Active Surveillance of Prostate Cancer: Current State of Practice and Utility of Multiparametric Magnetic Resonance Imaging

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Active surveillance (AS) is an alternative to immediate intervention in patients with very low- and low-risk prostate cancer. Ongoing reports from multiple AS programs have consistently demonstrated a very low rate of metastasis and prostate cancer-specific mortality in appropriately selected patients. Accordingly, AS has been adopted by major clinical organizations as a safe and effective management strategy. Clinical focus has now shifted to identifying the optimal approach to selecting and monitoring patients. Multiparametric magnetic resonance imaging (mpMRI) has emerged as one potentially helpful tool in the AS setting. The utility of mpMRI has been well demonstrated in the setting of screening and diagnosis, but its role in AS remains unclear. We summarize the published experience with AS and review pertinent, contemporary data on the use of mpMRI in the setting of AS.

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KEY WORDS

Active surveillance • Prostate cancer • Multiparametric magnetic resonance imaging

Active surveillance (AS) is a management strategy in which men with favorable-risk prostate cancer avoid or delay immediate intervention in favor of close monitoring. The concept was first proposed in the 1990s as a means to reduce the overtreatment of clinically insignificant cancers detected by widespread prostate-specific antigen (PSA)-based screening.[1,2] Although debate over the utility of PSA-based screening continues,[3-5] several large studies have demonstrated that early detection and effective treatment of higher-risk cancers are associated with reduced prostate cancer mortality.[6-8] As opposed to discarding screening altogether, AS presents an option to avoid overtreatment of screen-detected cancers unlikely to cause harm. Still, AS remains a work in progress, particularly as new tools such as multiparametric magnetic resonance imaging (mpMRI) are actively incorporated into previously reported protocols. We describe the current practice of AS and review initial data exploring mpMRI in the AS setting.

Current State of Active Surveillance

AS was vastly underutilized in the United States until the turn of the current decade. Data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry have revealed an increase in utilization of AS for low-risk cancers in the United States from 6% in 2000 to over 40% by 2013.[9-11] The utilization of AS is even higher worldwide. In Sweden, 91% of very low-risk patients and 74% of low-risk patients utilized AS in 2014.[12] Today, the National Comprehensive Cancer Network (NCCN), American Urological Association, and European Association of Urology all consider AS a primary management option in appropriately selected patients.[13-15] These organizations, and others, seek to expand the population considered eligible for AS.[16] As such, it is important to maintain a contemporary understanding of the protocols utilized and outcomes obtained with AS today.

Traditionally, monitoring on AS has consisted of frequent digital rectal examination, serum PSA testing, and transrectal ultrasound (TRUS)-guided biopsy.[1,2,8] Program-specific monitoring protocols are summarized in Table 2.[17-25] The majority of protocols require a confirmatory biopsy within 1 year of enrollment. Subsequent monitoring includes frequent examination and PSA testing, and abnormal findings uniformly trigger repeat "for-cause" biopsies. There is considerable variation, however, with respect to the frequency of scheduled biopsies. Johns Hopkins University has traditionally performed yearly biopsy in most men, but biopsy intervals have been increased with the advent of risk prediction tools.[28] The frequency of scheduled biopsies in other programs ranges from yearly to every 5 years. Accordingly, the threshold for conversion to treatment varies by program. For men with very low-risk disease, treatment is often recommended when the extent of cancer on biopsy exceeds entry criteria ($>$ 2 positive cores or $>$ 50% involvement of any positive core) and almost invariably performed when GS $\geq$ 3+4=7 cancer is detected. Although some programs previously recommended intervention based on adverse PSA kinetics, treatment is rarely initiated today in the absence of histologic changes. Instead, tools such as PSA kinetics are used to prompt repeat biopsy.

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Criteria for Selection, Monitoring, and Intervention

Previously reported AS enrollment criteria are outlined in Table 1.[17-25] Selection criteria are most commonly derived from NCCN definitions of very low-risk (clinical stage T1c, PSA density $<$ 0.15 ng/mL/cc, Gleason score [GS] $\leq$ 6, $\leq$ 2 positive biopsy cores, and $<$ 50% cancer involvement of any positive biopsy core) and low-risk (clinical stage $\leq$ T2a, PSA $<$ 10 ng/mL, and GS $\leq$ 6) cancer, which are modified Epstein and D'Amico criteria, respectively.[13,26,27] The lack of a universal protocol, however, allows for substantial variation in AS populations. The Johns Hopkins University (Baltimore, MD) program has traditionally emphasized the use of AS in very low-risk cancers, while recommending AS more selectively in low-risk men. As a result, 71% of the Johns Hopkins cohort harbors very low-risk disease, and 29% have low-risk disease.[17] At the other extreme, some programs have allowed for inclusion of patients with GS $\geq$ 3+4=7 tumors who are otherwise candidates for curative intervention.[18-20,22] Still, other programs have conditionally permitted AS of higher-grade tumors in the context of factors such as patient age and comorbidity status.[21,23,24]

Patient Outcomes

Table 3 lists cohort characteristics and outcomes from the two prospective AS cohorts reporting long-term (10- and 15-y) outcomes.[17,29]

TABLE 1

Eligibility Criteria for Active Surveillance Programs

Study (Program)	Clinical Stage	PSA, ng/mL	Gleason Score	Other Parameters
Tosoian JJ et al (Johns Hopkins University, Baltimore, MD)[17]	T1c	—	≤ 6	PSA density < 0.15 ng/mL/cc, ≤ 2 positive biopsy cores, ≤ 50% cancer involvement of any core
	≤ T2a	≤ 10	≤ 6	
Klotz L et al (Sunnybrook Health Sciences Centre, Toronto, Canada)[18]	—	≤ 10	≤ 6	
	—	10-20	≤ 3+4=7	Life expectancy < 10 y
Godtman RA et al (Göteborg Randomized, Population-Based Prostate Cancer Screening Trial, Göteborg, Sweden)[19]	—	—	—	Men diagnosed in the Göteborg screening trial who did not undergo treatment within 6 mo of diagnosis were classified to active surveillance
Bokhorst LP et al (PRIAS, multinational)[20]	≤ T2	≤ 10	≤ 6	PSA density < 0.20 ng/mL/cc, ≤ 2 positive biopsy cores
	—	—	3+4=7	≤ 2 positive biopsy cores, ≤ 10% cancer involvement of any core, age ≥ 70 y
Welty CJ et al (UCSF, San Francisco, CA)[21]	≤ T2	≤ 10	≤ 6	≤ 33% positive biopsy cores, ≤ 50% cancer involvement of any core
Selvadurai ED et al (Royal Marsden Hospital, London, UK)[22]	≤ T2	< 15	≤ 6	≤ 50% positive biopsy cores, age 50-80 y
	≤ T2	< 15	≤ 3+4=7	≤ 50% positive biopsy cores, age > 65 y
Thompson JE et al (St. Vincent's Prostate Cancer Centre, Sydney, Australia)[23]	≤ T2a	< 10	≤ 6	< 20% positive biopsy cores, < 30% cancer involvement of any core
Thomsen FB et al (University of Copenhagen, Copenhagen, Denmark)[24]	≤ T2a	≤ 10	≤ 6	≤ 3 positive biopsy cores, < 50% cancer involvement of any core
Soloway MS et al (University of Miami, Miami, FL)[25]	≤ T2	≤ 10	≤ 6	≤ 2 positive biopsy cores, ≤ 20% cancer involvement of any core

PRIAS, Prostate Cancer Research International: Active Surveillance; PSA, prostate-specific antigen; UCSF, University of California, San Francisco.

As noted, the Johns Hopkins cohort included only individuals with "favorable-risk" cancer, defined as NCCN very low- or low-risk cancer.[17] As such, no patients were enrolled with GS ≥ 3+4=7 disease. Subsequent monitoring was intensive, including annual prostate biopsy in most cases. The rates of treatment, metastasis, and prostate cancer-specific mortality (PCSM) at 10 years were 50%, 0.6%, and 0.1%, respectively. A similar pattern was observed at 15 years, with rates of 57%, 0.6%, and 0.1%, respectively.

By comparison, the Sunnybrook (Sunnybrook Health Sciences

TABLE 2

Monitoring Protocols for Active Surveillance Programs

Study (Program)	Surveillance Intervals			
	Digital Rectal Examination, *mo*	PSA Testing, *mo*	Confirmatory Biopsy, *y from diagnostic biopsy*	Repeat Biopsy, *y from previous biopsy*
Tosoian JJ et al (Johns Hopkins University, Baltimore, MD)[17]	6	6	1	1-2
Klotz L et al (Sunnybrook Health Sciences Centre, Toronto, Canada)[18]	—	3-6	1	3-4
Godtman RA et al (Göteborg Randomized, Population-Based Prostate Cancer Screening Trial, Göteborg, Sweden)[19]	3-6	3-6	Performed if < 2 mm of cancer present at diagnostic biopsy	2-3
Bokhorst LP et al (PRIAS, multinational)[20]	—	3-6	1	3 for the first 10 y then every 5 y thereafter
Welty CJ et al (UCSF, San Francisco, CA)[21]	6	3	1	1-2
Selvadurai ED et al (Royal Marsden Hospital, London, UK)[22]	3-6	3-6	1.5-2	2
Thompson JE et al (St. Vincent's Prostate Cancer Centre, Sydney, Australia)[23]	6-12	3-6	1	1-2 for the first postconfirmatory biopsy then every 3-5 y thereafter
Thomsen FB et al (University of Copenhagen, Copenhagen, Denmark)[24]	3	3	1	Variable
Soloway MS et al (University of Miami, Miami, FL)[25]	3-6	3-6	< 1	1

PRIAS, Prostate Cancer Research International: Active Surveillance; PSA, prostate-specific antigen; UCSF, University of California, San Francisco.

Centre, Toronto, Ontario, Canada) cohort included 213 men with intermediate-risk cancers and 732 with favorable-risk disease.[29] The favorable-risk cohort was found to have lower treatment rates (36% and 42% at 10 and 15 years, respectively) compared with Johns Hopkins, reflecting the program's less intensive monitoring schedule. The cumulative incidence of adverse oncologic outcomes was relatively higher at 10 and 15 years, with metastasis rates of 4% and 5%, respectively, and PCSM rates of 2% and 3%, respectively.

The 213 intermediate-risk patients from Sunnybrook included 128 men (60%) with GS ≥ 3+4=7 disease at enrollment.[29] When compared with the program's favorable-risk men, intermediate-risk men demonstrated higher rates of adverse oncologic outcomes at 10 years (metastasis 9%, PCSM 3%), with a notable increase at 15 years (metastasis 18%, PCSM 11%). These results, logically, suggest that intermediate-risk men under less intensive monitoring are at higher risk of adverse long-term outcomes. The findings from Sunnybrook are comparable with the observational cohort in the Prostate Testing for Cancer and Treatment (ProtecT) trial that included men with GS ≥ 3+4=7 and in which monitoring was not intensive.[30]

TABLE 3

Cohort Characteristics and Long-term Outcomes From Two Large, Prospective Active Surveillance Programs

Study (Program)	Cancer Risk	Cohort Size	Median Follow-up, *y*	Median Age, *y*	GS ≥ 3+4=7 at Enrollment *(%)*	Treatment		Metastatic Disease		Death From Prostate Cancer	
						10-y, %	15-y, %	10-y, %	15-y, %	10-y, %	15-y, %
Tosoian JJ et al (Johns Hopkins University, Baltimore, MD)[17]	Favorable risk	1298	5.0	66	0 (0)	50	57	0.6	0.6	0.1	0.1
Klotz L et al (Sunnybrook Health Sciences Centre, Toronto, Canada)[18]	Favorable risk	732	6.5	67	0 (0)	36	42	4	5	2	3
	Intermediate risk	213	6.7	72	128 (60)	39	52	9	18	3	11

GS, Gleason score.

Utility of mpMRI in Active Surveillance

Advancements in mpMRI allow for high-quality visualization of the prostate for cancer detection, especially in the anterior gland.[31,32] Several studies have demonstrated improved diagnostic accuracy using MRI/TRUS fusion biopsy (targeted biopsy [TB] with systematic biopsy [SB]) as compared with standard SB alone.[31,33,34] Still, the role of mpMRI in AS remains unclear.

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To this end, a systematic review in 2015 aimed to summarize the use of mpMRI in AS.[35] Among AS candidates, a positive finding on imaging increased the likelihood of detecting clinically significant disease at repeat biopsy. Notably, studies varied considerably in how positive imaging and significant cancer were defined. In light of limited data, the authors were ultimately unable to comment on the use of mpMRI in place of prostate biopsy. As such, several groups have continued to assess the utility of mpMRI in patient selection and monitoring for AS.

Patient Selection With mpMRI

A prevailing concern in AS is the possibility that an individual's true volume or grade of cancer is not adequately sampled on biopsy, resulting in disease misclassification.[36,37] To this end, a number of studies have examined the ability of mpMRI to identify suspicious lesions and facilitate sampling prior to AS.

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One study from the University College London Hospital (London, United Kingdom) assessed the utility of mpMRI in detecting higher-risk cancers in 194 men initially diagnosed with prostate cancer on TRUS-guided biopsy (median 12 cores, range 8-20).[38] At a median of 4 months (range 1.4-16) after diagnostic TRUS biopsy, patients underwent prostate mpMRI and subsequent transperineal template-guided prostate mapping (TPM) biopsy. TPM biopsies included at least 20 SB cores and a median of 48 cores (range 20-118), and some men (n = 23) underwent additional TB by cognitive registration.

The authors considered four different definitions of low-risk cancer: (1) GS 6 disease (regardless of core length); (2) maximum cancer core length (MCCL) < 50% on biopsy (regardless of GS); (3) GS 6

disease and MCCL < 50%; and (4) GS 6 disease, MCCL < 50%, PSA < 10 ng/mL, and < 50% biopsy cores positive. For each definition of low-risk cancer, reclassification was defined as a transition from low-risk cancer on TRUS-guided biopsy to higher-risk cancer on TPM biopsy. Notably, mpMRI was considered negative for Prostate Imaging Reporting and Data System (PI-RADS) scores of 1-2 and positive for scores of 4-5.[39] The negative predictive values (NPVs) and positive predictive values (PPVs) of these scores for reclassification were determined; scores of 3 were considered equivocal and excluded.

There were 137 men with low-risk cancer on TRUS-guided biopsy using definition 1 (GS 6 disease). Among 81 men who had a positive mpMRI, reclassification was detected on TPM biopsy in 48 (59%). On the other hand, a negative mpMRI result was associated with reclassification in 4 of 16 men, conferring a NPV of 75%. Forty of the 137 subjects (29%) had a score of 3 and were therefore not considered in these calculations. Definition 2 (MCCL < 50%) was initially met by 62 men. The PPV of a positive mpMRI was 67% (reclassification in 24 of 36 men), and the NPV was 100% (reclassification in 0 of 6 men). The positive and negative predictive values of mpMRI based on all four definitions of low-risk cancer are listed in Table 4.[38,40,41] Importantly, mpMRI scores of 1-2 appeared to accurately predict the absence of reclassification on TPM biopsy, with negative predictive values ranging from 75% to 100%.

Previous studies demonstrated that lower apparent diffusion coefficients (ADCs) obtained from diffusion-weighted MRI (DW-MRI) are associated with more aggressive prostate cancers.[42,43] Henderson and colleagues,[44] from Royal Marsden Hospital (London, United Kingdom), sought to determine if patient selection methods could be refined by using DW-MRI results obtained prior to enrollment in AS. The authors identified 86 men who met the Royal Marsden Hospital AS criteria (clinical stage ≤ T2a, PSA < 15 ng/mL, GS ≤ 3+4=7, and ≤ 50% positive biopsy cores) and underwent DW-MRI prior to enrollment. Patients were followed prospectively with serial SB every 24 months, regardless of pre-enrollment imaging findings. At a median follow-up of 9.5 years, the authors assessed pre-enrollment DW-MRI in patients who did and did not progress (defined by biopsy findings violating enrollment criteria and/or undergoing radical treatment).

Overall, the median tumor ADC at enrollment was 972 mm^2/s. On multivariable analysis, including initial PSA, clinical stage, and percentage of positive biopsy cores, a lower ADC was associated with a shorter time to adverse histology (hazard ratio [HR] 1.23, 95% confidence interval [CI], 1.06-1.44; $P = .002$) and a shorter time to radical treatment (HR 1.33, 95% CI, 1.14-1.54; $P = .001$). Notably, the median time to radical treatment was 9.3 years for patients with ADCs above the median compared with only 2.4 years for those with ADCs below the median. Although ADC was significantly associated with adverse histology, this report did not include more clinically useful measures such as NPVs or PPVs.

Jeong and colleagues[40] explored the utility of DW-MRI in excluding men who would otherwise qualify for AS. The authors retrospectively reviewed 117 patients who underwent radical prostatectomy (RP) between 2008 and 2013. All men met AS criteria as defined by the 2013 European Association of Urology guidelines (clinical stage ≤ T2a, PSA ≤ 10 ng/mL, GS ≤ 6, ≤ 2 positive biopsy cores, and ≤ 50% cancer involvement of any core). All patients underwent DW-MRI prior to RP, and ADC values were graded on a 5-point scale for suspicion of clinically significant disease. An unfavorable image was defined as an ADC suspicion score of 4-5. The outcome of interest was unfavorable pathology at RP (non–organ-confined disease or GS ≥ 4+3=7).

Of 117 patients, 12 (10%) demonstrated unfavorable pathology, of whom 9 (75%) also demonstrated unfavorable imaging. Using only ADC suspicion scores of 4-5 to predict the presence of unfavorable pathology, the PPV, NPV, sensitivity, and specificity were 28%, 97%, 75%, and 78%, respectively. The resultant area under the receiver operating characteristic curve (AUROC) was 80%. When biopsy core data were added to this model, the AUROC increased to 86%. The authors also showed that 71 of 117 patients (61%) demonstrated GS ≥ 3+4=7 at RP; among them, only 23 (32%) had unfavorable imaging. Although the performance metrics for GS ≥ 3+4=7 were not provided, it is apparent that scoring based on ADC is more predictive for the more extreme outcome.

Finally, Porpiglia and colleagues[41] reviewed 126 patients who were treated with robot-assisted RP between 2012 and 2015. All patients were eligible for AS based on the Prostate Cancer Research International: Active Surveillance (PRIAS) criteria (clinical stage ≤ T2, PSA ≤ 10 ng/mL, GS ≤ 6, PSA density < 0.20 ng/mL/cc, and ≤ 2 positive biopsy cores) and underwent mpMRI prior to RP. Images were graded using the PI-RADS scoring system, and a score of 4-5 was considered positive. The outcome of interest was pathologically insignificant prostate cancer, defined as organ-confined GS 6 disease with an index tumor volume ≤ 1.3 cm^3 and total tumor volume ≤ 2.5 cm^3.

TABLE 4

Performance Characteristics of Multiparametric Magnetic Resonance Imaging for Higher-risk Cancer in Men Diagnosed With Low-risk Cancer on Standard Biopsy

Study	n	Definition of Low-risk Cancer (Eligibility Criteria)	Definition of Positive Image Finding	Definition of Negative Image Finding	Definition of Pathologic Upgrading	PPV, %	NPV, %
Abd-Alazeez M et al[38]	137	GS ≤ 6	PI-RADS 4-5	PI-RADS 1-2	GS ≥ 3+4=7	59	75
	62	MCCL < 50%			MCCL ≥ 50%	67	100
	52	GS ≤ 6 and MCCL < 50%			GS ≥ 3+4=7 or MCCL ≥ 50%	75	83
	28	GS ≤ 6, MCCL < 50%, PSA < 10 ng/mL, and < 50% positive biopsy cores			GS ≥ 3+4=7 or MCCL ≥ 50%	60	100
Jeong CW et al[40]	117	Clinical stage ≤ T2a, PSA ≤ 10 ng/mL, GS ≤ 6, ≤ 2 positive biopsy cores, and ≤ 50% cancer involvement of any core	ADC suspicion score 4-5	ADC suspicion score ≤ 3	GS ≥ 3+4=7 or non–organ-confined disease	28	97
Porpiglia F et al[41]	126	Clinical stage ≤ T2, PSA ≤ 10 ng/mL, GS ≤ 6, PSA density < 0.20 ng/mL/cc, and ≤ 2 positive biopsy cores	PI-RADS 4-5	PI-RADS ≤ 3	GS ≥ 3+4=7, index tumor volume > 1.3 cm^3, or total tumor volume > 2.5 cm^3	61	74

ADC, apparent diffusion coefficient; GS, Gleason score; MCCL, maximum core cancer length; NPV, negative predictive value; PI-RADS, Prostate Imaging Reporting and Data System; PPV, positive predictive value; PSA, prostate-specific antigen.

Preoperative mpMRI results were positive in 69 of 126 men (55%); 57 patients had significant prostate cancer at RP, including 37 (65%) with GS ≥ 7 disease. mpMRI demonstrated a PPV, NPV, sensitivity, and specificity of 61%, 74%, 74%, and 61%, respectively, for pathologically significant cancer. When mpMRI results were added to PRIAS criteria, the AUROC for predicting pathologically insignificant disease improved by 5% (72% vs 77%; $P < .01$). They also considered the more restrictive Epstein criteria (NCCN very low-risk disease). Among the 63 men who met Epstein criteria at enrollment, the addition of mpMRI led to a 7% improvement in AUROC for predicting insignificant cancer (71% vs 78%; $P < .01$).

The primary objective of imaging patients already on AS is to detect progression of disease.

Patient Monitoring With mpMRI

Several programs have begun to utilize mpMRI for patient monitoring using various approaches. For example, all men enrolled in AS at Royal Marsden Hospital now undergo baseline and surveillance mpMRI.[22] At Sunnybrook, conversely, mpMRI is performed more selectively in men with an indication for closer scrutiny such as adverse PSA kinetics.[18] The primary objective of imaging patients already on AS is to detect progression of disease. Table 5 summarizes a list of studies comparing the detection rate of TB versus SB on MRI/TRUS fusion biopsy.[45-50]

Frye and associates[45] retrospectively identified 166 patients presenting from 2007 to 2015 with a visible lesion on initial mpMRI. All patients demonstrated prostate cancer on diagnostic MRI/TRUS fusion biopsy and met the National Institutes of Health criteria for low-risk (clinical stage ≤ T2a, PSA ≤ 20 ng/mL,

TABLE 5

Detection Rate of Targeted Biopsy Versus Systematic Biopsy on MRI/TRUS Fusion Biopsy

Study	n	Criteria for Population	Biopsy Setting (Median Number of Previous Biopsies)	Criteria for Targeted Biopsy	Number of Cores on Systematic Biopsy	Pathologic Upgrading (% of n)	Biopsy Detection Rate (% of Pathologic Upgrading)		
							Targeted Biopsy Alone	Systematic Biopsy Alone	Targeted and Systematic Biopsy
Frye TP et al[45]	166	NIH LR or IR	Confirmatory (1)	Increase in mpMRI suspicion score, lesion diameter, or number of lesions	12	49 (29.5)	22 (45)	15 (31)	12 (24)
Nassiri N et al[46]	259	Clinical stage T1c and GS 6 or 3+4=7	NR	UCLA and/or PI-RADS ≥ 3	12	33 (13)[a]	21 (64)	12 (36)	0 (0)
Ma TM et al[47]	73	No prior biopsies	Diagnostic (0)	PI-RADS ≥ 3	12	55 (75)[b]	12 (22)	14 (25)	29 (53)
	54	NCCN VLR or LR	Confirmatory (1)			12 (22)	3 (25)	6 (50)	3 (25)
	103	NCCN VLR or LR	Surveillance (3)			25 (24)	4 (16)	18 (72)	3 (12)
Tran GN et al[48]	207	NCCN LR or IR	Surveillance (2)	mpMRI score ≥ 3	14	83 (40)	49 (59)	30 (36)	4 (5)
Recabal P et al[49]	206[c]	GS 6	Surveillance (2)	mpMRI score ≥ 3	14	72 (35)	NR	25 (35)	NR
Felker ER et al[50]	49	GS 6	NR	Increase in suspicion score, doubling of volume, or decrease in ADC of 150 mm^2/s in the index lesion	12	19 (39)	9 (47)	7 (37)	3 (16)

[a]Pathologic upgrading was defined as GS ≥ 4+3=7.
[b]Diagnostic biopsy detected GS ≥ 3+4=7 cancer in 55 patients; the remaining 18 were diagnosed with GS 6 cancer.
[c]Only patients with a region of interest on mpMRI (n = 135) underwent MRI/TRUS fusion biopsy; all others received 14-core systematic biopsy.
ADC, apparent diffusion coefficient; GS, Gleason score; IR, intermediate risk; LR, low risk; NCCN, National Comprehensive Cancer Network; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; NIH, National Institutes of Health; NR, not reported; TRUS, transrectal ultrasound; UCLA, University of California – Los Angeles; VLR, very low risk.

and GS ≤ 6) or intermediate-risk (clinical stage ≤ T2a, PSA ≤ 20 ng/mL, GS ≤ 3+4=7, and ≤ 33% positive biopsy cores) disease. Patients underwent confirmatory fusion biopsy within 12 to 24 months of enrollment and mpMRI annually. A positive mpMRI result was defined as an increase in suspicion score, lesion diameter, or number of lesions. Progression of disease was considered an increase in pathologic grade group.[51]

During mean follow-up of 25.5 months (range 3-96), 107 men (64%) had a positive mpMRI and 49 men (29.5%) had disease progression. The PPV, NPV, sensitivity, and specificity of mpMRI for progression were 35%, 81%, 78%, and 41%, respectively. On fusion biopsy, TB alone identified 22 of 49 (45%) progression events, whereas 12-core SB alone identified 15 of 49 (31%; $P = .03$). The remaining 12 progressions (24%) were detected on both TB and SB. Furthermore,

the number of patients needed to biopsy to detect a progression event was 8.0 for TB and 3.1 for SB ($P < .001$).

Nassiri and associates[46] initiated a prospective AS registry in men who underwent TB and SB at diagnostic and confirmatory biopsy. The authors identified 259 men with clinical stage T1c disease and GS 6 (n = 196) or GS 3+4=7 (n = 63) cancer confirmed prior to enrollment. In addition to TB and SB, surveillance biopsies included resampling of previously positive biopsy sites that were tracked using the Artemis™ device (Epica Medical Innovations, San Clemente, CA). The outcome of interest was GS ≥ 4+3=7 or secondary Gleason pattern 5 disease (eg, GS 3+5=8).

During follow-up, the majority of men underwent one or two surveillance biopsies (mean 1.48 biopsies in the GS 6 cohort and 1.42 in the GS 3+4=7 cohort). Upgrading was detected in 17 men (9%) with GS 6 and 16 men (25%) with GS 3+4= 7 ($P < .01$). Interestingly, of the 33 upgrades, 21 (64%) were detected in targeted mpMRI regions of interest, 11 (33%) in tracked sites of previous positive biopsies, and 1 (3%) on systematic template biopsy. In a multivariable model, predictors of upgrading were GS 3+4=7 disease at baseline (HR 4.58, 95% CI, 2.14-9.80), mpMRI grade 5 lesions (HR 5.06, 95% CI, 1.65-15.52), and PSA density ≥ 0.15 (HR 2.38, 95% CI, 1.01-5.60).

Ma and coworkers[47] retrospectively identified men who underwent simultaneous 12-core SB and TB across three clinical settings. The study included 103 men actively enrolled in AS (median 5 years on AS; median 3 previous biopsies), 54 men with favorable-risk disease undergoing confirmatory biopsy, and a comparison group of 73 biopsy-naive men undergoing diagnostic biopsy (median PSA 7.3 ng/mL). The authors compared detection of GS ≥ 7 cancer using MRI/TRUS fusion biopsy (TB + 12-core SB) versus 12-core SB alone. Lesions were targeted on MRI/TRUS fusion biopsy if the PI-RADS score was ≥ 3, and 127 AS patients with negative mpMRI underwent systematic biopsy.

In the AS cohort, the addition of TB to SB did not significantly improve detection of upgrading (SB alone 20.4% vs SB + TB 24.3%; $P = .13$). Similarly, TB did not significantly increase detection of upgrading in men undergoing confirmatory biopsy (16.7% SB vs 22.2% SB + TB; $P = .25$). On the other hand, TB detected upgrading in an additional 16.4% of the diagnostic biopsy cohort (SB 58.9% vs SB + TB 75.3%; $P = .002$). Finally, upgrading was detected on SB in only 13 men (10%) who had a negative mpMRI result, demonstrating an NPV of 90% in the AS cohort.

Tran and colleagues[48] performed a similar study in 207 AS patients with NCCN low- and intermediate-risk disease who underwent fusion biopsy. The median number of previous biopsies for the cohort was 2 (interquartile range 1-3). The fusion biopsy included targeting of mpMRI-defined regions of interest and systematic sampling using an extended-sextant template. The median time between mpMRI and biopsy was 2.2 months. Of the 207 patients, 83 (40%) had upgrading. Of these, 49 (59%) were detected on TB alone, 30 (36%) were detected on SB alone, and four (5%) were detected on both TB and SB.

A subsequent analysis by Recabal and coworkers[49] sought to determine if TB alone could replace SB and if biopsy could be deferred altogether in cases of negative mpMRI results. The authors identified 206 men on AS with GS 6 disease who underwent mpMRI between 2014 and 2015. Notably, the median number of previous surveillance biopsies was 2. There were 71 men who did not have a region of interest detected on imaging (mpMRI score 1-2) and therefore underwent 14-core SB. Higher-grade cancer was detected in eight (11%) of these men. Men with at least one region of interest (mpMRI score 3-5) underwent TB in addition to the 14-core SB. Among 135 such patients, higher-grade cancer was detected on TB+SB in 64 men (47%). Use of TB alone would have missed higher-grade cancers in 17 of the 64 men (27%). Combining these findings, the authors concluded that an approach in which biopsy was deferred for negative mpMRI results and limited to TB in cases of positive mpMRI results would have failed to detect higher-grade cancer in 25 of the 206 subjects (12%).

Nomograms Including mpMRI

Felker and colleagues[50] retrospectively reviewed 49 men with GS 6 prostate cancer enrolled in AS. All subjects underwent two or more mpMRIs separated by at least 6 months, followed by fusion biopsy (TB + 12-core SB) using the Artemis™ device after each image. Progression on mpMRI was defined as an increase in index lesion suspicion score (5-point scale), a doubling of index lesion volume, or a decrease in index lesion ADC of 150 mm^2/s based on results from logistic regression. Pathologic upgrading was defined as the detection of GS ≥ 3+4=7.

During follow-up, 19 men (39%) had upgrading detected on TB+SB. Of these, upgrading was detected by TB alone in 9 (47%), SB alone in 7 (37%), and both TB and SB in 3 (16%); 10 of the 49 patients (20%) had mpMRI progression, of whom 7 (70%) had upgrading to GS ≥ 3+4=7. Progression on mpMRI was associated with a PPV of 69% for pathologic

upgrading, whereas the absence of progression on mpMRI yielded an NPV of 70%. The associated sensitivity and specificity were 37% and 90%, respectively. The AUROC of mpMRI for discriminating pathologic upgrading was 63%. Conversely, a model using MCCL ≥ 3 mm or PSA density ≥ 0.15 ng/mL/cc to predict upgrading yielded an AUROC of 87%. When mpMRI was added to this model, the AUROC improved to 91% (P = .044). Although significant, the authors deemed this an incremental improvement to the clinicopathologic variables in predicting upgrading to GS ≥ 3+4=7 on biopsy.

Lai and associates[52] developed a nomogram integrating clinical and imaging data to predict the probability of upgrading to GS ≥ 3+4=7 in the AS population. The authors identified 76 patients who were diagnosed with NCCN low-risk prostate cancer on prereferral TRUS biopsy between 2014 and 2016. All patients then underwent their first mpMRI followed by MRI/TRUS fusion biopsy (TB + extended-sextant SB). The mean duration between prereferral TRUS biopsy and confirmatory MRI/TRUS fusion biopsy was 625 days (range 38-2048).

In total, 20 men (26%) had upgrading on fusion biopsy. Upgrading was associated with a higher mean PI-RADS score (4.24 vs 3.49; P = .002), higher lesion density (6.1% vs 3.6%; P = .01), higher PSA (7.85 ng/mL vs 5.65 ng/mL; P = .047), higher PSA density (0.258 ng/mL/cc vs 0.136 ng/mL/cc; P = .008), and increased duration between diagnostic and confirmatory biopsies (846 d vs 540 d; P = .026). Cutoffs for the nomogram were set at the most optimal points based on logistic regression, which included PI-RADS 5, lesion density ≥ 5%, PSA density ≥ 0.18 ng/mL/cc, and duration between biopsies ≥ 446 days. This model demonstrated a PPV, NPV, sensitivity, and specificity of 57%, 93%, 80%, and 81%, respectively, in predicting upgrading on confirmatory MRI/TRUS fusion biopsy. The resultant AUROC for this nomogram, designed to predict upgrading to GS ≥ 3+4=7, was 84%.

Conclusions

Longitudinal data from multiple institutions have demonstrated the safety and effectiveness of AS in patients with very low- and low-risk prostate cancer. Published data indicate that men with favorable-risk cancer have a 36% to 50% likelihood of undergoing treatment in the first 10 years after enrollment in AS, and the 10-year cumulative incidence of metastatic disease and prostate cancer death range from 0.6% to 4% and 0.1% to 2%, respectively. AS protocols vary both within and between institutions, and the long-term risks of treatment, metastasis, and cancer death appear to differ based on the specific approach taken. This is not to imply that a more or less intensive approach to AS is superior, but rather that these estimates can be used to counsel individual patients and potentially identify an approach to AS most consistent with each patient's preferences. As currently available data have not identified a particularly favorable subset of men with GS ≥ 3+4=7 disease, intermediate- and higher-risk patients should be fully informed of the potential risks associated with AS. An important goal moving forward is to better identify which men with intermediate-risk disease can potentially be monitored safely on AS.

Meanwhile, there are substantial limitations to our understanding of mpMRI in the AS setting, as the majority of data have been obtained from retrospective experiences in which mpMRI was not uniformly applied. To better address this moving forward, the European School of Oncology Task Force developed a standardized protocol for reporting outcomes using mpMRI in AS, entitled the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) checklist.[53] Nonetheless, current data suggest that mpMRI may be most useful in ruling out the presence of occult higher-grade cancers, with an NPV ranging from 74% to 100%, depending on upgrading criteria. Although targeted biopsies appear to improve the detection of occult higher-grade lesions, most studies indicate that a sizable proportion of high-grade cancers are detected by systematic biopsy alone. Therefore, systematic biopsy should continue to be performed at the time of targeted biopsy in most settings. With greater understanding of the strengths and applications of mpMRI, there is hope that the need for repeat biopsies during AS can be reduced. ■

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References

1. Carter HB, Walsh PC, Landis P, Epstein JI. Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. *J Urol.* 2002;167:1231-1234.
2. Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. *J Urol.* 2002;167:1664-1669.

3. Schröder FH, Hugosson J, Roobol MJ, et al; ERSPC Investigators. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. 2009;360:1320-1328.
4. Andriole GL, Crawford ED, Grubb RL, 3rd, et al; PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*. 2009;360:1310-1319.
5. Shoag JE, Mittal S, Hu JC. Reevaluating PSA testing rates in the PLCO trial. *N Engl J Med*. 2016;374:1795-1796.
6. Schröder FH, Hugosson J, Roobol MJ, et al; ERSPC Investigators. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet*. 2014;384:2027-2035.
7. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med*. 2014;370:932-942.
8. Tosoian JJ, Carter HB, Lepor A, Loeb S. Active surveillance for prostate cancer: current evidence and contemporary state of practice. *Nat Rev Urol*. 2016;13:205-215.
9. Cooperberg MR, Broering JM, Kantoff PW, Carroll PR. Contemporary trends in low risk prostate cancer: risk assessment and treatment. *J Urol*. 2007;178:S14-S19.
10. Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990-2013. *JAMA*. 2015;314:80-82.
11. Murphy DG, Loeb S. Prostate cancer: growth of AS in the USA signals reduction in overtreatment. *Nat Rev Urol*. 2015;12:604-605.
12. Loeb S, Folkvaljon Y, Curnyn C, et al. Uptake of active surveillance for very-low-risk prostate cancer in Sweden [published online October 20, 2016]. *JAMA Oncol*. doi: 10.1001/jamaoncol.2016.3600
13. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer, Version 3.2016. National Comprehensive Cancer Center website. https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed May 14, 2017.
14. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. *J Urol*. 2013;190:419-426.
15. Mottet N, Bellmunt J, Briers E, et al. EAU - ESTRO - SIOG Guidelines on prostate cancer. European Association of Urology website. https://uroweb.org/wp-content/uploads/EAU-Guidelines-Prostate-Cancer-2016.pdf. Accessed May 15, 2017.
16. Chen RC, Rumble RB, Loblaw DA, et al. Active surveillance for the management of localized prostate cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice guideline endorsement. *J Clin Oncol*. 2016;34:2182-2190.
17. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. *J Clin Oncol*. 2015;33:3379-3385.
18. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*. 2015;33:272-277.
19. Godtman RA, Holmberg E, Khatami A, et al. Long-term results of active surveillance in the Goteborg Randomized, Population-based Prostate Cancer Screening Trial. *Eur Urol*. 2016;70:760-766.
20. Bokhorst LP, Valdagni R, Rannikko A, et al. A decade of active surveillance in the PRIAS study: an update and evaluation of the criteria used to recommend a switch to active treatment. *Eur Urol*. 2016;70:954-960.
21. Welty CJ, Cowan JE, Nguyen H, et al. Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. *J Urol*. 2015;193:807-811.
22. Selvadurai ED, Singhera M, Thomas K, et al. Medium-term outcomes of active surveillance for localised prostate cancer. *Eur Urol*. 2013;64:981-987.
23. Thompson JE, Hayen A, Landau A, et al. Medium-term oncological outcomes for extended vs saturation biopsy and transrectal vs transperineal biopsy in active surveillance for prostate cancer. *BJU Int*. 2015;115:884-891.
24. Thomsen FB, Berg KD, Roder MA, et al. Active surveillance for localized prostate cancer: an analysis of patient contacts and utilization of healthcare resources. *Scand J Urol*. 2015;49:43-50.
25. Soloway MS, Soloway CT, Eldefrawy A, et al. Careful selection and close monitoring of low-risk prostate cancer patients on active surveillance minimizes the need for treatment. *Eur Urol*. 2010;58:831-835.
26. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA*. 1994;271:368-374.
27. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280:969-974.
28. Mamawala MM, Rao K, Landis P, et al. Risk prediction tool for grade re-classification in men with favourable-risk prostate cancer on active surveillance. *BJU Int*. 2017;120:25-31.
29. Musunuru HB, Yamamoto T, Klotz L, et al. Active surveillance for intermediate risk prostate cancer: survival outcomes in the Sunnybrook Experience. *J Urol*. 2016;196:1651-1658.
30. Hamdy FC, Donovan JL, Lane JA, et al; ProtecT Study Group. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375:1415-1424.
31. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA*. 2015;313:390-397.
32. Ouzzane A, Puech P, Lemaitre L, et al. Combined multiparametric MRI and targeted biopsies improve anterior prostate cancer detection, staging, and grading. *Urology*. 2011;78:1356-1362.
33. Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. *Eur Urol*. 2015;68:438-450.
34. Valerio M, Donaldson I, Emberton M, et al. Detection of clinically significant prostate cancer using magnetic

MAIN POINTS

- Active surveillance (AS) is a management strategy in which men with favorable-risk prostate cancer avoid or delay immediate intervention in favor of close monitoring. The concept was first proposed as a means to reduce the overtreatment of clinically insignificant cancers detected by widespread prostate-specific antigen (PSA)-based screening.
- Traditionally, monitoring on AS has consisted of frequent digital rectal examination, serum PSA testing, and transrectal ultrasound-guided biopsy. New tools such as multiparametric magnetic resonance imaging (mpMRI) are being actively incorporated into previously reported protocols.
- Current data have not yet identified a favorable subset of men with intermediate-risk disease. Therefore, these patients should be counseled appropriately about the potentially increased risks of AS.
- There are substantial limitations to our understanding of mpMRI in the AS setting, as the majority of data have been obtained from retrospective experiences in which mpMRI was not uniformly applied. To better address this moving forward, the European School of Oncology Task Force developed a standardized protocol for reporting outcomes using mpMRI in AS, entitled the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) checklist.
- Current data demonstrate that mpMRI alone does not preclude the need for prostate biopsy. Furthermore, systematic biopsy should continue to be performed at the time of targeted biopsy in most settings.

resonance imaging-ultrasound fusion targeted biopsy: a systematic review. *Eur Urol.* 2015;68:8-19.
35. Schoots IG, Petrides N, Giganti F, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. *Eur Urol.* 2015;67:627-636.
36. Alam R, Carter HB, Landis P, et al. Conditional probability of reclassification in an active surveillance program for prostate cancer. *J Urol.* 2015;193:1950-1955.
37. Steinberg DM, Sauvageot J, Piantadosi S, Epstein JI. Correlation of prostate needle biopsy and radical prostatectomy Gleason grade in academic and community settings. *Am J Surg Pathol.* 1997;21:566-576.
38. Abd-Alazeez M, Ahmed HU, Arya M, et al. Can multiparametric magnetic resonance imaging predict upgrading of transrectal ultrasound biopsy results at more definitive histology? *Urol Oncol.* 2014;32:741-747.
39. Barentsz JO, Richenberg J, Clements R, et al; European Society of Urogenital Radiology. ESUR prostate MR guidelines 2012. *Eur Radiol.* 2012;22:746-757.
40. Jeong CW, Park YH, Hwang SI, et al. The role of 3-tesla diffusion-weighted magnetic resonance imaging in selecting prostate cancer patients for active surveillance. *Prostate Int.* 2014;2:169-175.
41. Porpiglia F, Cantiello F, De Luca S, et al. Multiparametric magnetic resonance imaging and active surveillance: how to better select insignificant prostate cancer? *Int J Urol.* 2016;23:752-757.
42. Vargas HA, Akin O, Franiel T, et al. Diffusion-weighted endorectal MR imaging at 3 T for prostate cancer: tumor detection and assessment of aggressiveness. *Radiology*. 2011;259:775-784.
43. Turkbey B, Shah VP, Pang Y, et al. Is apparent diffusion coefficient associated with clinical risk scores for prostate cancers that are visible on 3-T MR images? *Radiology*. 2011;258:488-495.
44. Henderson DR, de Souza NM, Thomas K, et al. Nine-year follow-up for a study of diffusion-weighted magnetic resonance imaging in a prospective prostate cancer active surveillance cohort. *Eur Urol.* 2016;69:1028-1033.
45. Frye TP, George AK, Kilchevsky A, et al. Magnetic resonance imaging-transrectal ultrasound guided fusion biopsy to detect progression in patients with existing lesions on active surveillance for low and intermediate risk prostate cancer. *J Urol.* 2017;197:640-646.
46. Nassiri N, Margolis DJ, Natarajan S, et al. Targeted biopsy to detect Gleason score upgrading during active surveillance for men with low versus intermediate risk prostate cancer. *J Urol.* 2017;197(3 Pt 1):632-639.
47. Ma TM, Tosoian JJ, Schaeffer EM, et al. The role of multiparametric magnetic resonance imaging/ultrasound fusion biopsy in active surveillance. *Eur Urol.* 2017;71:174-180.
48. Tran GN, Leapman MS, Nguyen HG, et al. Magnetic resonance imaging—ultrasound fusion biopsy during prostate cancer active surveillance. *Eur Urol.* 2017;72:275-281.
49. Recabal P, Assel M, Sjoberg DD, et al. The efficacy of multiparametric magnetic resonance imaging and magnetic resonance imaging targeted biopsy in risk classification for patients with prostate cancer on active surveillance. *J Urol.* 2016;196:374-381.
50. Felker ER, Wu J, Natarajan S, et al. Serial magnetic resonance imaging in active surveillance of prostate cancer: incremental value. *J Urol.* 2016;195:1421-1427.
51. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. *Eur Urol.* 2016;69:428-435.
52. Lai WS, Gordetsky JB, Thomas JV, et al. Factors predicting prostate cancer upgrading on magnetic resonance imaging—targeted biopsy in an active surveillance population. *Cancer*. 2017;123:1941-1948.
53. Moore CM, Giganti F, Albertsen P, et al. Reporting magnetic resonance imaging in men on active surveillance for prostate cancer: the PRECISE recommendations—a report of a European School of Oncology Task Force. *Eur Urol.* 2016;71:648-655.