available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Matthew R. Cooperberg and Daniel W. Lin on pp. 687–688 of this issue

Active Surveillance of Grade Group 1 Prostate Cancer: Long-term Outcomes from a Large Prospective Cohort

Jeffrey J. Tosoian [a,b,c,†], *Mufaddal Mamawala* [a,b,*,†], *Jonathan I. Epstein* [a,b,d], *Patricia Landis* [a,b], *Katarzyna J. Macura* [a,b,e], *Demetrios N. Simopoulos* [a,b], *H. Ballentine Carter* [a,b], *Michael A. Gorin* [a,b,e]

[a] *The James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA;* [b] *Department of Urology, Johns Hopkins University School of Medicine, Baltimore, MD, USA;* [c] *Department of Urology, University of Michigan, Ann Arbor, MI, USA;* [d] *Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA;* [e] *The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD, USA*

Article info

Article history:
Accepted December 17, 2019

Associate Editor:
Matthew Cooperberg

Keywords:
Active surveillance
Low-risk prostate cancer
Magnetic resonance imaging
Prostate-specific antigen
Prostate biopsy
Very-low-risk prostate cancer

Abstract

Background: Active surveillance (AS) is the preferred management option for most men with grade group (GG) 1 prostate cancer (PCa). Questions persist regarding long-term outcomes and the optimal approach to AS.
Objective: To determine survival and metastatic outcomes in AS patients. Secondary objectives were to measure the cumulative incidence and association of patient-level factors on biopsy grade reclassification.
Design, setting, and participants: A prospective, active, open-enrollment cohort study was conducted from 1995 through July 2018 at a tertiary-care academic institution. Patients with very-low-risk or low-risk PCa were enrolled.
Intervention: AS with semiannual prostate-specific antigen (PSA) and digital rectal examination, serial prostate biopsy, and multiparametric magnetic resonance imaging (mpMRI).
Outcome measurements and statistical analysis: The 10- and 15-yr cumulative incidences of primary and secondary outcomes were determined.
Results and limitations: Overall, 1818 men were monitored on AS for a median of 5.0 yr (interquartile range 2.0–9.0). There were 88 non-PCa deaths, four PCa deaths, and one additional case of metastasis. The cumulative incidence of PCa-specific mortality or metastasis was 0.1% (95% confidence interval, 0.04–0.6%) at both 10 and 15 yr. The 5-, 10-, and 15-yr cumulative incidences of biopsy grade reclassification were 21%, 30%, and 32%, respectively. On multivariable analysis, biopsy grade reclassification was associated with older age, African-American race, PSA density, and increased cancer volume on biopsy, and men who underwent mpMRI prior to enrollment were less likely to undergo grade reclassification. Our selection and monitoring are more stringent than many other contemporary AS programs.
Conclusions: In a large, single-institution, prospective AS cohort, the risk of cancer death or metastasis was <1% over long-term follow-up. Consistent with clinical guidelines, these data support the use of AS for the management of most men diagnosed with GG1 PCa.

[†] These authors contributed equally to this report.

[*] Corresponding author. James Buchanan Brady Urological Institute, The Johns Hopkins University School of Medicine, 600 N. Wolfe Street/Park 205, Baltimore, MD 21287, USA. Tel. +1-410-614-3724; Fax: +1-410-955-0833.
E-mail address: mmamawa1@jhmi.edu (M. Mamawala).

https://doi.org/10.1016/j.eururo.2019.12.017

Patient summary: This study investigated long-term outcomes in patients with grade group 1 prostate cancer managed with active surveillance (AS). Ten years after enrolling in AS, the risk of metastasis or death from prostate cancer was <1%, while 48% of men switched to treatment. Patients who underwent multiparametric magnetic resonance imaging (mpMRI)/ultrasound-fusion targeted biopsy prior to enrollment were less likely to experience biopsy grade reclassification during follow-up, suggesting a role for mpMRI as part of a comprehensive risk assessment to confirm AS eligibility. These findings support the safety of AS in most men with grade group 1 prostate cancer, but specific outcomes may differ in programs with less intensive monitoring.

1. Introduction

Active surveillance (AS) is the preferred management strategy for most men with grade group (GG) 1 prostate cancer (PCa) [1]. One concern surrounding AS has been the loss of a window of curability during the course of monitoring [2]. Over the past 2 decades, however, longitudinal data from several institutions have demonstrated the overall safety of AS, with 5- and 10-yr cancer-specific survival rates consistently exceeding 94% [3–7]. These findings have led to widespread acceptance of AS and its endorsement in clinical guidelines [8].

Nonetheless, many important questions persist regarding AS. First, data are limited regarding the durability of AS beyond 10 yr [2,3]. Second, the impact of patient-level demographic factors on outcomes remains unclear [1]. Moreover, serial prostate biopsies central to surveillance protocols [3,4] are associated with significant risks [9], and the role of multiparametric magnetic resonance imaging (mpMRI) as an alternative to biopsy is unclear [2]. We herein report outcomes from a large, prospective AS program with long-term follow-up, including our initial experience using mpMRI.

2. Patients and methods

2.1. Prospectively defined AS program

The Johns Hopkins AS program was initiated in 1995 as an option for men with very-low-risk (VLR) PCa [10], defined as clinical stage T1c, prostate-specific antigen (PSA) density (PSAD) <0.15 ng/ml, GG1, two or fewer positive biopsy cores, and ≤50% cancer involvement of any biopsy core [11]. Over time, an increasing number of patients were enrolled with low-risk (LR; clinical stage ≤T2a, PSA <10 ng/ml, and GG1) cancer (Supplementary Fig. 1).

All men were recommended to undergo follow-up biopsy within 12 mo of diagnosis (ie, confirmatory biopsy). In addition to semiannual PSA and digital rectal examination, our initial monitoring protocol included annual prostate biopsy. Prostate mpMRI without endorectal coil became available in January 2013, and mpMRI/ultrasound-fusion targeted biopsy became available in April 2014 [12]. Regions of interest were scored according to Prostate Imaging Reporting and Data System (PI-RADS) version 1 beginning in 2014 and PI-RADS version 2 beginning in 2016 [13]. PI-RADS ≥3 lesions were considered positive and targeted on mpMRI/ultrasound-fusion biopsies [14].

Definitive treatment (ie, radical prostatectomy [RP] or radiation therapy [RT]) was recommended to all patients with biopsy grade reclassification (GG ≥2). Treatment or continued AS was offered to men who underwent volume reclassification (defined by more than two positive cores and/or >50% involvement of a core). As 170 men began AS without confirmatory biopsy, we separately assessed outcomes in the 1648 men who were enrolled after confirmatory biopsy (Supplementary material; Supplementary Fig. 2). This study was approved by the Institutional Review Board.

2.2. Statistical analysis

Primary study outcomes were overall mortality, PCa-specific mortality (PCSM), and metastasis. Date and cause of death were obtained annually using the National Death Index (NDI) [15]. Secondary outcomes were biopsy grade reclassification to GG ≥2, reclassification to GG ≥3, and definitive treatment. Outcomes were assessed using competing-risk analysis, and volume reclassification, elective treatment, and all-cause mortality were considered competing risks [16].

We used multivariable analysis to identify patient-level factors associated with grade reclassification during follow-up. Variables included age, year of diagnosis, African-American (AA) race, PSAD, number of positive cores, maximum core involvement, and use of pre-enrollment mpMRI (ie, at the time of diagnostic or confirmatory biopsy). As men diagnosed with GG ≥2 PCa at diagnostic or confirmatory biopsy are not included in the AS program, and mpMRI scoring was not uniform until adoption of PI-RADS v2 in 2016, the impact of specific PI-RADS scores could not be assessed in the overall cohort. To measure the impact of specific mpMRI findings (categorized as none, PI-RADS 1–2, and PI-RADS 3–5) on the risk of grade reclassification, we performed multivariable analysis in the subpopulation of men with mpMRI scored according to PI-RADS v2 ($n = 357$). All tests were two sided, and statistical significance was set at $p < 0.05$. Statistical analyses were performed using SAS v.9.4 (SAS Institute Inc., Cary, NC, USA) and STATA v.13.1 (StataCorp, College Station, TX, USA).

3. Results

3.1. Study cohort

From January 1995 through June 2018, 1818 men with VLR and LR PCa were enrolled in AS (Table 1). The median follow-up for men at risk of upgrading was 5.0 yr (interquartile range [IQR] 2.0–9.0), and the median interval between biopsies was 13 mo (IQR 12–15). In total, 920 men had ≥5 yr of follow-up and 305 had ≥10 yr of follow-up. The cumulative incidences of ongoing cancer assessment (defined as: PSA, mpMRI, and/or prostate biopsy within 18 mo) at 3, 5, and 10 yr after diagnosis were 94%, 88%, and 78%, respectively. The cumulative incidences of loss to follow-up (defined as no contact for ≥18 mo) were 3%, 4%, and 6%, respectively. Patients lost to follow-up were significantly older and had lower-risk disease at last biopsy as compared with those not lost to follow-up (Supplementary Table 1).

Table 1 – Study cohort characteristics.

	Very low risk (n = 1293) Median (IQR) or n (%)	Low risk (n = 525) Median (IQR) or n (%)
Age at diagnosis (yr)	66 (61–69)	67 (62–71)
Race		
Caucasian	1138 (88)	445 (85)
African American	95 (7)	56 (11)
Other	60 (5)	24 (4)
Year of diagnosis		
≤2005	357 (28)	100 (19)
2006–2010	428 (33)	115 (22)
2011–2015	391 (30)	202 (38)
>2015	117 (9)	108 (21)
PSA (ng/ml)	4.6 (3.5–5.8)	5.9 (4.5–7.8)
PSA density (ng/ml/cc)	0.09 (0.07–0.12)	0.17 (0.12–0.21)
Number of cores positive for cancer	1 (1–1)	1 (1–3)
Maximum percent involvement of any core with cancer	5 (1–10)	10 (1–30)
Interval between diagnosis and confirmatory biopsy (mo)	12 (10–14)	12 (10–14)
Interval between surveillance biopsies (mo)	13 (12–15)	12 (12–15)
Number of surveillance biopsies	2 (1–4)	1 (1–3)
Follow-up in men at risk of biopsy grade reclassification[a] (mo)	68 (31–109)	37 (14–74)
Follow-up in men at risk of curative intervention[a] (mo)	67 (31–109)	36 (14–72)

IQR = interquartile range; PSA = prostate-specific antigen.
[a] Follow-up from the time of diagnosis.

3.2. *Primary outcomes: overall mortality, cancer-specific mortality, and metastatic disease*

During follow-up, 92 men died at a median age of 80 yr (IQR 74.5–85.0). There were 88 deaths due to non-PCa causes: 56 men (64%) were undergoing surveillance at the time of death, 16 (18%) underwent grade reclassification prior to death, and 16 (18%) underwent volume reclassification prior to death (Fig. 1). The cumulative incidences of all-cause mortality were 6.8% (95% confidence interval [CI], 5.1–8.9%) at 10 yr and 28% (95% CI, 21–37%) at 15 yr.

There were four PCa deaths. As previously described [17], one patient died 16 yr after enrollment due to metastatic PCa clonally distinct from his original cancer, and another died 15 mo from diagnosis after a recommendation to undergo AS [4]. Both men were enrolled with VLR PCa. There have since been two additional PCa deaths. One patient was diagnosed with LR PCa (GG1, PSAD 0.16) in 1994 at age 69 yr, underwent biopsy reclassification to GG2 and RP in 1995, began androgen-deprivation therapy in 2008, and died of PCa in 2017; another was diagnosed with VLR PCa in 1995 at age 66 yr, underwent grade reclassification to GG2 and RT in 1996, began androgen-deprivation therapy in 2008, and died of PCa in 2017.

The cumulative incidence of PCSM was 0.1% (95% CI, 0.01–0.4%) at both 10 and 15 yr. Considering all outcomes

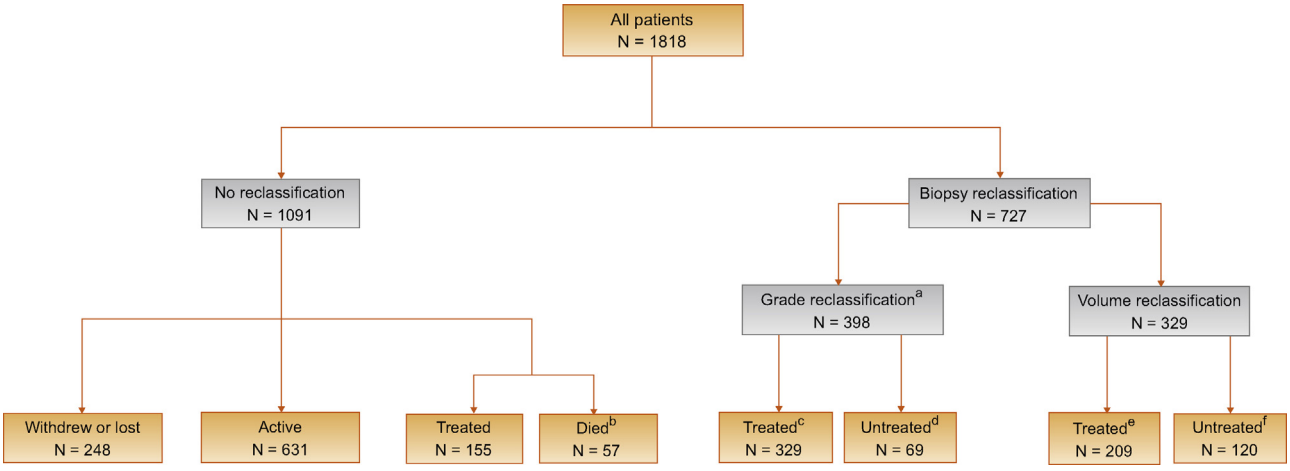

Fig. 1 – Flow diagram for the Johns Hopkins Active Surveillance Program showing outcomes at the time of last follow-up. [a] Treatment is recommended in all cases of grade reclassification. [b] Includes one death due to prostate cancer. [c] Includes 13 deaths due to non–prostate cancer causes and two deaths due to prostate cancer after treatment. [d] Includes 45 men who were undecided on treatment at time of analysis, 20 men with no treatment data available (withdrawn or lost), three men who died of non–prostate cancer causes, and one man who was found to have metastasis shortly after grade reclassification and subsequently died of prostate cancer. [e] Includes 12 men who died of non–prostate cancer causes after treatment. [f] Includes 90 men who elected to continue AS, 26 men with no treatment data available (withdrawn or lost), and four men who died of non–prostate cancer causes. AS = active surveillance.

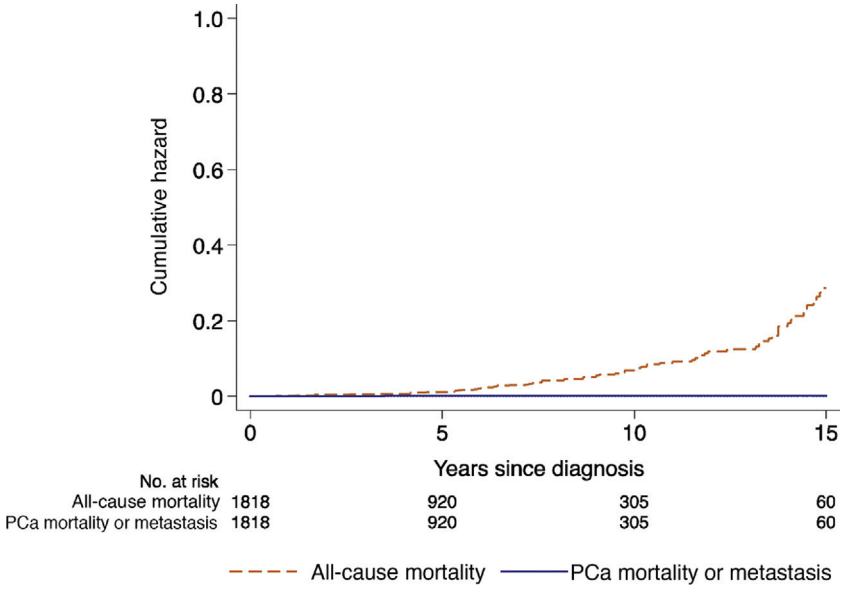

Fig. 2 – Cumulative hazard of all-cause mortality versus prostate cancer mortality or metastasis. PCa = prostate cancer.

observed during the study period between 1995 and 2018, the relative risk of non-PCa death to PCa death at 23 yr was 22 (95% CI, 8.1–60). One additional patient developed distant metastasis during follow-up. The patient was diagnosed with GG1 PCa (PSAD 0.08) in 2013 and underwent concordant confirmatory biopsy in 2015. Surveillance mpMRI in 2016 revealed a suspicious lymph node, and subsequent imaging findings (bone scan and on-study prostate-specific membrane antigen positron emission tomography/computed tomography) were consistent with bony metastases. The cumulative incidence of PCSM or metastasis was 0.1% (95% CI, 0.04–0.6%) at both 10 and 15 yr (Fig. 2).

3.3. *Secondary outcomes: biopsy grade reclassification and curative intervention*

Overall, 727 men underwent biopsy reclassification during follow-up. The 5-, 10-, and 15-yr cumulative incidences of grade reclassification were 21%, 30%, and 32%, respectively, and those of reclassification to GG $\geq$ 3 were 6.9%, 10%, and 11%, respectively (Fig. 3). Of the 693 men who underwent treatment, 538 (78%) elected treatment after biopsy reclassification and 155 (22%) pursued treatment due to a change in preference. The 5-, 10-, and 15-yr cumulative incidences of definitive treatment were 36%, 48%, and 52%, respectively. The 5-, 10-, and 15-yr cumulative incidences of clinical outcomes are listed in Table 2.

3.4. *Multivariable analysis: patient-level factors and pre-enrollment mpMRI*

Since mpMRI became available in 2013, 537 men underwent pre-enrollment mpMRI (ie, at the time of diagnostic or confirmatory biopsy). Of these men, 250 (47%) had positive mpMRI (PI-RADS 3–5) and underwent mpMRI/ultrasound-fusion targeted biopsy, while the remaining 287 (53%) underwent conventional transrectal ultrasound–guided biopsy. Patients who underwent mpMRI prior to enrollment in AS had higher PSA, PSAD, and maximum core involvement with cancer than those who did not (Supplementary Table 2).

On multivariable analysis, pre-enrollment mpMRI was associated with a reduced risk of grade reclassification (hazard ratio [HR] 0.66, 95% CI, 0.46–0.95, $p = 0.03$). Other factors associated with grade reclassification were older age (HR 1.02 per year, 95% CI, 1.001–1.04, $p = 0.04$), later year of diagnosis (HR 1.08 per year, 95% CI, 1.04–1.12, $p < 0.001$), AA race (HR 1.47, 95% CI, 1.19–2.22, $p = 0.03$), and measures of higher-risk disease (PSAD, number of positive cores, and maximum core involvement; Table 3). Baseline cancer characteristics and follow-up were not significantly different between AA and non-AA men (Supplementary Table 3).

3.5. *Findings on mpMRI*

To measure the impact of specific mpMRI findings on the risk of grade reclassification, we performed multivariable analysis in the subpopulation of men with mpMRI scored according to PI-RADS v2. Compared with negative mpMRI, undergoing positive mpMRI (HR 2.83, 95% CI 2.02–4.98, $p = 0.01$) and not undergoing mpMRI (HR 1.46, 95% CI, 1.07–2.63, $p = 0.04$) were associated with an increased risk of grade reclassification. Similarly, older age, later year of diagnosis, higher PSAD, and higher percentage of core involvement with cancer were associated with grade reclassification (Supplementary Table 4).

4. Discussion

AS is a widely accepted management option for men with GG1 PCa [1,2,8], but questions persist regarding long-term outcomes and the optimal approach to patient selection and

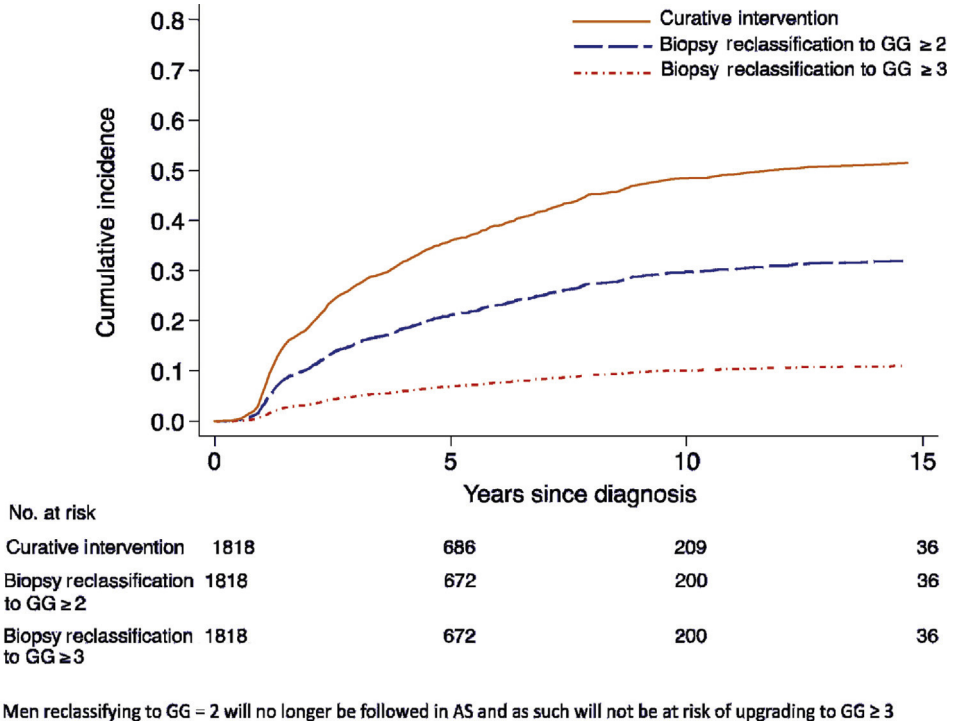

Fig. 3 – Cumulative incidence of biopsy grade reclassification and curative intervention from diagnosis for overall cohort. AS = active surveillance; GG = grade group.

Table 2 – Cumulative incidences of primary and secondary outcomes at 5, 10, and 15 yr from enrollment.

	Cumulative incidence (95% CI)		
	5 yr	10 yr	15 yr
Overall mortality	NC	6.8% (5.1–8.9%)	28% (21–37%)
PCSM	NC	0.1% (0.01–0.4%)	0.1% (0.01–0.4%)
PCSM or metastasis	NC	0.1% (0.04–0.6%)	0.1% (0.04–0.6%)
GR to ≥GG2	21% (19–23%)	30% (27–32%)	32% (29–35%)
GR to ≥GG3+	6.9% (5.8–8.3%)	10% (8.6–12%)	11% (9.3–13%)
Definitive treatment	36% (34–38%)	48% (45–51%)	52% (49–55%)

CI = confidence interval; GG = grade group; GR = grade reclassification; NC = not calculated; PCSM = prostate cancer-specific mortality.

Table 3 – Multivariable analysis for association between baseline characteristics and outcomes of any grade reclassification and grade reclassification to GG ≥3.

Characteristic	Adjusted HR (95% CI)	*p* value
Any grade reclassification		
Age (per yr)	1.02 (1.001–1.04)	0.04
Year of diagnosis (per yr)	1.08 (1.04–1.12)	<0.001
African-American race (vs non-AA)	1.47 (1.19–2.22)	0.03
No. of positive cores	1.26 (1.15–1.38)	<0.001
Maximum percent involvement of a core	1.00 (0.99–1.002)	0.7
PSA density (per 0.1-unit increase)	1.32 (1.12–1.57)	0.001
Underwent pre-enrollment mpMRI (vs no mpMRI prior to enrollment)	0.66 (0.46–0.95)	0.03
Grade reclassification to GG ≥3		
Age (per yr)	1.05 (1.02–1.09)	0.01
Year of diagnosis (per yr)	1.06 (1.01–1.13)	0.03
African-American race (vs non-AA)	1.64 (1.08–3.28)	0.02
No. of positive cores	1.11 (1.01–1.40)	0.04
Maximum percent involvement of a core	1.00 (1.00–1.001)	0.8
PSA density (per 0.1-unit increase)	1.19 (0.98–1.46)	0.2
Underwent pre-enrollment mpMRI (vs no mpMRI prior to enrollment)	0.46 (0.24–0.90)	0.02

AA = African American; CI = confidence interval; HR = hazard ratio; mpMRI = multiparametric magnetic resonance imaging; PSA = prostate-specific antigen.

monitoring [2–4]. Consistent with previous findings [4], the current analysis revealed 10- and 15-yr cumulative incidences of PCSM or metastasis to be <1%. Accordingly, we observed a 22-fold increased risk of dying from non-PCa causes than from PCa at the end of the overall study period. On multivariable analysis, we found that older age, AA race, and measures of cancer volume were associated with an increased risk of grade reclassification. Furthermore, the use of mpMRI prior to enrollment in AS was associated with a significant reduction in the risk of reclassification during follow-up. Thus, despite the evolving nature of surveillance methods, AS remains a safe option for the vast majority of men with GG1 PCa.

Acknowledging the promising outcomes of several AS programs [3–7], current focus has shifted to expanding the population of men eligible for AS and reducing the burden of invasive monitoring procedures (ie, biopsy). To this end, mpMRI and targeted biopsy have been adopted at many centers. In the current analysis, men who underwent mpMRI prior to enrollment in AS had higher PSA, PSAD, and cancer volume compared with those who did not. Nonetheless, pre-enrollment mpMRI was associated with a decreased risk of biopsy grade reclassification during follow-up (HR 0.66, 95% CI, 0.46–0.95, $p = 0.03$). While optimal timing for the use of mpMRI in AS remains unclear [14,18], our findings suggest that mpMRI may contribute to the following: (1) allowing higher-risk men (ie, increased GG1 cancer volume and/or PSAD) to enroll in AS and (2) decreasing the intensity of invasive monitoring. Thus, current practice at our institution includes mpMRI with targeted biopsy of PI-RADS ≥3 lesions prior to enrollment in AS, at the time of either diagnostic or confirmatory biopsy.

Older age and measures of higher-volume cancer have previously been established as risk factors for grade reclassification during AS [19,20]. While racial disparities in overall PCa incidence and outcomes have widely been reported, it remains unclear whether these findings reflect differences in socioeconomic factors (eg, access to care) or underlying differences in cancer biology [21,22]. Sundi et al [23] previously found that AA men meeting VLR criteria were more likely to have adverse surgical pathology than non-AA men. Leapman and colleagues [24], however, observed no significant differences in pathological and biochemical recurrence outcomes by race in an equal access health system. Consistent with the findings of Iremashvili et al [25], we detected an increased risk of grade reclassification in AA men on AS (HR 1.47, 95% CI, 1.19–2.22, $p = 0.03$) after adjustment for patient-level characteristics and use of mpMRI. Still, our findings are based on limited events, and the magnitude of the association is modest. Furthermore, it is unclear whether grade reclassification translates to longer-term outcomes such as metastasis and mortality. Thus, these data should not be used to exclude AA patients from AS, but rather represent a point for discussion in counseling and a critical subject of additional study.

It is important to discuss our findings in the context of the landmark ProtecT trial [26], which found that metastasis was significantly more common in men who underwent active monitoring than in those who underwent surgery or radiotherapy. The rate of metastasis observed in the active monitoring arm of ProtecT was greater than that reported by our AS cohort and others [3–7]. This can likely be explained by two factors. First, 23% of the ProtecT cohort harbored GG ≥2 PCa, including 2% with GG ≥4 PCa [26]. While there is debate regarding which men with favorable GG2 PCa should be eligible for AS, available data have consistently demonstrated higher rates of metastasis in men with higher-grade disease [6,27]. Second, the monitoring protocol used in ProtecT was limited to PSA testing every 3–12 mo, with use of biopsy considered only following a ≥50% PSA increase. By contrast, nearly all AS programs utilize scheduled biopsies, and the majority now utilize mpMRI [28]. Thus, the level of monitoring utilized in ProtecT does not reflect AS practiced today and endorsed by clinical guidelines.

Regardless, there is likely a less intensive approach to monitoring than ours that can achieve similar outcomes. The multi-institutional Prostate Cancer Research International Active Surveillance (PRIAS) study performs scheduled biopsies at years 1, 4, 7, and 10 of surveillance, with additional biopsies performed based on PSA kinetics [7]. PRIAS has similarly reported 10-yr cancer-specific mortality of <1%, although the associated 10-yr rate of discontinuing AS was 73%. Nonetheless, data from our program and others indicate that the risk of reclassification is highest initially and decreases with extended follow-up [29]. These findings suggest that a less intensive monitoring paradigm may be appropriate after a successful period of surveillance, but this must be balanced with the risk of older age consistently observed in this setting. Ultimately, a balance has to be reached between the risk of cancer progression and excessively burdensome monitoring. Certainly, contemporary monitoring protocols will bear little resemblance to those conceived in 1995, when resistance to the idea of cancer surveillance was high. Use of biopsy will continue to decrease, replaced instead by noninvasive alternatives such as imaging and blood or urine biomarkers. As we pursue such innovation, patient-specific risk factors should continue to drive personalized conversations weighing the risks and benefits of various management strategies.

There are limitations of our study. First, acknowledging the prolonged history of PCa and use of the NDI [30], our assessment of longer-term outcomes may be incomplete. Second, we do not routinely collect comorbidity data and therefore cannot evaluate comorbidities in our cohort. Third, implementation of mpMRI was based on provider discretion as opposed to a scheduled protocol, making it difficult to draw conclusions regarding the impact of mpMRI. Owing to the limited number of metastatic and lethal events, our multivariable analysis was based on biopsy grade reclassification—a surrogate measure that may not translate to long-term outcomes. Finally, our protocol was conceived to demonstrate the potential safety of AS in carefully selected and intensively monitored patients. Therefore, our observations may not reflect those expected in higher-risk patients or those under less intensive monitoring.

5. Conclusions

These data support the safety of AS as a guideline-endorsed, first-line management approach in most men with GG1 PCa. Patients should be counseled with regard to their personal preferences and informed of the limitations of currently available data. With additional follow-up of our cohort and others, optimal use of mpMRI and other technologies will be better defined, and the approach to AS will continue to evolve toward a sufficiently thorough, less invasive ideal.

***Author contributions*:** Mufaddal Mamawala had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Tosoian, Mamawala, Epstein, Landis, Macura, Simopoulos, Carter, Gorin.
Acquisition of data: Mamawala, Landis, Carter, Gorin.
Analysis and interpretation of data: Tosoian, Mamawala, Epstein, Macura, Simopoulos, Carter, Gorin.
Drafting of the manuscript: Tosoian, Mamawala, Epstein, Landis, Macura, Carter, Gorin.
Critical revision of the manuscript for important intellectual content: Tosoian, Mamawala, Epstein, Landis, Macura, Simopoulos, Carter, Gorin.
Statistical analysis: Mamawala, Carter, Gorin.
Obtaining funding: None.
Administrative, technical, or material support: Landis, Carter, Gorin.
Supervision: Tosoian, Mamawala, Epstein, Landis, Macura, Gorin, Carter.
Other: None.

Financial disclosures: Mufaddal Mamawala certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Katarzyna J. Macura has received research grants from GlaxoSmithKline, Profound Medical Corp., and Siemens Healthineers.

***Funding/Support and role of the sponsor*:** None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2019.12.017.

References

[1] Mohler J, Antonarakis E, Armstrong A, D'Amico A. NCCN clinical practice guidelines in oncology: prostate cancer. 2019 http://www.nccn.org/professionals/physician_gls
[2] Briganti A, Fossati N, Catto JWF, et al. Active surveillance for low-risk prostate cancer: the European Association of Urology Position in 2018. Eur Urol 2018;74:357–68.
[3] 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;33:272–7.
[4] 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;33:3379–85.
[5] 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;193:807–11.
[6] Godtman RA, Holmberg E, Khatami A, Pihl CG, Stranne J, Hugosson J. Long-term results of active surveillance in the Göteborg randomized, population-based prostate cancer screening trial. Eur Urol 2016;70:760–6.
[7] 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;70:954–60.
[8] Bekelman J, Rumble RB, Chen R, et al. Clinically localized prostate cancer: ASCO clinical practice guideline endorsement of an American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology guideline. J Clin Oncol 2018;36:3251–8.
[9] Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. Eur Urol 2013;64:876–92.
[10] Carter HB, Walsh PC, Landis P, Epstein JI. Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. J Urol 2002;167:1231–4.
[11] Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1 c) prostate cancer. JAMA 1994;271:368–74.
[12] Mullins JK, Bonekamp D, Landis P, et al. Multiparametric magnetic resonance imaging findings in men with low-risk prostate cancer followed using active surveillance. BJU Int 2013;111:1037–45.
[13] Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging – Reporting and Data System: 2015, version 2. Eur Urol 2016;69:16–40.
[14] Ma TM, Tosoian JJ, Schaeffer EM, et al. The role of multiparametric magnetic resonance imaging/ultrasound fusion biopsy in active surveillance. Eur Urol 2017;71:174–80.
[15] Centers for Disease Control and Prevention. National Death Index. https://www.cdc.gov/nchs/ndi/index.htm
[16] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
[17] Haffner MC, De Marzo AM, Yegnasubramanian S, Epstein JI, Carter HB. Diagnostic challenges of clonal heterogeneity in prostate cancer. J Clin Oncol 2015;33:e38–40.
[18] Klotz L, Loblaw A, Sugar L, et al. Active Surveillance Magnetic Resonance Imaging Study (ASIST): results of a randomized multicenter prospective trial. Eur Urol 2019;75:300–9.
[19] Druskin SC, Mamawala M, Tosoian JJ, et al. Older age predicts biopsy and radical prostatectomy grade reclassification to aggressive prostate cancer in men on active surveillance. J Urol 2019;201:98–104.
[20] Leapman MS, Cowan JE, Nguyen HG, et al. Active surveillance in younger men with prostate cancer. J Clin Oncol 2017;35:1898–904.
[21] Powell IJ, Bock CH, Ruterbusch JJ, Sakr W. Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men, and influences racial progression and mortality disparity. J Urol 2010;183:1792–7.
[22] Mahal BA, Aizer AA, Ziehr DR, et al. Trends in disparate treatment of African American men with localized prostate cancer across National Comprehensive Cancer Network risk groups. Urology 2014;84:386–92.
[23] Sundi D, Ross AE, Humphreys EB, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? J Clin Oncol 2013;31:2991–7.
[24] Leapman MS, Freedland SJ, Aronson WJ, et al. Pathological and biochemical outcomes among African-American and Caucasian men with low risk prostate cancer in the SEARCH database: implications for active surveillance candidacy. J Urol 2016;196:1408–14.

[25] Iremashvili V, Soloway MS, Rosenberg DL, Manoharan M, Tosoian JJ. Clinical and demographic characteristics associated with prostate cancer progression in patients on active surveillance. J Urol 2012;187:1594–600.
[26] Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375:1415–24.
[27] Musunuru HB, Yamamoto T, Klotz L, et al. Active surveillance for intermediate risk prostate cancer: survival outcomes in the Sunnybrook experience. J Urol 2016;196:1651–8.
[28] Velasquez MC, Prakash NS, Venkatramani V, Nahar B, Punnen S. Imaging for the selection and monitoring of men on active surveillance for prostate cancer. Transl Androl Urol 2018;7:228–35.
[29] Porten SP, Whitson JM, Cowan JE, et al. Changes in prostate cancer grade on serial biopsy in men undergoing active surveillance. J Clin Oncol 2011;29:2795–800.
[30] Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. J Am Med Assoc 1998;280:975–80.