^a	Location of csPCa recurrence		MRI findings		
				In- field	Out-of- field	Negative	Suspicious for recurrence	
		No. cores with GGG \geq 2					In- field	Out-of- field
Active surveillance	2	1	0.1		1	/		
	2	1	< 0.05		1		1	
	2	1	b		1			1
	2	1	b		1	1		
Radical prostatectomy	3	2	С	1	1	1		
	3	2	2.4		1	1		
Salvage cryoablation	2	1	0.4		1	1		
	4	3	C	1		1		
	2	1	0.6		1	1		
	3	4	6.8					1
Protocol deviation	2	8	5.6	1	1		1	
	2	1	1.2		-			

Table 2. Biopsy and Magnetic Resonance Imaging Findings of Men Who Had Recurrence of Clinically Significant Prostate Cancer Within36 Months of Cryoablation

Abbreviations: csPCa, clinically significant prostate cancer; GGG, Gleason grade group; GP, Gleason pattern; MRI, magnetic resonance imaging.

^a Length of GP4 was calculated for patients with recurrence of intermediate-risk disease (ie, GGG2 or GGG3).

^b Focus of GP4 was too small to be measured accurately.

^c Biopsy report was missing length or percent of GP4.

achieves confluent tissue destruction within the treatment volume. These encouraging results appear to meet the fundamental goal of PGA, which is confluent and durable tissue destruction, thereby establishing a standard for emerging technologies seeking validation in this space.

The primary end point in the present study was any csPCa on prostate biopsy. This registry protocol requires biopsy during the third year of follow-up, which is designated as the 2-year biopsy. Our modelestimated probabilities of recurrence of in-field, outof-field, and any csPCA recurrence by 36 months were 3%, 13%, and 14%, respectively. Despite these low recurrence rates, we were able to detect a statistically significant difference in time to out-of-field recurrence between those who did and did not have a contralateral GGG1 lesion at baseline.

Of the cases with csPCa recurrence on 2-year surveillance biopsy, MRI was suspicious for recurrence in only 2. The poor performance of surveillance MRI at 2 years suggests it is not a useful instrument for detecting early csPCa recurrence. We attribute this to the very low volume of GP4 in the majority of csPCa recurrences.

The current study reports model-estimated out-offield probability of recurrence of 13%, suggesting a need for improvements in patient selection. We have shown that 20% of men who are candidates for PGA undergoing RP have demonstrable occult "contralateral" GP4.¹ It is therefore not surprising that some men undergoing PPGCA exhibited csPCa on the 2-year biopsy. The low volume of occult GGG2 and 3 is below the detection limits of mpMRI. Furthermore, it is important to note that 10% and 25% of men with GGG2 and 25% and 50% of men with GGG3 disease will develop biochemical recurrence at 2 and 8 years following RP, respectively.¹⁷ Even patients with intermediate-risk disease undergoing the standard of care RP have a significant risk of biochemical recurrence due to a positive surgical margin or occult metastatic disease—so all treatments carry a risk of recurrence.

The management of the men identified with csPCa recurrence is shown in Table 2. Overall, 4, 4, and 2 cases were managed with active surveillance, salvage PGCA, and RP, respectively. All cases managed with active surveillance had a single biopsy core showing \leq 0.1 mm of GP4 disease. Active surveillance is a guideline-appropriate management for low-volume GGG2.^{19,20} The majority of cases managed with salvage RP had more than 1 biopsy core showing GGG≥2. Our freedom from failure rate of 97% at 36 months after PGA is encouraging and is consistent with a 93.3% 3-year freedom from failure rate for 87 men with intermediate-risk prostate cancer undergoing PPGCA reported by Shah et al.²¹ The modelestimated freedom from failure rate of 98% at 3 years after PGA is encouraging.

The challenge with all treatments for prostate cancer is balancing oncologic and functional outcomes. We have reported no incontinence at any time following PPGCA, and preservation of potency at 2 years in 70% and 93% of all men and men with no erectile dysfunction at baseline, respectively.²² Our encouraging oncologic outcomes were achieved with equally encouraging functional outcomes.

There are many strengths of the present study. All men enrolled in our prospective outcomes study were strongly encouraged to undergo surveillance MRI and magnetic resonance fusion-target biopsy at 2 years, as well as regular PSA measurement. The observed compliance with routine 2-year biopsy is the highest level reported to date. In addition, the intensity of the surveillance biopsy protocol is comparable to the pretreatment diagnostic biopsy, which remains the standard of care for cancer detection.

This study also has multiple notable limitations. An important limitation is that these very encouraging observations may not be generalizable to patient populations at other medical centers and less experienced surgeons. Additionally, there are limitations inherent to the statistical analyses that must be acknowledged, particularly as they pertain to our mpMRI test characteristics and the structure of our survival models/analyses. Performance of mpMRI in detecting 2-year recurrence is dependent on the intensity of prior biopsy surveillance intensity. Given that many men in our cohort underwent biopsy at least once prior to 2-year surveillance, those who recurred earlier with more aggressive disease did not undergo mpMRI, likely resulting in poorer test characteristics than would be observed in a surveillancenaïve population. However, since many real-world oncologic surveillance protocols have similarly early intense screening protocols, our results are likely generalizable. Additionally, to calculate positive and negative predictive values of mpMRI at 2-year followup, model-generated recurrence rates were used to estimate values that may be reflective of the broader population. Another important consideration is the statistical approach used to handle other-cause death in our survival models. Any method for censoring other-cause death has the risk of introducing statistical bias; however, since only 2 men died of nonprostatic causes in this study, competing risk analysis was not feasible and it is exceedingly unlikely that censoring was impactful on the study's results.

CONCLUSIONS

Our exceptionally low probability of csPCa in-field recurrence in men with intermediate-risk disease validates the durable and confluent treatment destruction of PPGCA in the AZ, thus establishing a technical standard for achieving this critical end point of PGA strategies. The relatively low detection rate of out-of-field csPCa is also encouraging, especially since many of the detected csPCas were very low volume and managed with active surveillance. The 97% probability of freedom from failure at 3 years is also very encouraging especially due to the high proportion of men undergoing an intensive posttreatment protocol biopsy. All of these men would have been appropriate candidates for whole gland treatment at the time of diagnosis. Further reports from this protocol on routine surveillance including biopsy at 5 years will assess longer-term oncologic control of men with intermediate-risk disease undergoing PPGCA.

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EDITORIAL COMMENT

We are now firmly in the era where we need to be deescalating treatment for suitable men with localized prostate cancer. The role of focal therapy or partial gland ablation is becoming clearer, and data such as those published this month by Dr Wysock et al add to our understanding of patient selection, follow-up, and pathological response rates from partial gland cryoablation.¹ Inclusion criteria were grade group (GG) 2 or GG3 localized unilateral disease. Outfield GG1 disease was allowed. Three-year pathological in-field recurrence-free survival was 97%, whilst out-of-field recurrence-free survival was 86%. They commented that MRI-based follow-up may be appropriate, however will miss low-volume recurrence. There is no clear consensus yet on how best to perform and analyze post-partial ablation multiparametric MRI. The TARGET (Trans-Atlantic Recommendations for prostate Gland Evaluation with MRI after focal Therapy) consensus meeting was recently completed and will hopefully add to this field.

Results such as these need to be taken in the context of studies such as the 15-year PROTECT trial update showing that whilst there was no difference in survival between up-front radical treatment and initial active monitoring, approximately 60% of those within the monitoring arm underwent treatment over the surveillance period.² These radical treatments, come at a significant impact on quality of life, and recent sobering data from the PACE-A trial³ and Kings College London⁴ (Mac-Askill, AUA 2023) show real-world pad-free rates from radical prostatectomy of 53%-75%. In contrast, pad-free rates from focal ablation consistency approach 95%-100%.⁵ It is also very unlikely, in intermediate-risk disease, that any survival advantage will be seen over a prolonged follow-up period from up-front partial gland ablation compared to the traditional radical treatments.⁶

As with all treatment options, there are tradeoffs to be made. The gain in functional outcome preservation with focal ablation needs to be balanced against the need for a more intensive surveillance protocol and further treatments in up to 1 in 3. Ultimately, though, it should be for the patient to decide. We have moved from a paternalistic model of health care to one of informed decision-making. It should be the patient who decides which trade-offs they are prepared to make, and whilst discussing concerns regarding recurrence we must bear in mind that even radical treatments have a risk of recurrence.

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REPLY BY AUTHORS

I (HL) and my colleagues appreciate and enthusiastically endorse all of the comments articulated by Professor Shah.

I performed my first focal therapy (FT) for prostate cancer (PCa) in 2014. My enthusiasm for FT in selected cases of low- and intermediate-risk PCa was based upon the following assumptions: MRItargeted + systematic biopsy reliably identified site(s) of clinically significant PCa; active surveillance was an appropriate management strategy for PCa undetected by MRI-targeted + systematic biopsy; energy sources were available to reliably eradicate the index lesion; preserving quality of life was a high priority for men with PCa; FT would improve quality of life outcomes relative to whole gland treatments; the availability of salvage therapies for disease recurrences; and careful monitoring would ensure that oncologic outcomes would not be compromised.

To date, we have enrolled over 400 men undergoing primary partial gland cryoablation into our prospective outcomes registry. While we believe selected cases of high-volume/low-risk and low-volume/high-risk are appropriate candidates for FT, the present study was limited to men with intermediaterisk disease, often designated as "ideal" candidates for FT.¹

Over the last decade, we and others have validated almost all the assumptions made in 2014 regarding FT. While we have yet to optimize candidate selection, treatment templates, energy sources, and follow-up testing, the present study adds to the literature that FT achieves a favorable balance between oncologic and functional outcomes and should be part of the shared care discussion.

My only reservation about FT is whether men will comply with the requirement for a lifetime of surveillance in order to ensure oncologic outcomes are not compromised.

Taimur T. Shah^{1,2}

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