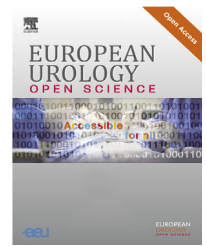


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European Association of Urology



## Prostate Cancer

# Prostate Cancer Patients Under Active Surveillance with a Suspicious Magnetic Resonance Imaging Finding Are at Increased Risk of Needing Treatment: Results of the Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) Consortium

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## Abstract

**Background:** The inclusion criterion for active surveillance (AS) is low- or intermediate-risk prostate cancer. The predictive value of the presence of a suspicious lesion at magnetic resonance imaging (MRI) at the time of inclusion is insufficiently known.

**Objective:** To evaluate the percentage of patients needing active treatment stratified by the presence or absence of a suspicious lesion at baseline MRI.

**Design, setting, and participants:** A retrospective analysis of the data from the multicentric AS GAP3 Consortium database was conducted. The inclusion criteria were men with grade group (GG) 1 or GG 2 prostate cancer combined with prostate-specific antigen <20 ng/ml. We selected a subgroup of patients who had MRI at baseline and for whom MRI results and targeted biopsies were used for AS eligibility. Suspicious MRI was defined as an MRI lesion with Prostate Imaging Reporting and Data System (PI-RADS)/Likert  $\geq 3$  and for which targeted biopsies did not exclude the patient for AS.

<sup>†</sup> The Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) Consortium members are presented in the [Supplementary material](#).

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**Outcome measurements and statistical analysis:** The primary outcome was treatment free survival (FS). The secondary outcomes were histological GG progression FS and continuation of AS (discontinuation FS).

**Results and limitations:** The study cohort included 2119 patients (1035 men with nonsuspicious MRI and 1084 with suspicious MRI) with a median follow-up of 23 (12–43) mo. For the whole cohort, 3-yr treatment FS was 71% (95% confidence interval [CI]: 69–74). For nonsuspicious MRI and suspicious MRI groups, 3-yr treatment FS rates were, respectively, 80% (95% CI: 77–83) and 63% (95% CI: 59–66). Active treatment (hazard ratio [HR] = 2.0,  $p < 0.001$ ), grade progression (HR = 1.9,  $p < 0.001$ ), and discontinuation of AS (HR = 1.7,  $p < 0.001$ ) were significantly higher in the suspicious MRI group than in the nonsuspicious MRI group.

**Conclusions:** The risks of switching to treatment, histological progression, and AS discontinuation are higher in cases of suspicious MRI at inclusion.

**Patient summary:** Among men with low- or intermediate-risk prostate cancer who choose active surveillance, those with suspicious magnetic resonance imaging (MRI) at the time of inclusion in active surveillance are more likely to show switch to treatment than men with nonsuspicious MRI.

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## 1. Introduction

Active surveillance (AS) decreases the harms of screening and overdiagnosis of men with a low or intermediate risk of prostate cancer (PCa) progression. The main goal of AS is to avoid or delay the use of treatments without compromising patients' long-term survival [1].

Selection criteria were traditionally based on prostate-specific antigen (PSA)  $< 10$  ng/ml, T stage  $\leq T2a$ , and International Society of Urological Pathology (ISUP) grade group (GG) 1 at systematic biopsy (SB) defining cancers at low risk [2]. SB is associated with misclassification due to underestimation of the tumour volume or GG at entry [1]. Addition of magnetic resonance imaging (MRI) as a selection tool decreases the risk of missing clinically significant disease before AS is started. It was reported that 10% of men eligible for AS based on SB are reclassified to have a clinically significant PCa (CSPCa) by MRI and targeted biopsy (TB) [3]. In the ASIST study, the use of MRI at entry or during the 1st year of AS resulted in significantly fewer rates of AS discontinuation (19% vs 35%) and progression at biopsy to GG  $\geq 2$  cancer (9.9% vs 23%) after 2 yr of follow-up [4]. MRI and MRI-TB for suspicious MRI (Prostate Imaging Reporting and Data System [PI-RADS] score 3–5) are now recommended in the European association of Urology 2020 guidelines, in addition to standard biopsy for men on AS [5].

In the Movember multicentric international GAP3 database [6], we identified a subgroup of patients who had MRI at baseline, and for whom MRI results and TBs were used for AS eligibility. Importantly, these were patients who still met AS eligibility criteria after their initial TBs. The aim of our study was to evaluate the percentage of patients needing active treatment stratified by the presence or absence of a suspicious lesion at baseline MRI. The primary outcome was treatment free survival (FS). The

secondary outcomes were histological GG progression FS and all men continuing AS (discontinuation FS).

## 2. Patients and methods

### 2.1. Study population

Between 2014 and 2016, the GAP3 database was created by combining patient data from established AS cohorts worldwide. Requirements for participation included an active registry of AS patients over the last 2 yr or more, including at least 50 patients annually and ethical approval for sharing digital patient data in a centralised, uniform, and consensus-based AS database (v3.3). To date, 25 cohorts from the USA, Canada, Asia, Australia, the UK, and Europe fulfilled the requirements for participation and joined the initiative, resulting in data for a total of 21 647 men on AS.

We retrospectively included from the GAP3 database all patients from 13 cohorts in eight countries on AS who had MRI performed at "baseline" with its results documented (Fig. 1). The use of MRI and inclusion in the GAP3 database differed between cohorts. In this study, baseline MRI definition was MRI performed in the 3 mo before diagnosis or during the 1st year after inclusion. Some investigators performed MRI upfront at the time of the first diagnosis, and therefore cases reclassified to CSPCa not considered for AS were not included in the GAP3 database. Other investigators included in the GAP3 database patients selected for AS based on PSA, T stage, and ISUP GG based on SBs, and performed MRI during the 1st year of follow-up. Some of these patients were reclassified to CSPCa at rebiopsy based on MRI-TB results and were therefore excluded. Since baseline MRI results when performed within 12 mo after AS inclusion can lead to reclassification up to 6 mo after MRI, the period range for reclassification was up to 18 mo after diagnosis.

### 2.2. Exclusion criteria

The exclusion criteria included baseline MRI performed earlier than 3 mo before diagnosis or more than a year after diagnosis, PSA  $> 20$  ng/ml, and GG 3, 4, or 5 at inclusion; patients who were reclassified within

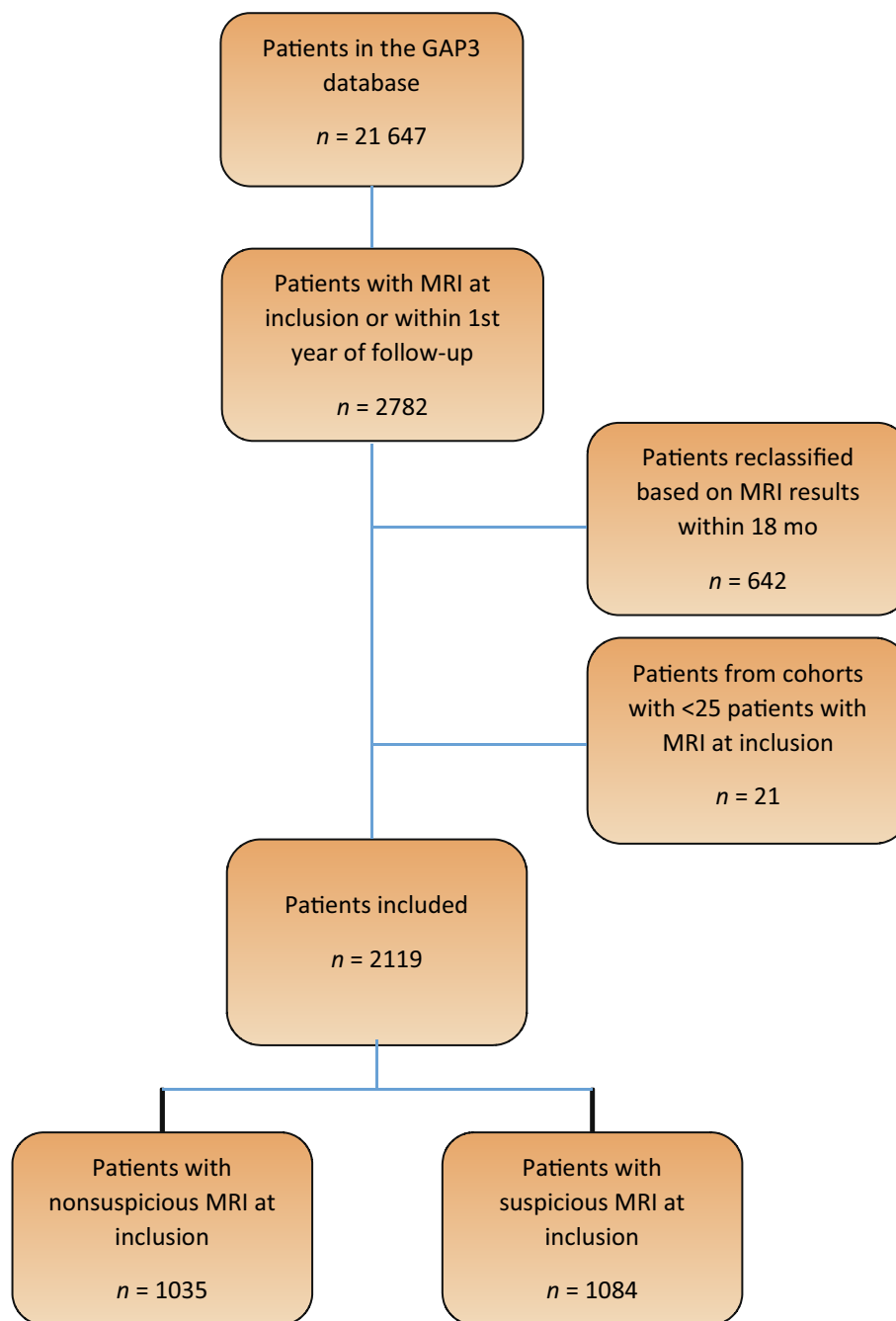


Fig. 1 – Flowchart. MRI = magnetic resonance imaging.

18 mo after diagnosis if baseline MRI was performed after inclusion were also excluded. In addition, cohorts with <25 patients with MRI at inclusion were excluded.

### 2.3. Definition of suspicious and nonsuspicious MRI

Baseline MRI was considered suspicious when the item “suspicious lesions found on MRI” was filled in the Movember GAP3 database with “yes” or “equivocal”, and as nonsuspicious when the column was filled in the Movember GAP3 database with “no”. Inclusion of equivocal lesions at MRI as suspicious lesions was decided because in the literature around 20% of equivocal lesions are positive for cancer at TB [7]. A sub-analysis of patients ( $n = 737$ ) with available Likert or PI-RADS scores for

clinically significant disease (1, “highly unlikely”; 2, “unlikely”; 3, “indeterminate” or “equivocal”; 4, “likely”; and 5, “highly likely”) was performed by stratifying patients into three groups with subsequent assessment scores of 1–2, 3, and 4–5 for the likelihood of PCa.

### 2.4. Collected data

Available data, as described previously [6], included age, PSA at inclusion, PSA density, T stage at digital rectal examination, number of biopsy cores with PCa, maximum % PCa in any core, and Gleason grade group.

The available MRI data were suspicious lesion found on MRI, number and location of the lesion on MRI, and Likert or PI-RADS score (reported in 737 cases). PI-RADS score v.1 was used for patients included before

2016 and PI-RADS score v.2 was used for patients included after 2016. The concordance between MRI and TB results was not available. We collected the AS discontinuation status and date, the cause of discontinuation, and the death status. With respect to reasons for discontinuation, the following information was available for most cohorts: “convert to watchful waiting”, “clinical progression”, “pathological progression”, “clinical and pathological progression”, “PSA progression (PSA doubling time <3 yr)”, “other PSA kinetics”, “patient choice/anxiety”, “doctor’s anxiety”, “radiological progression”, “died”, “lost to follow-up”, “other/unknown”, or “still on active surveillance”.

## 2.5. Follow-up

With respect to follow-up, almost all protocols recommended serial measurements (with a variation in time intervals) of serum PSA levels, digital rectal examination, and surveillance biopsy sampling in order to identify pathological progression. Several protocols considered MRI for routine use in AS, again with many differences between recommended frequencies.

## 2.6. Study design

The primary outcome was active treatment FS, which was defined as undergoing radical prostatectomy, radiation therapy, brachytherapy, focal therapy, or androgen deprivation treatment. Censoring time was defined as the date of the last recorded clinical appointment or stopping AS due to other reasons. Secondary outcomes were GG progression, which was defined as upgrading at follow-up biopsy (GG >1 for GG 1 at inclusion and GG >2 for GG 2 at inclusion) or high-grade progression

defined as upgrading at follow-up biopsy to GG >2 based on per-protocol or for cause biopsy, and all-cause AS discontinuation defined as progression, conversion to active treatment without evidence of progression, transition to watchful waiting, anxiety, non-PCa death, and other/unknown. According to Bruinsma et al [8], we defined any upgrading or upstaging after confirmed inclusion as progression. A subanalysis of Gleason GG 1 patients was also performed.

## 2.7. Statistical analysis

We used survival analysis to compare the risks of switching to active treatment, cancer grade progression, and AS discontinuation for patients in different MRI groups. The event in survival analysis is defined as switching to active treatment, cancer grade progression, or AS discontinuation. Firstly, we performed the Kaplan-Meier analysis and estimated the probabilities of survival for patients in suspicious and nonsuspicious MRI groups. Subsequently, we fitted stratified Cox proportional hazard models [9], with stratified baseline survivals for different cohorts, to estimate pooled hazard ratios (HRs) for the covariates of interest. Covariates include patients’ baseline MRI and PSA density (calculated as PSA level divided by prostate volume). Analyses were performed in R version 3.6.1.

## 3. Results

### 3.1. Cohort characteristics

In total, 2119 patients were included from 13 cohorts (Table 1). Our study cohort contained 1035 men with non-

**Table 1 – Patients and AS characteristics for the 13 GAP3 selected cohorts (n = 2119)**

Cohorts	Number of patients	Median age (IQR)	Median follow-up (IQR)	Suspicious MRI, n (%)	Switch to active treatment, n (%)	Biopsy progression, n (%)	AS discontinuation all causes at any time, n (%)
Atlanta	53	62 (56–69)	13 (10–25)	46 (87)	13 (25)	1 (2)	18 (34)
Bordeaux	166	65 (60–68)	27 (11–47)	93 (56)	49 (30)	6 (4)	50 (30)
Helsinki	42	66 (61–72)	36 (23–43)	27 (64)	16 (38)	1 (2)	18 (43)
Hopkins	216	66 (62–69)	19 (13–30)	175 (81)	57 (26)	12 (6)	80 (37)
Lille	227	65 (60–69)	29 (17–51)	127 (56)	58 (26)	12 (5)	66 (29)
London-UCL	303	62 (57–67)	26 (3–51)	138 (46)	90 (30)	10 (3)	108 (36)
Melbourne	73	65 (58–69)	14 (0–27)	65 (89)	17 (23)	0 (0)	24 (33)
MUSIC	305	64 (59–69)	12 (6–16)	158 (52)	46 (15)	8 (3)	54 (18)
PRIAS	225	64 (59–69)	21 (13–31)	72 (32)	32 (14)	8 (4)	45 (20)
Singapore	48	66 (61–70)	17 (13–34)	5 (10)	28 (58)	3 (6)	29 (60)
Sydney	104	59 (53–66)	48 (38–64)	44 (42)	35 (34)	10 (10)	40 (38)
UCSF	194	62 (57–67)	47 (26–75)	67 (35)	45 (23)	21 (11)	51 (26)
Valencia	163	65 (60–70)	38 (14–55)	67 (41)	67 (41)	8 (5)	75 (46)

AS = active surveillance; IQR = interquartile range; MRI = magnetic resonance imaging.

**Table 2 – AS patients’ characteristics at entry (n = 2119)**

Baseline characteristics	Nonsuspicious MRI	Suspicious MRI	Overall patients
Number of patients	1035	1084	2119
Age at diagnosis (yr), median (IQR)	63 (58–68)	65 (59–69)	64 (59–69)
Follow-up (mo), median (IQR)	27 (13–51)	18 (11–38)	23 (12–43)
PSA (ng/ml), median (IQR)	5.3 (3.7–7.3)	5.4 (3.8–7.2)	5.3 (3.8–7.3)
PSA density (ng/ml <sup>2</sup> ), median (IQR)	0.11 (0.07–0.16)	0.11 (0.07–0.16)	0.11 (0.07–0.16)
Number of biopsy cores with prostate cancer, median (IQR)	1 (1–2)	2 (1–3)	1 (1–2)
Maximum percentage of cancer in any core (%), median (IQR)	10 (5–20)	14 (5–29.3)	10 (5–24.89)
T stage at DRE, number (%)			
T1	730 (71)	650 (60)	1380 (65)
T2	97 (9)	107 (10)	204 (10)
TX	208 (20)	327 (30)	535 (25)
Grade group 2, n (%)	110 (11)	134 (12)	244 (12)

AS = active surveillance; DRE = digital rectal examination; IQR = interquartile range; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

suspicious MRI and 1084 with suspicious MRI; 1875 men (88%) had GG 1 at baseline, whilst the remaining 244 (12%) had GG 2 cancer. The median age at diagnosis was 64 yr (interquartile range [IQR]: 59–69), median PSA was 5.3 ng/ml (3.8–7.3), and 65% of men had a nonpalpable tumour. Patients and tumour characteristics were comparable between nonsuspicious MRI and suspicious MRI except for tumour visibility at MRI. Patients' characteristics are summarised in Table 2. The median follow-up for the cohort was 23 mo (IQR: 12–43).

### 3.2. Clinical events

#### 3.2.1. Whole cohort

For the whole cohort, treatment FS, biopsy upgrading FS, and AS discontinuation FS were 71% (95% confidence interval [CI]: 69–74), 84% (95% CI: 82–86), and 67% (95% CI: 65–71) at 3 yr respectively.

An overview of clinical outcomes is summarised in Table 3. Types of active treatment, number with histological progression at biopsy, and cumulative reasons for AS discontinuation during follow-up in both MRI groups for the whole series are shown in Table 4. No cancer-specific deaths were reported. Results per centre are described in Supplementary Tables 1–4. At 3 and 5 yr, treatment FS rates were 80% (95% CI: 77–83) and 70% (95% CI: 66–74) for nonsuspicious MRI, and 63% (95% CI: 59–66) and 49% (95% CI: 44–54) for suspicious MRI patients, respectively (Fig. 2A). Switch to treatment was significantly higher in suspicious MRI men than in nonsuspicious MRI men (HR = 2.00, 95% CI: 1.65–2.42). In total, 392 men had histological progression at biopsy during follow-up, including 101(5%) patients who

had a high-grade progression (GG >2; Table 4). The 3- and 5-yr histological progression FS rates were 89% (95% CI: 86–91) and 81% (95% CI: 77–85) in nonsuspicious MRI, and 79% (95% CI: 76–82) and 70% (95% CI: 65–75) in suspicious MRI men, respectively (Table 3). Histological progression at biopsy was significantly higher in suspicious MRI than in nonsuspicious MRI men (HR = 1.88, 95% CI: [1.47–2.42]). High-grade histological progression FS rates at 3 yr were 97% (95% CI: 95–98) in suspicious MRI men and 93% (95% CI: 91–95) in suspicious MRI men. Histological progression at biopsy to a higher grade (GG >2) was significantly higher in suspicious MRI than in nonsuspicious MRI men (HR = 2.85, *p* < 0.001). At 3 and 5 yr, all-cause AS discontinuation FS rates were 76% (95% CI: 73–79) and 63% (95% CI: 59–67) for nonsuspicious MRI, and 58% (95% CI: 54–62) and 42% (95% CI: 38–47) for suspicious MRI patients, respectively (Fig. 2B). Causes of discontinuation in the two groups are summarised in Table 4. AS discontinuation was significantly higher in suspicious MRI than in nonsuspicious MRI men (HR = 1.77, 95% CI: 1.48–2.10).

#### 3.2.2. Subcohort of GG 1 only

The 3- and 5-yr treatment FS rates were 82% (95% CI: 79–85) and 72% (95% CI: 68–77) for those with nonsuspicious MRI, and 66% (95% CI: 62–70) and 52% (95% CI: 47–57) for those with suspicious MRI, respectively. Switch to treatment was significantly higher in the suspicious MRI group (HR = 1.90, 95% CI: 1.54–2.36). The 3- and 5-yr histological progression FS rates were 89% (95% CI: 86–91) and 80% (95% CI: 76–84) for those with nonsuspicious MRI, and 78% (95% CI: 74–81) and 69% (95% CI: 64–74) for those with

**Table 3 – Cumulative incidence of switch to active treatment, histological progression at biopsy, and AS discontinuation (all causes) during follow-up % (95% CI) for the whole series of 2119 patients**

		Number at risk	All-time HR (95% CI)	3 yr % (95% CI)	3 yr HR (95% CI)	5 yr % (95% CI)	5 yr HR (95% CI)	
Switch to active treatment for all GG 1 and 2	All	2119		29 (26–31)		40 (37–43)		
	Nonsusp MRI	1035		20 (17–23)		30 (26–34)		
	Susp MRI	1084	2.00 (1.65–2.42)	37 (34–41)	1.72 (1.38–2.14)	51 (46–56)	1.86 (1.53–2.27)	
	Likert 1–2	185		17 (11–23)		26 (18–34)		
	Equivocal	208	2.12 (1.43–3.15)	31 (24–37)	1.56 (0.98–2.48)	42 (32–50)	1.80 (1.20–2.72)	
Switch to active treatment for GG 1	Likert 4–5	344	4.18 (2.82–6.19)	45 (39–51)	2.79 (1.72–4.52)	58 (50–64)	3.75 (2.49–5.65)	
	All	1875		26 (23–28)		37 (34–40)		
	Nonsusp MRI	925		18 (15–21)		28 (24–32)		
	Susp MRI	950	1.90 (1.54–2.36)	34 (30–38)	1.64 (1.29–2.10)	47 (42–52)	1.76 (1.41–2.20)	
	AS discontinuation for all GG 1 and 2	All	2119		32 (30–35)		46 (43–49)	
AS discontinuation for all GG 1 and 2	Nonsusp MRI	1035		23 (20–26)		37 (32–41)		
	Susp MRI	1084	1.77 (1.48–2.10)	41 (37–45)	1.67 (1.37–2.05)	56 (51–61)	1.67 (1.40–2.00)	
	Likert 1–2	185		18 (12–24)		34 (25–43)		
	Equivocal	208	1.92 (1.33–2.78)	33 (25–39)	1.56 (0.99–2.46)	45 (36–54)	1.58 (1.08–2.31)	
	Likert 4–5	344	3.75 (2.59–5.43)	48 (41–53)	2.87 (1.78–4.63)	60 (53–67)	3.29 (2.24–4.83)	
AS discontinuation for GG 1	All	1875		30 (27–32)		43 (40–47)		
	Nonsusp MRI	925		22 (19–25)		34 (30–39)		
	Susp MRI	950	1.67 (1.38–2.03)	38 (34–42)	1.58 (1.27–1.98)	53 (48–58)	1.57 (1.28–1.91)	
	Biopsy upgrading for all GG 1 and 2	All	2119		16 (14–18)		24 (21–27)	
	Biopsy upgrading for all GG 1 and 2	Nonsusp MRI	1035		11 (9–14)		19 (15–23)	
Susp MRI		1084	1.88 (1.47–2.42)	21 (18–24)	1.69 (1.26–2.27)	30 (25–35)	1.69 (1.30–2.20)	
Likert 1–2		185		17 (11–22)		27 (18–35)		
Equivocal		208		19 (12–25)		27 (18–36)		
Likert 4–5		344	2.05 (1.39–3.03)	35 (29–41)	1.34 (0.84–2.14)	48 (39–55)	1.72 (1.15–2.56)	
Biopsy upgrading for GG 1	All	1875		17 (14–19)		25 (22–28)		
	Nonsusp MRI	925		11 (9–14)		20 (16–24)		
	Susp MRI	950	1.97 (1.52–2.56)	22 (19–26)	1.8 (1.33–2.43)	31 (26–36)	1.72 (1.31–2.25)	

AS = active surveillance; CI = confidence interval; GG = grade group; HR = hazard ratio versus nonsusp MRI or Likert 1–2; MRI = magnetic resonance imaging; Nonsusp MRI = nonsuspicious MRI; Susp MRI = suspicious MRI.



**Table 4 – Types of active treatment, number of histological progression at biopsy, and reasons for AS discontinuation during follow-up in both MRI groups for the whole series of 2119 patients**

		Nonsuspicious MRI	Suspicious MRI	All
Types of treatment <sup>a</sup>	Radical prostatectomy	126	208	334
	Radiation therapy	30	54	84
	Brachytherapy	20	41	61
	Focal therapy	37	42	79
	ADT/others	18	26	44
Histological progression at biopsy	GG 1 to >GG 1	125	165	290
	GG 1 and GG 2 to >GG 2	37	63	100
Reasons for discontinuation (n = 528)	Pathological progression	96	136	232
	Clinical progression	21	47	68
	Clinical and pathological progression	12	27	39
	Radiological progression	14	10	24
	Radiological and pathological progression	5	2	7
	PSA progression (PSA-DT <3 yr)	5	16	21
	Other PSA kinetics (PSA V >0.5 ng/ml)	4	5	9
	Patient choice/anxiety	23	39	62
	Physician anxiety	7	0	7
	Death from other cause	9	8	17
	Lost to FU	17	13	30
Convert to WW	8	4	12	

ADT = androgen deprivation therapy; AS = active surveillance; FU = follow-up; GG = grade group; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSA-DT = PSA doubling time; WW = watchful waiting.

<sup>a</sup> Some patients had multiple treatments.

suspicious MRI, respectively. Histological progression at biopsy was significantly higher in the suspicious MRI group (HR = 1.97, 95% CI: 1.52–2.56; Fig. 2C). The 3- and 5-yr AS discontinuation FS rates were 78% (95% CI: 75–81) and 66% (95% CI: 61–70) for patients with nonsuspicious MRI, and 62% (95% CI: 58–66) and 47% (95% CI: 42–52) for patients with suspicious MRI at inclusion, respectively. AS discontinuation was significantly higher in the suspicious MRI group (HR = 1.67, 95% CI: 1.38–2.03).

### 3.2.3. Subanalysis of Likert/PI-RADS data

The treatment FS rates at 3 and 5 yr were, respectively, 83% (95% CI: 78–89) and 74% (95% CI: 66–82) for those with Likert/PI-RADS score 1–2, 70% (95% CI: 63–77) and 59% (95% CI: 50–69) for those with score 3, and 55% (95% CI: 50–61) and 42% (95% CI: 35–49) for those with score 4–5. Switch to treatment was significantly lower for those with score 1–2 versus score 3 versus score 4–5 (HR = 2.12, 95% CI: 1.43–3.15; HR = 4.18, 95% CI: 2.82–6.19). The 3-yr histological progression FS rates were 83% (95% CI: 78–89), 71% (95% CI: 75–88), and 65% (95% CI: 59–71) for those with Likert/PI-RADS scores 1–2, 3, and 4–5, respectively. There was no significant difference for histological progression between patients with a score of 1–2 at MRI versus those with a score of 3, but there was significantly more histological progression for those with score 4–5 (HR = 2.05, 95% CI: 1.39–3.03). The 3-yr AS discontinuation FS rates were 82% (95% CI: 76–87), 67% (95% CI: 41–75), and 52% (95% CI: 47–59) for patients with MRI scores 1–2, 3, and 4–5 at inclusion, respectively. AS discontinuation was significantly lower in those with score 1–2 versus score 3 versus score 4–5 (HR = 1.92, 95% CI: 1.33–2.78; HR = 3.75, 95% CI: 2.59–5.43).

## 4. Discussion

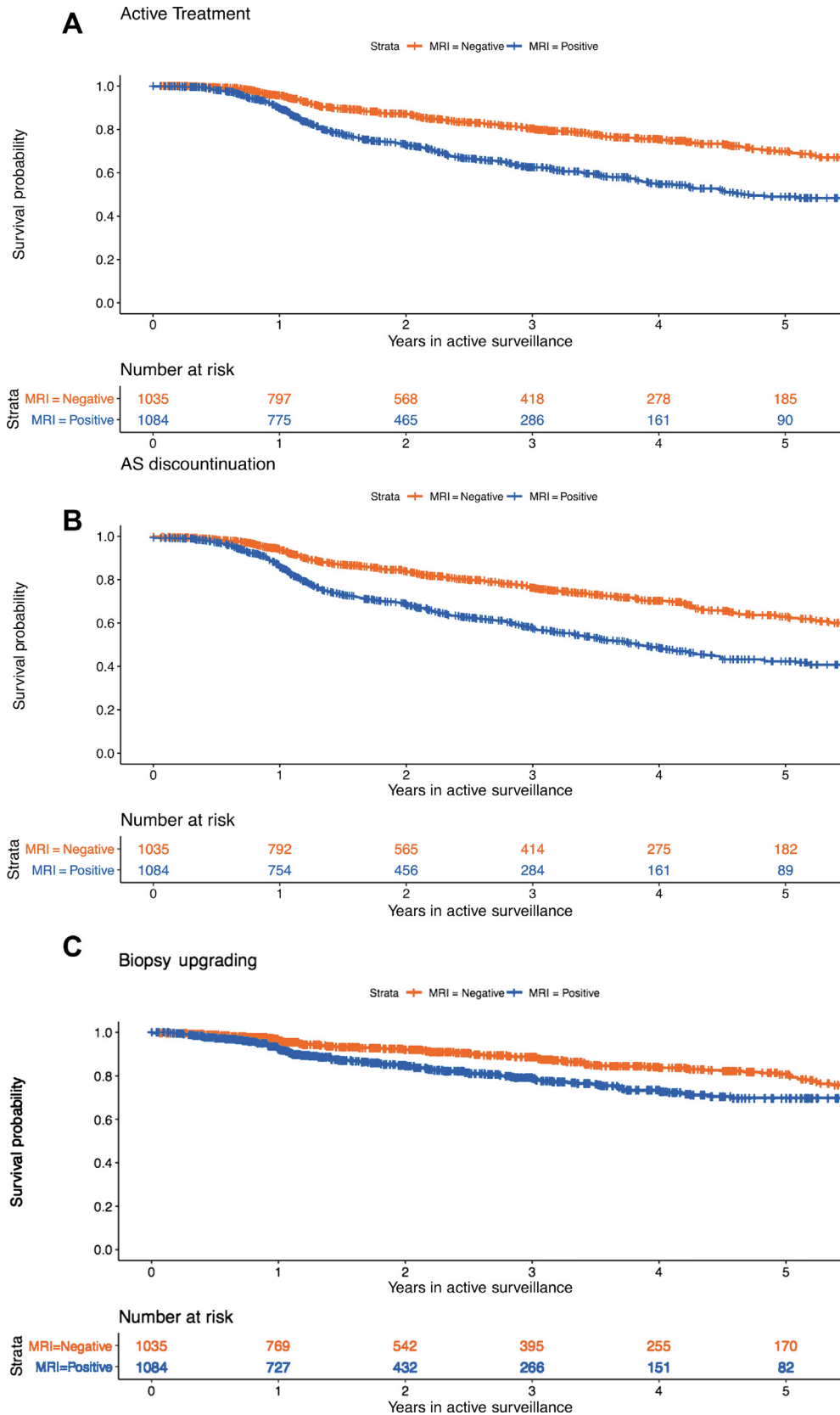
We need AS outcomes from international multicentric cohorts. One of the main outcomes is the length of time we can defer treatment and have the patient on AS. In the

whole GAP3 MRI cohort, 3- and 5-yr treatment FS rates were 71% and 60%, respectively. These outcomes can be shared with patients at the time of treatment decision.

AS eligibility criteria are of importance for this risk of switch to treatment. MRI has been proved to increase staging and grading, and as such resulted in a decrease of 10% of reclassification rate within the 1st year on AS [3]. Some patients with suspicious MRI are still eligible for AS. Our work was aimed to compare the risk of switching from AS to active treatment depending on MRI risk category at baseline. We showed that the risk to switch to treatment, the risk of histological progression, and the risk of AS discontinuation are lower if the MRI at the time of inclusion is nonsuspicious.

Further studies on different follow-up protocols for patients with negative or positive MRI should be performed.

These results confirm the findings that were already reported in monocentric studies [10–12]. Stavrinides et al [11] showed that event FS (defined as PCa treatment, transition to watchful waiting, or death) and treatment FS were lower in patients with MRI-visible (Likert 4–5) disease. In the Princess Margaret Cancer Centre cohort, it was reported that 51% of men with suspicious baseline MRI received definitive treatment within 5 yr, compared with 27% and 21% of men with equivocal and negative MRI, respectively [13]. Hsiang et al [14] found that initial and follow-up MRI PI-RADS risk scores were related to upgrading on subsequent follow-up biopsy. Chu et al [15] showed that associations between visible MRI lesions and AS outcomes appear stronger with serial examination. This is in agreement with our results, where the estimated treatment FS rates at 3 yr are 70% for the nonsuspicious MRI and 49% for the suspicious MRI group. In the Lille and Cambridge cohorts who received MRI at inclusion [16,17], histological progression FS rates at a median follow-up of 36 and 39 mo were, respectively, close to the results of 89% and 81% for nonsuspicious MRI, and 79% and 70% for suspicious MRI at 3 yr and 5 yr in the GAP3 cohort. Mamawala et al



**Fig. 2 – (A) Active treatment-free survival curves for GG 1 + GG 2 patients according to MRI groups. (B) AS discontinuation-free survival curves for GG 1 + GG 2 patients according to MRI groups. (C) Histological GG progression-free survival curves for GG 1 + GG 2 patients according to MRI groups. AS = active surveillance; GG = grade group; MRI = magnetic resonance imaging.**

[10] showed that the 2- and 4-yr upgrade FS rates were significantly lower for the negative MRI group (93% and 83%, respectively) than for the positive MRI group (74% and 59%, respectively). These rates are close to the 27.5% progression in the whole Movember cohort at 5 yr [18].

Our results show that men with suspicious MRI are more likely to receive definitive treatment, more likely to have upgrading on follow-up biopsy, and more likely to discontinue AS, compared with men with negative MRI, although tumour characteristics were not statistically different between the two groups except for visibility at MRI but a trend towards higher-volume disease at biopsy (Table 2). It could have been expected that patients with suspicious MRI present more frequently with GG 2. It can be explained by undersampling of the visible lesion at TB or a false positive result of MRI and by the use of inclusion criteria.

The potential impact of these findings is that suspicious MRI does not necessarily exclude a patient from AS since a substantial number of men with suspicious MRI did not progress on AS, but it is clearly suggested that those with suspicious MRI may have to be followed more closely than a patient with nonsuspicious MRI. It also questions the accuracy of TB to sample an MRI lesion and eventually reclassify PCa before inclusion.

These rates may reflect in part tumours with rapid growth and in part tumours that were missed by the diagnostic tests used for the selection criteria. Hence, if MRI accuracy is high to eliminate significant tumours, its negative predictive value goes from 75% to 95%, explaining that there are still some significant tumours that are missed at entry. Progression happens over time when an initial non-significant PCa progresses or when a new significant lesion grows. Inoue et al [19] modelled that the probability of true grade progression ranges from 1.2% to 2.4% per year of AS. Theoretically, 5–10% of CSPCa are missed at entry, and progression ranges from 1.2% to 2.4% per year of AS, which means that reclassification/progression should range from 8.6% to 17.2% at 3 yr and from 11% to 22% at 5 yr. Our results showing a 70% (66–74%) 5-yr treatment FS rate for nonsuspicious MRI patients are concordant with this model. It is important to note that only 2119 (10%) out of 21 643 patients of the world's largest AS cohort had baseline MRI. MRI was not routinely used when GAP3 started but has since become an increasingly utilised diagnostic tool.

There are some limitations that need to be considered in this study. Firstly, the number of patients with MRI at baseline is small and represents <15% of the GAP3 database. This concern can be explained by the fact that many patients of the cohorts were included before guidelines recommend MRI at baseline in 2019. Most of the included patients were coming from MRI expert centres, which used either Likert or PI-RADS scores as routine MRI scores. The GAP3 database is purely a retrospective database resulting in limited control over data collection and a lack of availability of some data of interest, such as the quality of prostate MRI in different cohorts, radiological experience of the included centres, biopsy strategies (transperineal or transrectal), and targeting system. True inclusion time in AS for the MRI cohort was defined as 3 mo after the MRI date, to allow for reclassification for significant PCa. Some centres performed MRI

in the 3 mo before the first diagnosis and others during the 1st year after diagnosis. This heterogeneity may represent a bias. Another limitation was the impossibility from the database to cross the MRI and TB data at diagnosis. In consequence, the definition of positivity and negativity of the MRI were purely at imaging and not confirmed by TB data in the database. Moreover, differences of PI-RADS score version were not taken into account. However, all investigators said that in case of suspicious MRI, TBs were performed and results were taken into account to exclude patients who were at high risk. In addition, outcomes for primary and secondary endpoints differ between cohorts. The criteria for inclusion differ, and this was reported for our GAP3 Consortium [1]. The likelihood of suspicious MRI prompting treatment is also likely to differ between cohorts, as does the likelihood of men being offered or choosing AS for GG 2 disease. The time of follow-up was limited, and so mid- to long-term differences in oncological outcomes could not be evaluated. The heterogeneity of AS protocol and heterogeneity of included patients as described in previous papers may include a selection bias, but the prevalence of outcomes reported in our study are, therefore, likely more representative of the average PCa population [20].

## 5. Conclusions

The risk of switching to treatment, histological progression, and AS discontinuation are higher in cases of suspicious MRI at inclusion. This information should be shared with patients at inclusion.

**Author contributions:** Jonathan Olivier 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:* Olivier, Moore, Villers.

*Acquisition of data:* Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) Consortium.

*Analysis and interpretation of data:* Li, Nieboer, Denton.

*Drafting of the manuscript:* Olivier, Helleman, Villers.

*Critical revision of the manuscript for important intellectual content:* Roobol, Gnanapragasam, Frydenberg, Sugimoto, Carroll, Morgan, Valdagni, Rubio-Briones, Robert, Stricker, Hayen, Schoots, Haider, Moore.

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*Obtaining funding:* Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) Consortium.

*Administrative, technical, or material support:* Helleman.

*Supervision:* Villers.

*Other:* None.

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design, collection, analysis or interpretation of data, or in the drafting of this paper. For information, contact Dr. M.J. Roobol: m.roobol@erasmusmc.nl.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euros.2021.11.006>.

## References

- [1] Bruinsma SM, Bangma CH, Carroll PR, et al. Active surveillance for prostate cancer: a narrative review of clinical guidelines. *Nat Rev Urol* 2016;13:151–67.
- [2] Lam TBL, MacLennan S, Willemse P-P-M, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel consensus statements for deferred treatment with curative intent for localised prostate cancer from an international collaborative study (DETECTIVE study). *Eur Urol* 2019;76:790–813.
- [3] Ouzzane A, Renard-Penna R, Marliere F, et al. Magnetic resonance imaging targeted biopsy improves selection of patients considered for active surveillance for clinically low risk prostate cancer based on systematic biopsies. *J Urol* 2015;194:350–6.
- [4] Klotz L, Pond G, Loblaw A, et al. Randomized study of systematic biopsy versus magnetic resonance imaging and targeted and systematic biopsy in men on active surveillance (ASIST): 2-year postbiopsy follow-up. *Eur Urol* 2020;77:311–7.
- [5] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2021;79:243–62.
- [6] Bruinsma SM, Zhang L, Roobol MJ, et al. The Movember Foundation's GAP3 cohort: a profile of the largest global prostate cancer active surveillance database to date. *BJU Int* 2018;121:737–44.
- [7] Schoots IG. MRI in early prostate cancer detection: how to manage indeterminate or equivocal PI-RADS 3 lesions?. *Transl Androl Urol* 2018;7:70–82.
- [8] Bruinsma SM, Roobol MJ, Carroll PR, et al. Expert consensus document: Semantics in active surveillance for men with localized prostate cancer—results of a modified Delphi consensus procedure. *Nat Rev Urol* 2017;14:312–22.
- [9] Klein JP, Moeschberger ML. *Survival analysis: techniques for censored and truncated data*. ed. 2. New York, NY: Springer; 2003.
- [10] Mamawala MK, Meyer AR, Landis PK, et al. Utility of multiparametric magnetic resonance imaging in the risk stratification of men with grade group 1 prostate cancer on active surveillance. *BJU Int* 2020;125:861–6.
- [11] Stavrinides V, Giganti F, Trock B, et al. Five-year outcomes of magnetic resonance imaging-based active surveillance for prostate cancer: a large cohort study. *Eur Urol* 2020;78:443–51.
- [12] Gallagher KM, Christopher E, Cameron AJ, et al. Four-year outcomes from a multiparametric magnetic resonance imaging (MRI)-based active surveillance programme: PSA dynamics and serial MRI scans allow omission of protocol biopsies. *BJU Int* 2019;123:429–38.
- [13] Deniffel D, Salinas E, Ientilucci M, et al. Does the visibility of grade group 1 prostate cancer on baseline multiparametric magnetic resonance imaging impact clinical outcomes?. *J Urol* 2020;204:1187–94.
- [14] Hsiang W, Ghabili K, Syed JS, et al. Outcomes of serial multiparametric magnetic resonance imaging and subsequent biopsy in men with low-risk prostate cancer managed with active surveillance. *Eur Urol Focus* 2021;7:47–54.
- [15] Chu CE, Cowan JE, Lonergan PE, et al. Diagnostic accuracy and prognostic value of serial prostate multiparametric magnetic resonance imaging in men on active surveillance for prostate cancer. *Eur Urol Oncol*. In press. <https://doi.org/10.1016/j.euo.2020.11.007>.
- [16] Olivier J, Kasivisvanathan V, Drumez E, et al. Low-risk prostate cancer selected for active surveillance with negative MRI at entry: can repeat biopsies at 1 year be avoided? A pilot study. *World J Urol* 2019;37:253–9.
- [17] Thurtle D, Barrett T, Thankappan-Nair V, et al. Progression and treatment rates using an active surveillance protocol incorporating image-guided baseline biopsies and multiparametric magnetic resonance imaging monitoring for men with favourable-risk prostate cancer. *BJU Int* 2018;122:59–65.
- [18] Van Hemelrijck M, Ji X, Helleman J, et al. Reasons for discontinuing active surveillance: assessment of 21 centres in 12 countries in the Movember GAP3 Consortium. *Eur Urol* 2019;75:523–31.
- [19] Inoue LYT, Trock BJ, Partin AW, Carter HB, Etzioni R. Modeling grade progression in an active surveillance study. *Stat Med* 2014;33:930–9.
- [20] Kalapara AA, Verbeek JFM, Nieboer D, et al. Adherence to active surveillance protocols for low-risk prostate cancer: results of the Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance initiative. *Eur Urol Oncol* 2020;3:80–91.