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Evolution of Active Surveillance of Prostate Cancer: Impact of Magnetic Resonance Imaging, Magnetic Resonance Imaging–Guided Biopsy, and Focal Therapy

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Full-length article available at https://doi.org/10.1097/JU.0000000000004559.

Study Need and Importance: Active surveillance (AS) is now a guideline recommendation for men with low-risk prostate cancer (PCa), but guidelines for follow-up are still evolving. MRI and MRI-guided biopsy (MRGB)—as protocol-mandated baseline and follow-up mileposts of a large AS program—have yet to be reported. Along with MRI, evolving over the past 2 decades, is the concept of focal therapy (FT), which might in some men provide extension of the surveillance. In this article, we report the incorporation of MRI, MRGB, and FT into an AS protocol.

What We Found: Among 869 men with low- and favorable intermediate-risk PCa enrolled in an AS protocol, which mandated baseline and follow-up MRGBs, we found that during 4.1 median years of follow-up (range 1-12), the absence of progression was correctly identified by MRI (negative predictive value) in 90% to 95% of men entering with low risk and 70% for men with favorable intermediate risk (Figure). PSA density (>0.15) modulated these results. Significant deferral of surgery or radiation (radical prostatectomy/radiation therapy [RP/RT]) resulted when FT was used in men whose PCa progressed: 5-year freedom from RP/RT was 84% in the FT group vs 46% without FT ($P < .01$).

Limitations: The work is a prospective cohort study at one academic medical center. At the site (University of California, Los Angeles), a substantial in-depth experience with MRI and MRGB (>15 years) and a considerable experience with FT (>10 years) might limit generalizability. Furthermore, patient selection for FT was not standardized.

Interpretation for Patient Care: When men enter AS with low-risk PCa diagnosed by MRGB, subsequent biopsy can be safely avoided when MRI is negative.

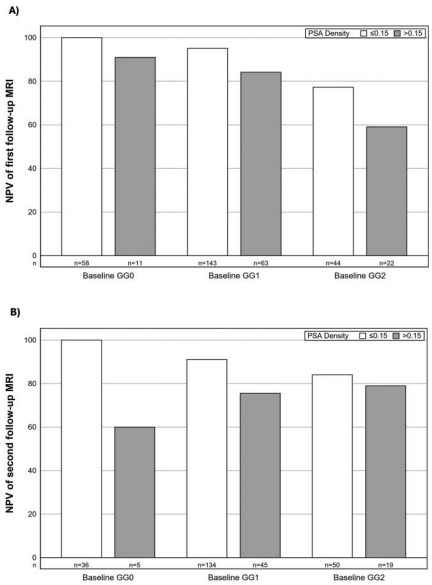

Figure. A, Chart showing negative predictive value (NPV) of MRI at the time of first follow-up biopsy. NPV = accuracy of negative MRI (no lesions) in predicting absence of ≥ Grade Group (GG) 3 on MRI-guided biopsy. A negative MRI was found in 341/664 men at the first follow-up biopsy. Regardless of PSA density, NPV was high (84%-100%) among men with GG0 or GG1 at baseline, but lower for men with GG2 (59%-77%). B, NPV of MRI at the time of second follow-up biopsy was similar to that found at the first follow-up biopsy.

For men entering AS with favorable intermediate-risk PCa, the negative predictive value of follow-up MRI is less reliable. PSA density > 0.15 favors biopsy in indeterminate cases. When PCa progression is found, FT can be considered as a way to extend AS, that is, a decisional crossroad, not a mandatory path to RP/RT.

THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000004559
Vol. 214, 177-187, August 2025
Printed in U.S.A.

THE JOURNAL of UROLOGY®
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Evolution of Active Surveillance of Prostate Cancer: Impact of Magnetic Resonance Imaging, Magnetic Resonance Imaging–Guided Biopsy, and Focal Therapy

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Purpose: We aimed to determine if, using baseline MRI-guided biopsy (MRGB), durability of active surveillance (AS) could be predetermined, follow-up biopsies avoided, and if by incorporating focal therapy (FT), AS extended.

Materials and Methods: A cohort of 869 men in the University of California, Los Angeles, protocol study of AS (2010-2022) was analyzed. Inclusion criteria were baseline MRGB showing Grade Group (GG) ≤ 2 and ≥ 1 year enrollment. After 2016, FT was offered to men with GG2 and those progressing to GG3.

Results: The 869 men accrued 3500 patient-years of follow-up (median follow-up 4.1 years). At baseline, men were GG1 (505), GG2 (174), or "GG0" (190), the latter describing those with prior diagnostic GG1 or 2, but negative baseline MRGB. Overall, progression to $\geq$ GG3 among the 664 with serial MRGB was 7% for GG0, 19% for GG1, and 34% for GG2. During follow-up, the absence of progression (negative predictive value) was correctly identified by MRI in nearly 95% of men with baseline GG0, 90% of men with GG1, and 70% of men with GG2. FT was performed in 99/393 eligible men (25%); among them, 5-year probability of radical prostatectomy/radiation therapy–free survival was 84% compared with 46% in the no-FT group ($P < .01$).

Submitted July 31, 2024; accepted April 1, 2025; published April 21, 2025.

Funding/Support: This work was supported in part by Grants R01CA158627, R01CA218547, and R01CA195505 from the National Cancer Institute; by the Jean Perkins Foundation; and programmatically by the UCLA Clinical Translational Science Institute and Jonsson Comprehensive Cancer Center.

Conflict of Interest Disclosures: Dr Marks and Dr Natarajan are co-founders of Avenda Health, and Dr Priester is a data scientist at Avenda Health. Dr Marks has equity in the company, but receives no compensation from it. The present work started 8 years prior to the inception of Avenda Health, which does not make any products or services for men on active surveillance. Dr Brisbane is an investigator for EDAP and Angiodynamics. No other disclosures were reported.

Ethics Statement: The study has been approved annually by the UCLA Institutional Review Board since inception. All subjects provided written informed consent with guarantees of confidentiality.

Author Contributions:

Conception and design: Marks, Natarajan, Delfin.
Data analysis and interpretation: Marks, Martin, Kwan, Nguyen, Brisbane, Gonzalez.
Data acquisition: Marks, Delfin, Gonzalez, Felker, Sisk, Priester, Brisbane, Delfin.
Critical revision of the manuscript for scientific and factual content: Marks, Martin, Kwan, Nguyen.
Drafting the manuscript: Marks, Martin, Kwan, Nguyen, Felker, Sisk, Brisbane.
Statistical analysis: Kwan, Nguyen, Marks, Martin, Gonzalez.
Supervision: Marks, Kwan, Martin.

Data Sharing: All data in the manuscript, and all source materials, are the property of the University of California and will be retained for at least 7 years. Dr Leonard Marks is the custodian of record and has full access. Data will be shared electronically upon appropriate request.

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THE JOURNAL OF UROLOGY®
https://doi.org/10.1097/JU.0000000000004559
Vol. 214, 177-187, August 2025
Printed in U.S.A.

Conclusions: Durability of AS may be linked to baseline MRGB. In men starting AS with MRGB and low-risk prostate cancer, subsequent MRI exhibits high negative predictive value, indicating routine follow-up biopsy is avoidable. In some men, FT may allow extension of AS and deferral of surgery or radiation.

Key Words: active surveillance, prostate cancer, MRI, MRI-guided biopsy, focal therapy

Active surveillance (AS)—the vigilant deferral of definitive treatment—was proposed in the 1990s as a management strategy for some men with prostate cancer (PCa).[1-3] AS was originally intended for men with "insignificant" cancers,[2] and selection criteria were stringent.[4] However, as long-term safety data have become available, selection criteria have become less restrictive.[5,6] The term "insignificant" has largely been replaced by "low and intermediate risk," and enrollment in AS programs has burgeoned over the past decade.[7] Since 1 in 8 American men will be diagnosed with PCa in their lifetime and since with contemporary biopsy, low/intermediate risk is now the PCa most commonly found,[8] AS is of increasing importance.

Thus, we evaluated 2 relatively new concepts—-MRI and focal therapy (FT)—which were routinely incorporated into this AS program. Prostate MRI to detect PCa and guide biopsy was not generally available until some 10 to 15 years ago, well after the AS concept had started to gain traction. Now, the value of MRI in prostate diagnostics has become clear,[9] and thus, the use of MRI in AS programs is increasing.[10-12] We also examined the role that FT, a tumor-focused ablation, which has evolved via MRI localization of PCa, might play in an AS program.[13]

Herein, MRI-guided biopsy (MRGB) was performed at baseline and throughout follow-up. We hoped to determine whether the routine use of baseline MRGB might allow predetermination of outcomes and allow follow-up biopsies to be reduced or eliminated.[14] In addition, FT was offered to select men, aiming to extend the deferral of surgery or radiation (radical prostatectomy/radiation therapy [RP/RT]). Preliminary results from the University of California, Los Angeles (UCLA), registry have been reported in part.[15-19]

MATERIALS AND METHODS

This study is an analysis of prospectively-acquired data from the 1081 men who signed consent and enrolled in the UCLA registry between 2010 and 2022. The registry has been approved annually by the Institutional Review Board at UCLA since its creation in 2009 (NCT00949819). Of the 1081 enrollees, 869 (80%) formed the analytic cohort after meeting all the following baseline criteria: (1) MRGB, (2) Gleason Grade Group (GG) $\leq$ 2 on that biopsy, and (3) enrollment for at least 1 year (Figure 1).

Baseline biopsy was defined as the first MRGB performed at UCLA, which was a first-ever biopsy in 210 men or a confirmatory biopsy in 659 men. We defined "GG0" as a prior diagnostic biopsy with GG1 or 2 but negative baseline MRGB.[20] Throughout the 12-year study period, patients were monitored with semiannual digital rectal examination and PSA testing. Follow-up biopsies were performed through MRGB every 12 to 24 months, as previously detailed.[18]

After 2016, when $\geq$ GG3 was found during follow-up or when GG2 was found at any point, a partial gland ablation ($\leq$50% of 1 lobe) by high-intensity focused ultrasound (HIFU) or cryotherapy (CRYO) was offered if considered technically feasible.[19,21] Otherwise, RP/RT was advised for men upgrading to GG3, GG4, or GG5. To facilitate coregistration of prostatectomy findings with preoperative MRI and biopsy, excised prostates were placed into custom molds and sectioned whole in a uniform orientation at 4.5-mm slice intervals.[22]

MRGB

Multiparametric MRI of the prostate was performed within 1 month of each MRGB. MRGB was the sole metric for determining tumor progression, as previously reported.[18] In brief, the Prostate Imaging Reporting and Data System (PIRADS) v2.1 scoring system was used for assigning an MRI grade (Likert and PIRADS v1.0 before 2016). MRI-visible regions of interest (ROIs) contoured by dedicated radiology staff and transmitted electronically into a fusion device for biopsy guidance. An experienced uroradiologist (>1000 prostate MRI readings) supervised all MRI interpretation.

All biopsies were performed transrectally in an outpatient clinic by coauthor LSM using an Artemis image fusion device (Eigen, Inc), a biopsy gun, 18 ga hollow needles, and local anesthesia. At baseline MRGB, 12 systematic samples were taken according to a spatial template.[18] At every biopsy session, 3 to 5 samples were taken from any PIRADS grades 3 to 5 lesions. In addition, at follow-up sessions, 2 to 4 samples were also taken from any prior positive sites, which had been tracked in the fusion device (Supplemental Figure 1, https://www.jurology.com); the absence of a lesion on MRI did not preclude follow-up biopsy.

Biopsy sampling methods, including tracking, are shown in Supplemental Figure 1 (https://www.jurology.com). Biopsy site tracking—the electronic recording of a prior intraprostatic site containing cancer for later repeat sampling—was facilitated by electronic recording of such sites in the fusion device.[17] Tracking was used routinely in follow-up biopsy sessions. Prophylaxis was a quinolone antibiotic until 2017, at which time, because of a 4% rate of postbiopsy sepsis, a single dose of ertapenem (500 mg) was substituted, after which no further sepsis was encountered. A fellowship-trained uropathologist performed all pathologic analyses.

Interventions

After 2016, FT was offered to participants who were diagnosed with GG2 at any time point or GG3 in follow-

up. The decision to undergo FT was the choice of each individual participant on physician consultation. In addition to personal preference, factors that influenced the decision included age, comorbidities, and technical considerations relating to performance of FT (eg, intraprostatic location and size of MRI lesion).

All FT treatments were performed at UCLA under general anesthesia in the outpatient surgery center. Details of UCLA focal CRYO procedure were recently reported.[23] Focal HIFU treatment has been performed at UCLA since Food and Drug Administration clearance in 2015.[24] Treatment focality (up to 50% of prostate) was guided by precedent biopsy sites tracked from the MRI/US fusion device.[17] Selection of FT modality was individualized, CRYO generally being preferred for prostates > 50 mL or anterior lesions and HIFU for small prostates and posterior lesions. All patients undergoing FT were followed further in protocols, which mandated MRGB at 6 and 18 months after treatment (NCT03620786, NCT03503643).

Outcomes

The primary end points were (1) progression to ≥ GG3 (progression-free survival [PFS]) and (2) any "event," defined as progression to ≥ GG3, intervention with RP/RT without progression, PCa metastases, or death from any cause (event-free survival [EFS]). Time to event was calculated as interval from baseline MRGB to any event. For PFS and EFS analyses, patients were censored on the date of last in-person visit. Death was also a criteria for being censored in PFS analysis, but included as an end point for EFS analysis. A secondary interval, time between eligibility of FT (first diagnosis of GG2 or GG3) and receipt of RP/RT, was also recorded. Frequency of RP/RT without upgrading beyond GG2 (an "anxiety event") was also analyzed.

Statistical Analysis

Categorical variables were reported as numbers with percentages and continuous variables as means (SD) or medians (IQR). Pearson χ^2 (or Fisher exact) and t tests (or Wilcoxon rank-sum or Kruskal-Wallis) were used for bivariate comparisons. Time-to-event analyses were conducted to calculate PFS and EFS probabilities with Kaplan-Meier curves (log-rank for baseline GG) and adjusted HR (aHR) with Cox proportional hazards regression. Models included the following variables chosen a priori: age, prostate volume, PSA density (PSAD), PIRADS, ROI diameter, and maximum cancer core length (MCCL). ROI diameter and MCCL were dichotomized by median values of 12 mm and 2.5 mm, respectively. Negative predictive value (NPV) of MRI was calculated for ≥ GG3 progression stratified by baseline GG and PSAD. The Cochran-Armitage test was used to determine trend significance (Figure 2). SAS 9.4 was used for all statistical analyses with an α set at .05.

RESULTS

Subjects in Cohort

Among the 1081 men enrolled, 869 met inclusion criteria and formed the study cohort. Approximately 70% identified themselves as White, 5% Black, 5% Asian, 7% Hispanic, and 13% did not disclose. The mean age was 65 years (SD 7). Baseline characteristics of the 869 men were stratified by GG: GG0 (n = 190, 22%), GG1 (n = 505, 58%), and GG2 (n = 174, 20%). GG at baseline was associated with PSA level, PSAD, PIRADS grade, ROI diameter, and MCCL (all $P < .01$; Table 1).

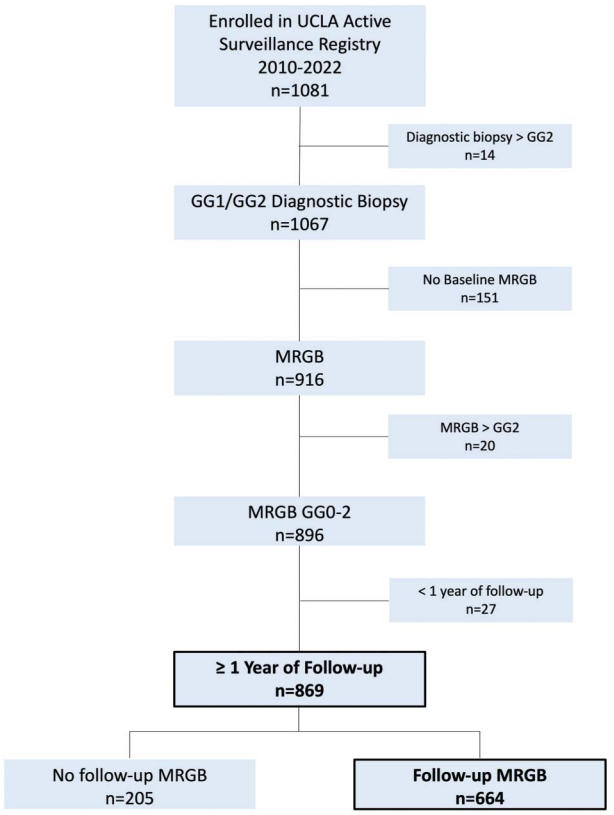

Figure 1. Flow diagram of participants. The study cohort was formed from the 1081 men who enrolled in the University of California, Los Angeles (UCLA), Active Surveillance registry between 2010 and 2022. Excluded were men whose diagnostic biopsy showed prostate cancer > Grade Group (GG) 2, who had no baseline MRI-guided biopsy (MRGB), whose baseline MRGB showed prostate cancer > GG2, and who had less than 1 year of follow-up. Thus, 869 men formed the study cohort, of whom 664 had at least 1 follow-up MRGB.

Employment of MRGB

A total of 2374 MRGBs were performed: 1 per subject at baseline (n = 869) and another 1505 in a subset of 664 men studied serially for > 1 year, during some 3500 person-years of follow-up. During follow-up, an average of 2.3 (SD 1.5) MRGBs/subjects were obtained (range 1-9). For the 869 patients in the event-free analysis, the median follow-up (baseline MRGB to last clinic visit) was 4.1 years (IQR, 2.1-6.8; range 1-12.5). For the subset of 664 in the progression-free analysis, the median follow-up (baseline to last MRGB) was 2.8 years (IQR, 1.3-4.2; range 1-12.3). The median interval between baseline and first follow-up MRGB was 1.0 year and between first and second follow-up MRGB was 1.5 years.

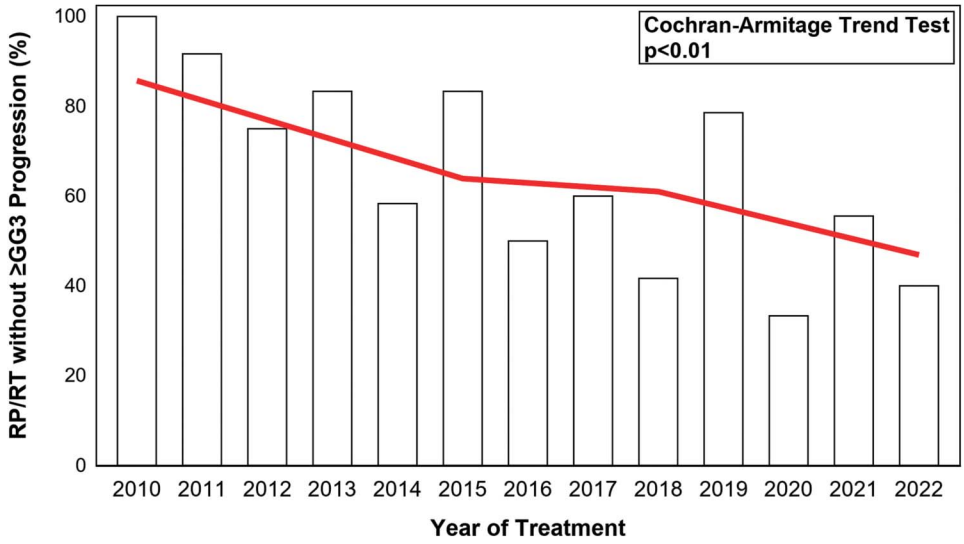

Figure 2. Chart showing percent of men undergoing surgery (RP) or radiation (RT) without biopsy-proven progression over time. Trend line shown in red. In the first quarter of the study, RP/RT without progression was elected in 86% (30/35) and in the last quarter 47% (15/32), a decline of 39%. Linear trend $P < .01$. Among the 64 patients with Grade Group (GG) 1 at baseline who underwent anxiety-driven RP/RT, 34 had upgraded to GG2 (53.1%) at RP/RT.

Follow-Up Biopsy Method and Detection of PCa

Over the entire follow-up period, 132/664 patients upgraded to GG3 or greater (Supplemental Figure 1, https://www.jurology.com). Of men with GG0 or GG1 at baseline (532), 190 progressed to GG2. Among the upgrades to GG3 or higher, 45% were detected by targeted biopsy only and 40% by systematic biopsy only. Tracking biopsy detected 51 (39%) of the 132 upgrades. Among these 51 men, 80% of the upgrades were found only by tracking

Table 1. *Patient Characteristics at Baseline MRI-Guided Biopsy (N = 869)*[a]

	Grade Group								
	0[b] (n = 190)		1 (n = 505)		2 (n = 174)		Total/overall (N = 869)		*P* value
Age, mean (SD), y	64.14	(7.73)	64.99	(7.68)	66.08	(7.54)	65.02	(7.68)	.054[c]
Race/ethnicity, No. (%)									.3[d]
White	144	(75.8)	339	(68.1)	117	(68.0)	600	(69.8)	
Asian	10	(5.3)	22	(4.4)	11	(6.4)	43	(5.0)	
Black	10	(5.3)	23	(4.6)	9	(5.2)	42	(4.9)	
Hispanic	8	(4.2)	40	(8.0)	13	(7.6)	61	(7.1)	
Other/unknown	18	(9.5)	74	(14.8)	22	(12.7)	114	(13.2)	
PSA, median (IQR), ng/mL	4.1	(2.3-6.1)	5.3	(3.7-7.3)	6.0	(4.4-8.4)	5.2	(3.3-7.3)	< .01[e]
Prostate volume, median (IQR), cc	50.6	(35.9-68.0)	47.0	(35.8-65.0)	48.0	(35.0-63.6)	48.0	(35.3-66.0)	.8[e]
PSA density, No. (%), ng/mL/cc									< .01[d]
≤0.15	168	(88.9)	376	(75.4)	109	(62.6)	653	(75.8)	
>0.15	21	(11.1)	123	(24.7)	65	(37.4)	209	(24.2)	
PIRADS v2 grade, No. (%)									< .01[d]
0	102	(53.7)	180	(35.6)	52	(29.9)	334	(38.4)	
3	52	(27.4)	139	(27.5)	46	(26.4)	237	(27.3)	
4	34	(17.9)	141	(27.9)	49	(28.2)	224	(25.8)	
5	2	(1.1)	45	(8.9)	27	(15.5)	74	(8.5)	
No. of ROIs per patient, No. (%)									
0	84	(47.2)	135	(28.3)	43	(25.2)	262	(31.7)	< .01[d]
1	53	(29.8)	232	(48.6)	91	(53.2)	376	(45.5)	
≥2	41	(23.0)	110	(23.1)	37	(21.6)	188	(22.8)	
Largest ROI diameter, median (IQR), mm	11	(9-14)	12	(9-15)	14	(9-18)	12	(9-15)	.010[e]
	(n = 94)		(n = 342)		(n = 128)		(n = 564)		
MCCL, median (IQR), mm	—		2	(1-4)	4	(3-6)	3	(1-5)	< .01[e]

Abbreviations: MCCL, maximum cancer core length; PIRADS, Prostate Imaging Reporting and Data System; ROI, region of interest.
[a] Compared to eligible men (n = 869), ineligible men (n = 215) had similar baseline PSA levels (P = not significant) and were more likely to be older (median age 67 vs 65; $P < .01$) and more often identified as non-White (48% vs 37%; $P < .01$).
[b] Grade Group 0 refers to patients with prior ultrasound-guided biopsy showing Grade Group 1 or Grade Group 2, but negative baseline MRI-guided biopsy, indicating very low risk.
[c] ANOVA *F*-test.
[d] χ^2 test.
[e] Kruskal-Wallis test.

biopsy. Thus, 40 upgrades would have gone undetected without tracking. Among the tracking biopsies showing GG3, 25 (49%) were within a targeted ROI, 20 (39%) were from systematic biopsy sites, and 6 (12%) had at least one positive tracked core in both.

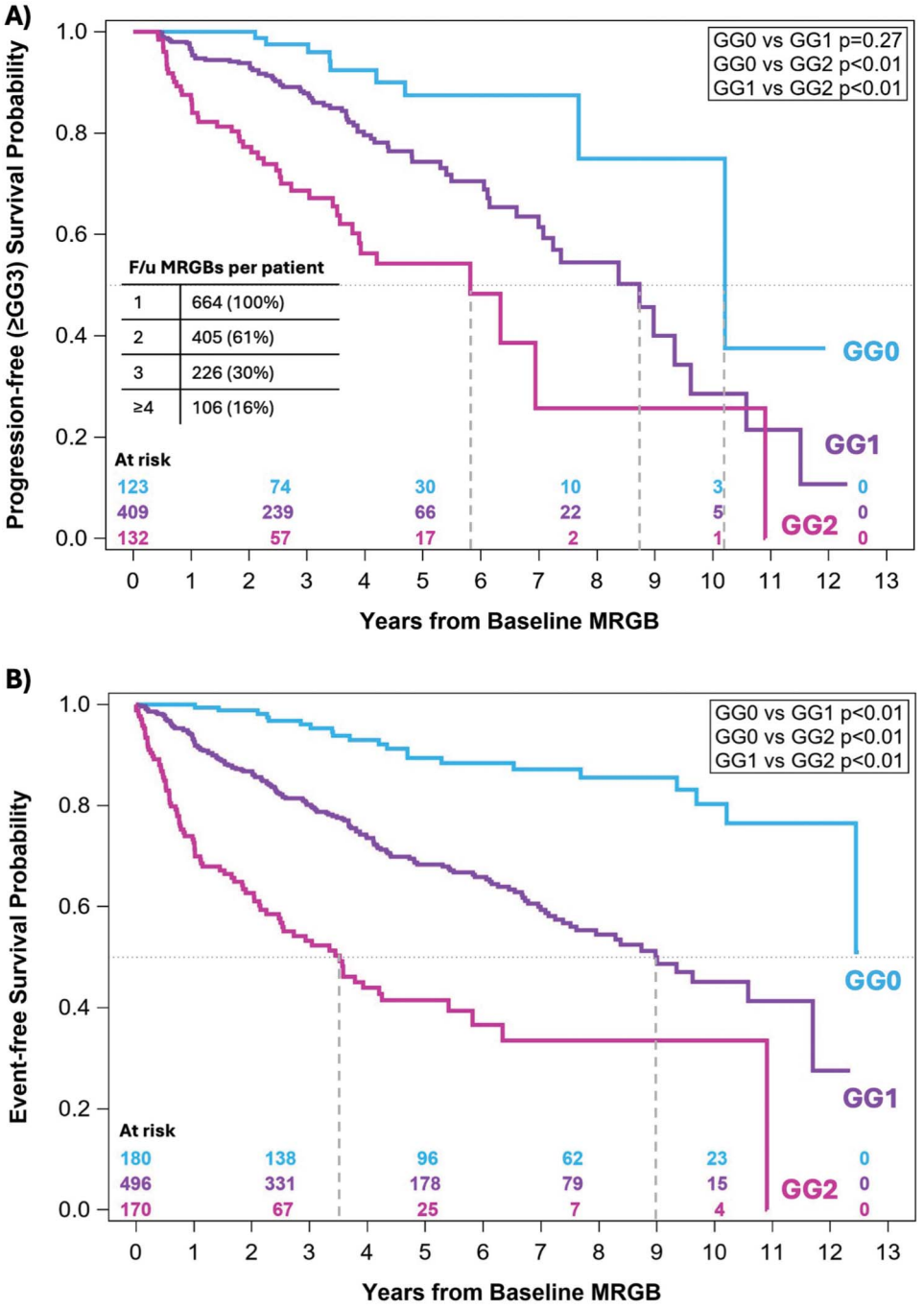

Figure 3. A, Kaplan-Meier curves showing progression-free survival (<Grade Group [GG] 3) of prostate cancer for the 664 men followed with serial MRI-guided biopsy (MRGB) for at least 1 year from baseline MRGB to ≥ GG3 progression before any treatment, definitive or focal. The median time to first follow-up (F/u) biopsy was 1.2 years for men with GG0, 1.0 years for men with GG1, and 0.7 years for men with GG2 ($P < .01$). Five years after baseline probability of remaining progression-free was 87% for men with GG0, 75% for men with GG1, and 54% for men with GG2. Median progression-free survival was 10.2 years for men with GG0, 8.7 (95% CI 7.1, 9.6) years for men with GG1, and 5.8 (95% CI 3.8, 10.9) years for men with GG2. Median (95% CI) time to ≥ GG3 progression was 3.0 (2.0, 5.0) years among men with GG0 at baseline compared with 2.9 (1.3, 4.2) years and 2.2 (1.0, 3.8) years for men with GG1 and GG2, respectively ($P < .01$). The 5-year probability of progression-free survival for a man with GG0 at baseline is 90% compared with 80% for GG1 and 42% for GG2. B, Kaplan-Meier curves showing event-free survival for all 889 men. An "event" is defined as ≥ GG3 progression, intervention with surgery or radiation (regardless of GG), or prostate cancer metastases or death (there were none). Median event-free survival was 9.0 (7.5) years for men with GG1 and 3.5 (95% CI 2.5, 5.4) years for men with GG2; men with GG0 never reached median survival. Event-free survival was significantly different between all pairs of GG comparisons.

Retention Rate of Men in AS

Figure 3, A shows Kaplan-Meier curves for PFS (<GG3) of men in AS stratified by baseline GG (n = 664). The median PFS time was 10.2 years for men with GG0, 8.7 (95% CI 7.1, 9.6) years for men with GG1, and 5.8 (95% CI 3.8, 10.9) years for men with GG2. PFS of GG0 and GG1 were not significantly different, but each was significantly longer than GG2 ($P < .01$). Overall, only 9 of 123 men with GG0 at baseline progressed to ≥ GG3 as compared with 78 of 409 men with GG1 and 45 of 132 men with GG2 (Table 2). Five years after baseline MRGB, PFS was 89% in men with GG0, 68% in men GG1, and 42% in men with GG2.

In Figure 3, B, EFS for all 869 men is shown. There were 266 events, including all occurrences that would terminate AS: 132 with ≥ GG3 progression, 115 electing RP/RT without progression, and 19 non-PCa deaths. The median (95% CI) EFS was 9.0 (7.5, NA) years for men with baseline GG1 and 3.5 (2.5, 5.4) years for men with GG2; men with GG0 never reached median survival. EFS was significantly different between all pairwise GG comparisons. No PCa metastases or PCa deaths were observed.

Baseline Predictors of GG3 Progression

In Figure 4, baseline metrics potentially associated with upgrading to ≥ GG3 are shown with aHR (95% CI) from a Cox regression. Men with GG2 at baseline were likely to progress to > GG3 (aHR 3.8, 95% CI, 1.7-8.7). Men with baseline GG1 progressed similarly as men with GG0 (P = NS). The baseline PIRADS scores were not significantly different from each other; MRI was thus classified for the time-to-event analyses as positive or negative. The only other predictor significantly associated with progression was MCCL (aHR 1.8, 95% CI, 1.2-2.7).

NPV of MRI During Follow-Up

In Figure 5, the NPV of MRI during follow-up biopsies is shown. For men with GG0 or GG1 with low PSAD at baseline, the lack of an MRI lesion was predictive of the absence of progression ≥ GG3 at the time of first follow-up biopsy (NPV 91%-100%; Figure 5, A). MRI performed similarly at second follow-up biopsy (Figure 5, B).

Table 2. *Overall Clinical Outcomes (N = 869)*

	GG0 (n = 190)	GG1 (n = 505)	GG2 (n = 174)
Failure events, No.			
≥GG3[a]	9	78	45
RP/RT[b]	5	74	36
Deceased	7	9	3
Total	21	161	84
Other exits (n = 72), No. (%)			
Followed elsewhere	11.1 (21)	3.2 (16)	2.3 (4)
Withdrew consent	1.1 (2)	0.8 (4)	1.2 (2)
Lost to follow-up	3.7 (7)	3.0 (15)	0.6 (1)

Abbreviations: GG, Grade Group; RP, radical prostatectomy; RT, radiation therapy.
[a] Six hundred sixty-four men with serial MRI-guided biopsy.
[b] Men undergoing RP/RT without progressing to ≥ GG3.

Intervention With FT

Of 370 men eligible for FT, 99 (27%) received either CRYO (n = 74) or HIFU (n = 25). PCa characteristics of eligible men who received FT were similar to those who did not (Figure 6). The 2 groups were compared in a Kaplan-Meier plot, the end point being time to RP/RT. The time to median RP/RT-free survival of men who did not undergo FT was 3.7 years. Men who received FT did not reach median survival ($P < .01$).

Of the 271 patients who did not receive FT, 128 eventually underwent RP/RT compared with 10 who did receive FT. The 5-year probability of RP/RT-free survival in the FT group was 84% compared with 46% in the no-FT group ($P < .01$). The advantage persisted throughout at least 10 years of follow-up (Figure 6). In a sensitivity analysis, interval to FT (ie, FT at the time of eligibility vs delayed intervention) did not significantly affect RP/RT-free survival.

After FT, biopsy was performed at 6 to 12 months in 87/99 men to confirm outcomes. Most men undergoing FT (59/87, 68%) had a favorable pathologic outcome on follow-up biopsy (Supplemental Figure 2, https://www.jurology.com).

RP/RT

Of the 869 men, RP/RT was employed in 181 (21%) over the 12 years of the study, 111 undergoing RP and 70 RT. Disease progression to ≥ GG3 was the cause for RP/RT in 66/181 (36%). Other men elected to undergo definitive treatment without progression to ≥ GG3 (64%, 115/181), an "anxiety event." Frequency of anxiety events declined over years of the study (Figure 2; $P < .01$). RP/RT was received by 8 of 123 for men with baseline GG0, 116 of 409 with GG1, and 57 of 142 with GG3. Of the 111 men who received RP, 81 had whole mount pathologic study of the excised organ.[22] GG on last MRGB was concordant with final GG in 48/81 (59%); in 13/81 (16%), MRGB underestimated; and in 20/81 (25%), MRGB overestimated final GG (Supplemental Figure 3, https://www.jurology.com). Only 3/81 instances were high-grade PCa (GG4, 5) missed by MRGB.

DISCUSSION

In this study, a large contemporary cohort of men undergoing AS was analyzed to determine if the routine use of MRGB and FT might improve outcomes. In comparison with earlier AS studies, incorporating MRI and FT seems to improve AS in

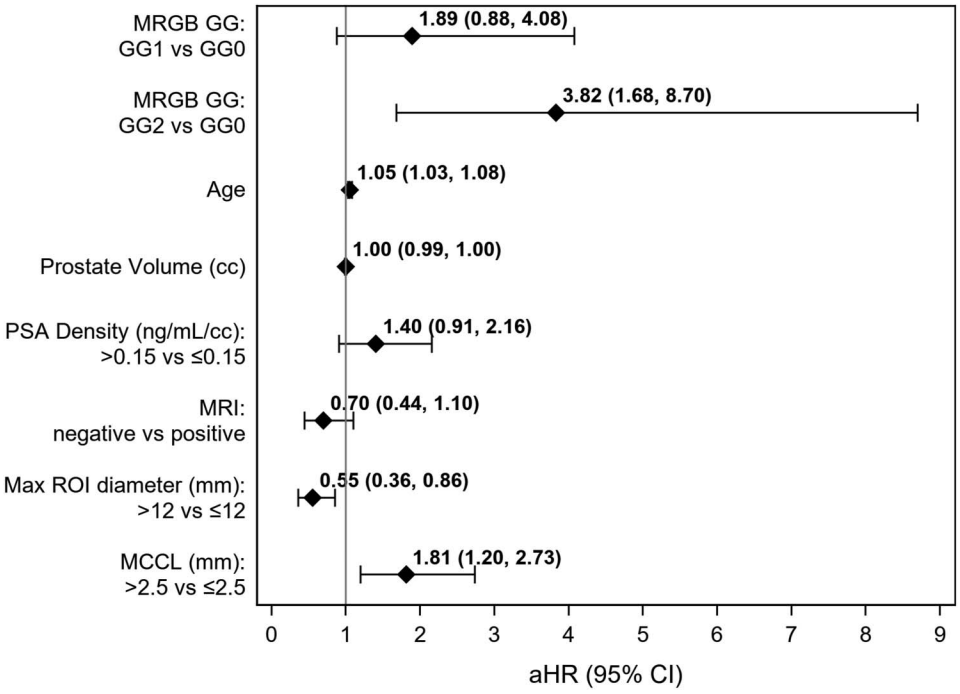

Figure 4. Forest plot showing association of baseline metrics with ≥ Grade Group (GG) 3 on last follow-up MRI-guided biopsy (MRGB). Only GG and maximum cancer core length (MCCL) were significantly associated with progression. HRs with CIs are included for each baseline predictor included in the Cox regression model. Prostate Imaging Reporting and Data System v2.0 scoring system was used for assigning an MRI grade (Likert and Prostate Imaging Reporting and Data System v1.0 before 2014). aHR indicates adjusted HR; ROI, regions of interest.

the following ways: (1) increased reliability of baseline biopsy as an outcome predictor, (2) increased years of AS eligibility, (3) reduction of anxiety-driven RP/RT, and (4) avoidance of some follow-up biopsies.

MRGB for men undergoing AS has been advocated by Stavrinedes et al,[10] Klotz et al,[12] Amin et al,[25] and others. The present work, wherein all 869 subjects underwent MRGB at baseline and through a median follow-up time of 4.1 (2.1-6.8) years (n = 659), confirms and expands earlier work. The present data, using MRGB as the AS baseline, show that long-term probability of success can be stratified from the outset and further, baseline MRGB can provide a guide for omission of some follow-up biopsies. In the current cohort, PFS was substantially longer than that reported in earlier series, where only ultrasound-guided biopsy was performed and FT was not offered.

These data support the use of baseline MRGB to select men for AS and advise them of probable outcomes. Men with GG0 at baseline MRGB seem not to require routine biopsies when follow-up MRI is negative, at least in the early years of follow-up. For men with GG1 and GG2 PCa at baseline, the decision to omit a follow-up biopsy when concurrent MRI is negative would be influenced by concurrent PSAD. In cases where follow-up biopsy is indicated, electronic tracking of prior biopsy sites was found to be a valuable adjunct.

Interval indicators of AS outcomes, for example, MRI changes over time, have been evaluated by Giganti et al[26] in the PRECISE study. However, in the PRECISE study, biopsy—the gold standard of comparison—was only performed at baseline but not routinely during follow-up. Chesnut et al[27] and Bhanji et al[28] conclude that MRI changes should not routinely replace biopsy. The recently updated PRECISE recommendations reported no consensus on how to determine tumor size and proposed additional research is needed.[29] The role of interval changes in MRI and PSAD in our cohort, where MRGBs are performed routinely throughout follow-up, is a subject of a future analysis.

The term "anxiety event" has been used to describe the opting-out of AS in favor of RP/RT, despite no evidence of PCa progression. In the early years of the study, such events were common, but as the study matured, anxiety events decreased significantly. This change may have been related to the increasing acceptance of AS generally,[7] the overall safety data documented herein, the accuracy of MRGB, or to the management of lower urinary tract symptoms among patients in AS.[30]

FT prolonged the duration of AS for the 27% of eligible men who underwent HIFU or CRYO.

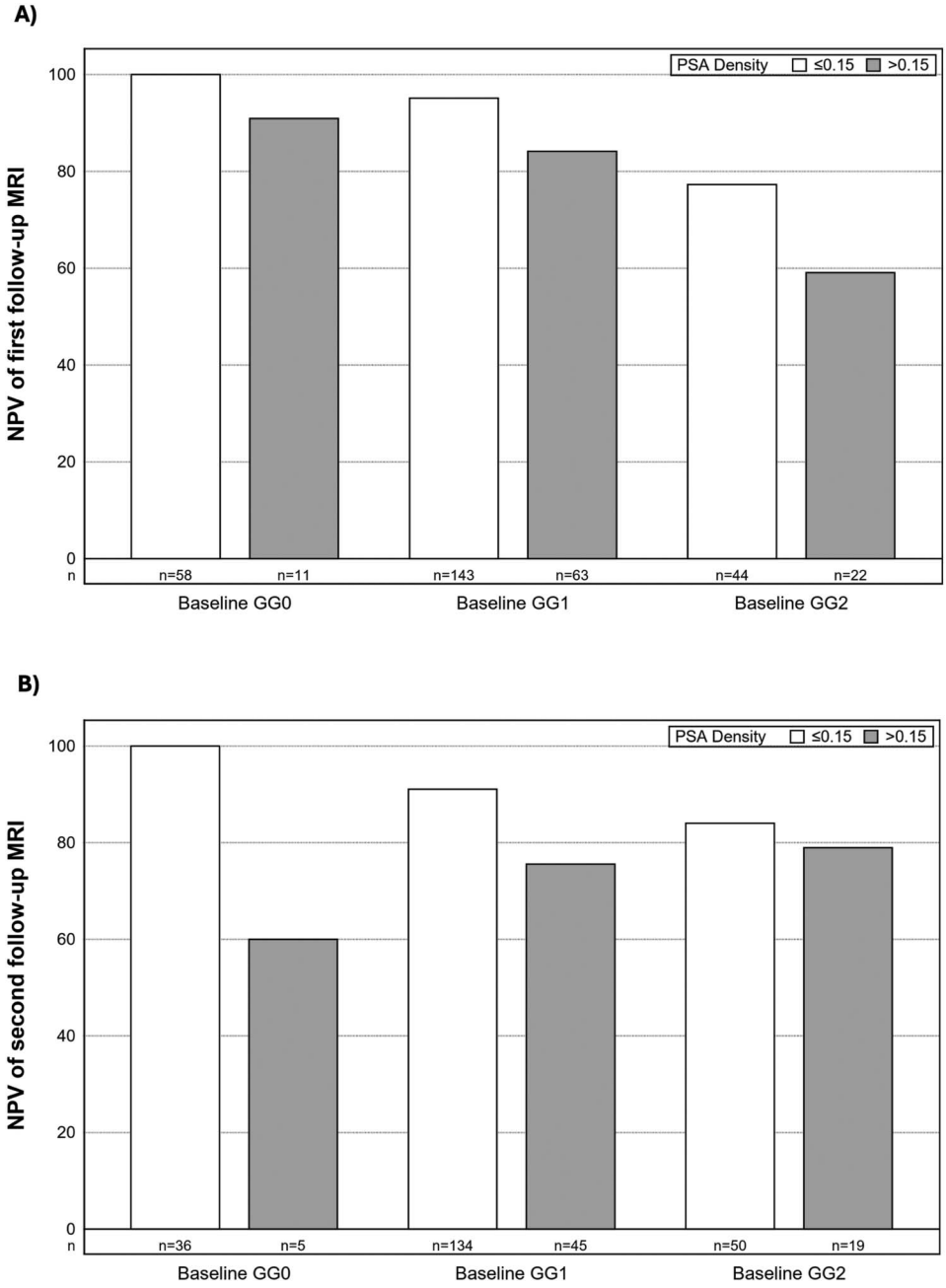

Figure 5. A, Chart showing negative predictive value (NPV) of MRI at time of the first follow-up biopsy. NPV = accuracy of negative MRI (no lesions) in predicting absence of ≥ Grade Group (GG) 3 on MRI-guided biopsy. A negative MRI was found in 341/664 men at the first follow-up biopsy. Regardless of PSA density, NPV was high (84%-100%) among men with GG0 or GG1 at baseline, but lower for men with GG2 (59%-77%). B, NPV of MRI at time of second follow-up biopsy was similar to that found at the first follow-up biopsy.

Although selection of patients for FT was not standardized, the men who received FT had similar cancer characteristics to their counterparts who did not. Moreover, in follow-up biopsies, most men undergoing FT had their PCa eliminated, diminished, or downgraded by the treatment. Although the numbers are small and follow-up relatively brief, the near-term advantage of FT in avoiding surgery or radiation is clear (Figure 6). FT as part of AS was suggested by Fasulo et al.[13] The use of FT to extend AS warrants consideration in prospective evaluation. In the future, for some men, when upgrading is found, FT may be considered a crossroad in AS, not a mandatory path to RP/RT.

Limitations of this study include single center enrollment, possible selection bias at cohort formation, lack of randomization, nonstandardized selection for FT, and relatively brief follow-up. As all patients were recruited at a single academic center with in-depth experience with MRI and FT, the findings

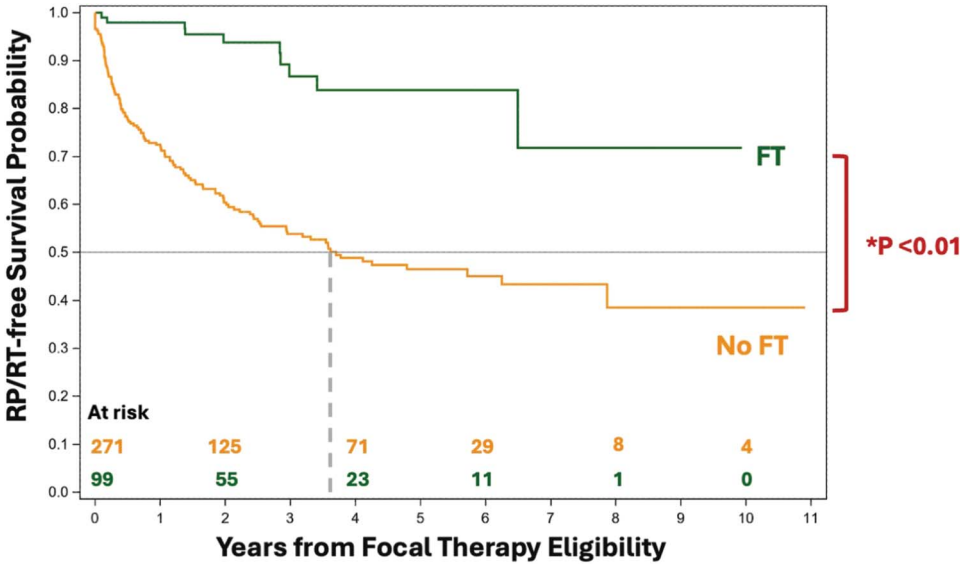

Figure 6. Kaplan-Meier curves showing years in active surveillance from focal therapy (FT) eligibility (first diagnosis of Grade Group 2 or 3) to radical prostatectomy/radiation therapy (RP/RT; surgery or radiation). Among those eligible (n = 370), 99 (27%) received FT; in the chart, they are compared against the 271 men who did not. Men who underwent FT were older, had smaller prostates, and had longer maximum cancer core lengths than men who did not. All other cancer characteristics (PSA, PSA density, Prostate Imaging Reporting and Data System, maximum region of interest diameter, and Grade Group) did not differ between groups. Post-FT biopsies showed that in most patients, the treatment resulted in disappearance, downgrading, or significant diminution of clinically significant prostate cancer (Supplemental Figure 2, https://www.jurology.com).

herein may be limited in generalizability. Despite these limitations, the findings reported herein are consistent with a large body of work attesting to the value of the new technologies in other applications.

CONCLUSIONS

AS has evolved over the past 30 years, at least partly because of 2 new technologies. The precision of AS can be increased and its inclusiveness expanded by routine use of MRGB and, when appropriate, FT.

ACKNOWLEDGMENTS

The UCLA active surveillance project was inspired by the pioneering work of H. Ballentine Carter and colleagues at Johns Hopkins.

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