Repeated MRIs during Active Surveillance: natural history of prostatic lesions and upgrading rates

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Abstract

Objectives:

To test upgrading rates in patients on Active Surveillance (AS) for prostate cancer (PCa) after serial multiparametric magnetic resonance imaging (mpMRI) scans.

Methods:

Retrospective analysis of 558 patients. Five different criteria of mpMRI progression were used: 1) PI-RADS score increase;2) lesion size increase;3) EPE score increase;4) overall mpMRI progression;5) number of criteria for mpMRI progression (0 vs. 1 vs. 2-3). Moreover, two definitions of PCa upgrading were evaluated:1) ISUP GG≥2 with >10% of pattern 4;2) ISUP GG≥3. The estimated annual percent changes (EAPC) methodology depicted temporal trends of mpMRI progression criteria. Sensitivity, specificity, positive predictive (PPV) and negative predictive value (NPV) of mpMRI progression criteria were analysed. Multivariable logistic regression models tested PCa upgrading rates.

Results:

Lower rates over time of all mpMRI progression criteria were observed. The NPV of serial mpMRIs spans from 90.5 to 93.5% (ISUP GG≥2 with >10% of pattern 4 PCa upgrading) and from 98 to 99% (ISUP GG≥3 PCa upgrading), according to the different

mpMRI progression criteria. A PSA-D cut-off of 0.15 ng/ml/ml sub stratified those patients who could skip a prostate biopsy. In multivariable logistic regression models testing PCa upgrading rates, all five mentioned mpMRI progression criteria achieved independent predictor status.

Conclusion:
During AS, approximately 27% of patients experience mpMRI progression at first repeated scan. However, the rates of mpMRI progression decrease over time at subsequent mpMRIs. Patients with stable mpMRI findings and with PSA-D<0.15 ng/ml/ml could safely skip surveillance biopsies. Conversely, patients who experience mpMRI progression should undergo a prostate biopsy.

Keywords: Active Surveillance; multiparametric magnetic resonance imaging; prostate biopsy; PI-RADS score; EPE score

1. Introduction

Active Surveillance (AS) protocols rely on repeated prostate biopsies to assess and monitor prostate cancer (PCa) progression (1). However, excessive and invasive surveillance testing may unnecessarily decrease compliance to AS, leading patients to switch to active treatment (AT) (2,3). To reduce the frequency of prostate samplings while simultaneously increase patient compliance, multiparametric magnetic resonance imaging (mpMRI) has been implemented in several AS series (4). However, it remains unclear whether mpMRI can safely replace repeated biopsies during follow-up (5,6). To date, conflicting results have been reported in previous analyses that tested the diagnostic accuracy of serial mpMRI scans in men on AS (7–17). However, most of these studies were limited by the low number of patients enrolled (7,8,13,15,16) or by the short follow-up time (9,15–17). Moreover, only few previous analyses focused on the natural history of mpMRI prostatic lesions over time and found a small annual growth rate in most of the cases (18,19).

This said, robust data from large, contemporary and homogeneous cohorts of AS patients followed with repeated mpMRI scans are urgently needed. We tried to give a first answer to fill this gap.

2. Materials and methods

2.1 Study population (Supplementary Figure 1)

This retrospective data analysis was approved by the Institutional Review Board of the European Institute of Oncology.

Overall, 961 patients with PCa were enrolled in AS between 2008 and 2020. AS inclusion criteria were the following: prostate specific antigen (PSA)≤10 ng/ml; clinical stage cT1c/cT2a; International Society of Urological Pathology Grade Group (ISUP GG) 1 PCa with ≤3 positive cores or ISUP GG2 PCa with pattern 4≤10% in a single core. AS protocol consisted of: repeated PSA testing every 6 months; clinical assessment every 12 months and repeated surveillance biopsies at 12, 36 and 84 months. From 2013, all patients underwent confirmatory mpMRI at AS begin and, eventually, targeted biopsies of all Prostate Imaging Reporting and Data System (PI-RADS) score ≥3 lesions (20–23). Moreover, repeated mpMRIs were performed before all surveillance targeted (PI-RADS≥3 lesions) or systematic (PI-RADS≤2 lesions) prostate biopsies. Additional prostate samplings or mpMRI scans were taken at any time according to clinician preference.

Patients were switched to AT due to: 1) ISUP GG upgrading (ISUP GG≥2 with >10% of pattern 4); 2) volume upstaging (>3 positive cores); 3) rising PSA; 4) patient preference. For final analyses, we excluded all patients that did not undergo confirmatory mpMRI at AS begin (n=268). Then, we selected only patients submitted to at least two consecutive mpMRI scans (n=558). This patient subgroup was used to study the natural history of mpMRI prostatic lesions over time. Finally, we excluded all patients that were lost at follow-up (n=101) or that were not submitted to surveillance prostate biopsies (n=93). Overall, 364 patients were used to test PCa upgrading rates.

2.2 mpMRI protocol

All mpMRI scans were performed on a 1.5-T scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany) with a phased-array coil. MpMRI protocol was compliant with the ESUR guidelines (22). Specifically, sagittal, coronal and axial T2- weighted images, axial diffusion weighted and dynamic axial T1-weighted images were obtained after injection of contrast agent. All images were analysed by three dedicated radiologists (GP, SA, PP) with, respectively, 6, 3 and 2 years of experience at study beginning. Suspicious lesions were scored according to PI-RADS v1 (2013-2015) (22) and PI-RADS v2 (2015-thereafter) guidelines (23). All mpMRIs performed at other centres were reviewed by our radiologists and, in case of low quality images, were repeated at our hospital.

2.3 Variables and outcomes of interest

Five different definitions of mpMRI progression were used (Supplementary Figures 2-3):

-PI-RADS score increase: 1) novel PI-RADS≥4 lesion in patients with PI-RADS≤3 lesions; 2) novel PI-RADS 5 lesion in patients with PI-RADS 4 lesions.

-Lesion size increase: enlargement of ≥3 mm (largest dimension).

-Extraprostatic extension (EPE) score, defined according to 2012 ESUR prostate MR Guidelines (22), increase: 1) novel EPE≥3 lesion in patients with EPE≤2 lesions; 2) novel EPE≥4 lesion in patients with EPE 3 lesions; 3) novel EPE 5 lesion in patients with EPE 4 lesions.

-Overall mpMRI progression (NO vs. YES): at least one criterion among PI-RADS score vs. Lesion size vs. EPE score increase.

-Number of mpMRI progression criteria (among PI-RADS score vs. Lesion size vs. EPE score increase): 0 vs. 1 vs. 2-3 criteria.

We focused on PCa upgrading rates on repeated surveillance biopsies. Two different definitions of PCa upgrading were used (24): 1) ISUP GG≥2 with >10% of pattern 4; 2) ISUP GG≥3.

2.4 Statistical analyses

Differences in medians and proportions were evaluated by, respectively, the Kruskal-Wallis and chi-square tests. First, temporal trends of mpMRI progression

criteria after repeated mpMRI scans were evaluated with the estimated annual percent changes (EAPC) methodology. Second, we tested sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the five mentioned mpMRI progression criteria. Third, multivariable logistic regression models tested PCa upgrading rates at surveillance biopsies.

R software environment was used in all statistical analyses and graphics (version 3.4.3). All tests were two sided with a level of significance set at $p<0.05$.

3. Results

3.1 Descriptive analyses (Table 1)

At AS begin, 250 (44.8%) vs. 176 (31.5%) vs. 125 (22.4%) vs. 7 (1.3%) men had PI-RADS score≤2 vs. 3 vs. 4 vs. 5 lesions, respectively. Moreover, 534 (95.7%) vs. 22 (3.9%) vs. 2 (0.4%) mpMRI lesions were EPE score≤2 vs. 3 vs. 4. Median (IQR: interquartile range) mpMRI lesion size was 8.5 (7-11) mm.

3.2 Natural history of mpMRI prostatic lesions

Median (IQR) follow-up time was 36 (23-52) months. Overall, 245 (43.9%) vs. 179 (32.1%) vs. 87 (15.6%) vs. 47 (8.4%) patients underwent 1 vs. 2 vs. 3 vs. 4 repeated mpMRI scans, respectively.

Lower rates over time of PI-RADS score increase (EAPC:-22.5%;p=0.03;Figure 1a), lesion size increase (EAPC:-33.5%;p=0.003;Figure 1b) and EPE score increase (EAPC:-35.5%;p=0.1; Figure 1c) were observed after serial (from 1 to 4) mpMRI scans. Moreover, lower rates of overall mpMRI progression (EAPC:-31.3%;p=0.004;Figure 1d) were recorded. Last, the percentage of 1 (EAPC:-35.7%;p=0.04) and 2-3 criteria (EAPC:-27%;p=0.02) for mpMRI progression decreased over time (Figure 1e).

3.3 Diagnostic accuracy of serial mpMRI scans

Of all 364 patients, 268 (73.6%) vs. 78 (21.4%) vs. 18 (4.9%) underwent 1 vs. 2 vs. ≥3 surveillance biopsies, respectively (Supplementary Table 1). Overall, 91 (25%) and 21 (5.8%) patients experienced ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading.

Rates of ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading according to the five different definitions of mpMRI progression are reported in Figure 2.

Sensitivity, specificity, PPV, NPV for PI-RADS score increase in predicting ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading were, respectively, 42%, 88%, 33%, 91.5% and 52%, 85.5%, 9.5%, 98% (Table 2). Sensitivity, specificity, PPV, NPV for lesion size increase in predicting ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading were, respectively, 46%, 82.5%, 37%, 91.5% and 62%, 80%, 8.5%, 98.5%. Sensitivity, specificity, PPV, NPV for EPE score increase in predicting ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading were, respectively, 27.5%, 96%, 50%, 90.5% and 33.5%, 94%, 14%, 98%. Last, sensitivity, specificity, PPV, NPV for overall

mpMRI progression in predicting ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading were, respectively, 61.5%, 78.5%, 28.5%, 93.5% and 66.5%, 74.5%, 7%, 99%.

3.4 Logistic regression models

In multivariable logistic regression models (Table 3a) predicting ISUP GG≥2 with >10% of pattern 4 PCa upgrading, PI-RADS score increase (Odds Ratio [OR]:1.12;p=0.002), lesion size increase (OR:1.06;p=0.04), EPE score increase (OR:1.34;p<0.001) and overall mpMRI progression (OR:1.22;p<0.001) achieved independent predictor status. Moreover, compared to 0 criteria, 1 (OR:1.12;p<0.001) and 2-3 (OR:1.34;p<0.001) criteria for mpMRI progression were associated with higher rates of PCa upgrading.

In multivariable logistic regression models (Table 3b) predicting ISUP GG≥3 PCa upgrading, PI-RADS score increase (Odds Ratio [OR]:1.04;p=0.04), lesion size increase (OR:1.03;p=0.03), EPE score increase (OR:1.07;p=0.004) and overall mpMRI progression (OR:1.05;p<0.001) achieved independent predictor status. Moreover, compared to 0 criteria, 2-3 (OR:1.11; p<0.001) criteria for mpMRI progression were associated with higher rates of PCa upgrading.

3.5 Repeated mpMRI scans, PSA-D and baseline PI-RADS score

ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3 PCa upgrading rates according to mpMRI progression criteria and PSA-D cut-off of 0.15 mg/ml/ml and 0.20 mg/ml/ml are, respectively displayed in Figure 3 and Supplementary Figure 4. Upgrading rates according to baseline PI-RADS score are depicted in Supplementary Figure 5.

4. Discussion

The vast majority of AS patients are reluctant to undergo repeated prostate samplings (3). Indeed, it was estimated that the compliance rate for prostate biopsies decreases over time (81%, 60%, 53% and 33% at 1, 4, 7 and 10 years, respectively) (2). MpMRI has been proposed as an alternative to monitor PCa progression (5,6). However, conflicting results have been previously observed in several AS cohorts that investigated the reliability of repeated mpMRI scans over time (7–17). Due to the lack of robust data to support the use of serial mpMRIs during AS, we tested mpMRI diagnostic accuracy in the largest series to date (n=558) of AS patients submitted to confirmatory mpMRI at AS begin and followed with repeated scheduled mpMRI scans. Specifically, we analysed five different criteria of mpMRI progression: 1) PI-RADS score increase, 2) lesion size increase, 3) EPE score increase, 4) overall mpMRI progression, 5) number of mpMRI progression criteria. Our results showed several important findings.

First, we focused on the natural history of mpMRI prostatic lesions after serial repeated mpMRI scans during AS (from 1 to 4). Here, we observed lower rates over time of all five mentioned criteria for mpMRI progression. To the best of our knowledge, these results were not previously reported in none of the mentioned AS series. Conversely, our findings are consistent with three previous reports that focused on the natural history of mpMRI suspicious lesions (no AS setting) (25–27), which confirmed that overall changes in size and PI-RADS score over time are infrequent. Our results should be used for patient counselling and for optimizing AS interval imaging follow-up. Specifically, patients should be informed about the 27% probability of overall mpMRI progression at first repeated scan. Moreover, the observed lower rates of progression at subsequent mpMRIs (from 2 to 4) should discourage the use of too frequent repeated mpMRIs during follow-up. Our results are supported by the use of trend analyses (EAPC) that were, to the best our knowledge, not previously reported. This said, the observed trends over time could be a product of the definitions used for the five mentioned criteria of mpMRI progression. However, it should be stated that these definitions are consistent with other analyses that focused on the same topic (7,10).

Second, we tested the ability of serial mpMRI scans to exclude PCa progression during AS. To not overestimate the diagnostic accuracy of mpMRI, we analysed only patients submitted to repeated surveillance biopsies during follow-up (n=364) and we used two different definitions of PCa upgrading, as previously reported by Gandaglia et

al. (24). We observed that the NPV of serial mpMRIs spans from 90.5 to 93.5% (ISUP GG≥2 with >10% of pattern 4 PCa upgrading) and from 98 to 99% (ISUP GG≥3 PCa upgrading), according to the different criteria used for mpMRI progression. PSA-D provided other important information in this patient category. Specifically, patients without mpMRI progression (regardless of mpMRI criteria used) and with PSA-D levels<0.15 ng/ml/ml could safely skip surveillance biopsies, since only 4-5% (ISUP GG≥2 with >10% of pattern 4 PCa upgrading) and 1-2% (ISUP GG≥3 PCa upgrading) of them exhibit PCa progression. Our data are consistent with other previous analyses that tested the NPV of mpMRI to exclude csPCa (28) and the ability of PSA-D to sub stratify those patients who require a prostate biopsy (29,30). Moreover, our results support other previous retrospective series (8,11,12) and the recently published MRIAS trial (10) that suggested the possibility to omit surveillance biopsies in patients with stable mpMRI findings during AS. However, our results also contrast other previous analyses in which mpMRI alone resulted insufficient to detect grade reclassification during AS (7,9,13,14,16). Our findings are supported by the non-negligible follow-up time (median: 36 months) and by the use of five different definitions for mpMRI progression. This said, it should be stated that our analysis is biased by its retrospective and single-centre nature. In consequence, results from other multi-institutional and, ideally, prospective studies are needed before recommending AS programs modifications.

Third, we then tested the ability of serial mpMRI scans to predict PCa progression during AS. Again, to not underestimate the diagnostic accuracy of mpMRI, we restricted our analysis to patients submitted to repeated surveillance biopsies during follow-up (n=364). Here, we observed that all mentioned criteria for mpMRI progression achieved independent predictor status in multivariable logistic regression models predicting PCa upgrading at surveillance biopsies. Moreover, we tested for dose-response and we confirmed that an increasing number of mpMRI progression criteria (0 vs. 1 vs. 2-3) is directly proportional to the magnitude of the two examined endpoints. Despite the use of multivariable models, that were fully adjusted for all available patient and tumor characteristics, we cannot recommend immediate switch to AT in those patients who experience mpMRI progression during AS. Specifically, the PPV of serial mpMRIs spans from 33 to 50% (ISUP GG≥2 with >10% of pattern 4 PCa upgrading) and from 7 to 14% (ISUP GG≥3 PCa upgrading), according to the different criteria used for mpMRI progression. In consequence, mpMRI progression should only be considered a trigger

for immediate re-biopsy and not a valid criterion for discontinuing AS, as previously suggested by all other AS series (7–9,11–17).

Taken together, we provided robust data to support the use of repeated mpMRI scans during AS and to optimize interval imaging follow-up. First, we demonstrated that approximately 27% of patients experience mpMRI progression at first repeated scan. However, too frequent repeated mpMRIs during follow-up should be discouraged. Second, we demonstrated that patients without mpMRI progression and with PSA-D levels<0.15 ng/ml/ml could safely avoid prostate biopsies. Third, we also demonstrated that mpMRI progression should only be considered a trigger for immediate re-biopsy and not a valid criterion for discontinuing AS. This said, it should be stated that our results were obtained after excluding patients that did not undergo repeated prostate biopsies during AS. Specifically, 101 (52%) men were lost at follow-up after performing baseline mpMRI and a single repeated mpMRI scan at 12 months after AS begin. Moreover, the remaining 93 (48%) patients underwent only repeated mpMRI scans during follow-up, but were not submitted to repeated prostate biopsies due to patient/clinician preference. Specifically, 56 (60%) vs. 27 (29%) vs. 10 (11%) of them underwent 2 vs. 3 vs. 4 repeated mpMRIs and, of those, 4 (4.3%) men were switched to AT. In consequence, over-/underestimation of the accuracy of repeated mpMRI scans during AS could not be excluded.

Despite its novelty our study has limitations. First, the current data are retrospective and influenced by inherent selection bias. Second, as previously stated, our results could be a product of the definitions used for mpMRI progression. Moreover, we did not rely on the PRECISE criteria for documenting changes in MRI findings during AS, as recently published (8,11,16,17,31–33). However, previous analyses that tested the reliability of the PRECISE criteria in men on AS showed discordant results (11,12,16,17). Third, we scored suspicious lesions according to PI-RADS v1 (2013-2015) and PI-RADS v2 (2015-thereafter) (22,23). Although this limitation could have generated heterogeneity of the data, it represents daily practice. Fourth, we tested only two commonly used PSA-D cut-offs, namely 0.15 and 0.2 ng/ml/ml. In consequence, other analyses should test the most accurate PSA-D threshold for recommending prostate biopsies in men on AS (29). Fifth, we were unable to distinguish PCa progressions within and without the target. Sixth, we did not rely on other scales, rather than the one proposed by the ESUR prostate MRI Guidelines (22), to assess the probability of EPE (34–36). Seventh, we used specific AS

inclusion criteria. Moreover, all mpMRI scans were evaluated by expert radiologists (37) and, in consequence, no low quality images were taken into account. Therefore, external validation of our findings is urgently needed.

5. Conclusion

During AS, approximately 27% of patients experience mpMRI progression at first repeated scan. However, the rates of mpMRI progression decrease over time at subsequent mpMRIs. Patients with stable mpMRI findings and with PSA-D<0.15 ng/ml/ml could safely skip surveillance biopsies. Conversely, patients who experience mpMRI progression should undergo a prostate biopsy.

Conflicts of interest: None

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Figure legends

Figure 1: Temporal trends of mpMRI progression criteria in 558 AS patients enrolled between 2008 and 2020.

a) PI-RADS score
b) Lesion size
c) EPE score
d) Overall mpMRI progression
e) Number of criteria for mpMRI progression

EAPC: estimated annual percent change
CI: confidence interval
mpMRI: multiparametric magnetic resonance imaging
PI-RADS: Prostate Imaging Reporting and Data System
EPE: extraprostatic extension.

Figure 2: Barplots depicting prostate cancer upgrading rates at repeated biopsies (ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3), according to mpMRI progression criteria, in 364 AS patients enrolled between 2008 and 2020.

a) PI-RADS score
b) Lesion size
c) EPE score
d) Overall mpMRI progression
e) Number of criteria for mpMRI progression

EAPC: estimated annual percent change
CI: confidence interval
mpMRI: multiparametric magnetic resonance imaging
ISUP GG: International Society of Urological Pathology grade group
PI-RADS: Prostate Imaging Reporting and Data System
EPE: extraprostatic extension

Figure 3: Barplots depicting prostate cancer upgrading rates at repeated biopsies (ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3), according to mpMRI progression criteria and PSAD (cut-off: 0.15 ng/ml/ml), in 364 AS patients enrolled between 2008 and 2020.

a) PI-RADS score
b) Lesion size
c) EPE score
d) Overall mpMRI progression
e) Number of criteria for mpMRI progression

EAPC: estimated annual percent change
CI: confidence interval
mpMRI: multiparametric magnetic resonance imaging
PSAD: Prostate Specific Antigen density
ISUP GG: International Society of Urological Pathology grade group
PI-RADS: Prostate Imaging Reporting and Data System

EPE: extraprostatic extension

Supplementary Figure 1: Consort Diagram with inclusion and exclusion criteria.

AS: Active Surveillance

PSA: Prostate Specific Antigen

cT: clinical T stage

mpMRI: multiparametric magnetic resonance imaging

ISUP GG: International Society of Urological Pathology grade group

Supplementary Figure 2: A 63 years old patient that was diagnosed with single core positive for ISUP GG1 prostate cancer. Baseline mpMRI showed a 6 mm PI-RADS score 4, EPE score 2 lesion in the PZ of the prostate, right side, at the level of the base. This lesion remained stable at a second mpRMI that was perfomed after 1 year of AS.

A) T2- weighted images of baseline mpMRI
B) ADC map of baseline mpMRI
C) T2- weighted images of repeated mpMRI
D) ADC map of repeated mpMRI

AS: Active Surveillance

mpMRI: multiparametric magnetic resonance imaging

ISUP GG: International Society of Urological Pathology grade group

PI-RADS: Prostate Imaging Reporting and Data System

EPE: extraprostatic extension

PZ: peripheral zone

ADC: apparent diffusion coefficient

Supplementary Figure 3: A 66 years old patient that was diagnosed with 3 cores positive for ISUP GG1 prostate cancer. Baseline mpMRI showed a 5 mm PI-RADS score 4, EPE score 1 lesion in the PZ of the prostate, right side, medium/base level. This lesion experienced radiological progression at a second mpMRI that was perfomed after 1 year of AS (23 mm, PI-RADS score 5, EPE score 4).

A) T2- weighted images of baseline mpMRI
B) ADC map of baseline mpMRI
C) T2- weighted images of repeated mpMRI

D) ADC map of repeated mpMRI

AS: Active Surveillance
mpMRI: multiparametric magnetic resonance imaging
ISUP GG: International Society of Urological Pathology grade group
PI-RADS: Prostate Imaging Reporting and Data System
EPE: extraprostatic extension
PZ: peripheral zone
ADC: apparent diffusion coefficient

Supplementary Figure 4: Barplots depicting prostate cancer upgrading rates at repeated biopsies (ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3), according to mpMRI progression criteria and PSAD (cut-off: 0.2 ng/ml/ml), in 364 AS patients enrolled between 2008 and 2020.

a) PI-RADS score
b) Lesion size
c) EPE score
d) Overall mpMRI progression
e) Number of criteria for mpMRI progression

EAPC: estimated annual percent change
CI: confidence interval
mpMRI: multiparametric magnetic resonance imaging
PSAD: Prostate Specific Antigen density
ISUP GG: International Society of Urological Pathology grade group
PI-RADS: Prostate Imaging Reporting and Data System
EPE: extraprostatic extension

Supplementary Figure 5: Barplots depicting prostate cancer upgrading rates at repeated biopsies (ISUP GG≥2 with >10% of pattern 4 and ISUP GG≥3), according to overall mpMRI progression (NO vs. YES), in 364 AS patients enrolled between 2008 and 2020, according to baseline PI-RADS score.

AS: Active Surveillance

mpMRI: multiparametric magnetic resonance imaging

ISUP GG: International Society of Urological Pathology grade group

PI-RADS: Prostate Imaging Reporting and Data System

Table 1 Clinical characteristics and mpMRI findings at AS begin of 558 patients enrolled between 2008 and 2020. Data are shown as medians for continuous variables or as counts and percentages (%) for categorical variables.

	Overall (n = 558)
Age (years)	63 (58-69)
Median (IQR)	
PSA (ng/ml)	5.9 (4.5-7.8)
Median (IQR)	
PSAD (ng/ml/ml)	0.1 (0.1-0.2)
Median (IQR)	
cT	
cT1c	518 (92.8)
cT2a	40 (7.2)
Diagnostic biopsy cores	14 (12-16)
Median (IQR)	
Diagnostic biopsy positive cores	
1	331 (59.3)
2	144 (25.8)
3	83 (14.9)
ISUP GG	
1	537 (96.2)
2	21 (3.8)
Number of PNBs	
0	452 (81)
1	72 (12.9)
≥2	34 (6.1)
Prostate volume (ml)	
Median (IQR)	50 (37-68)
PI-RADS score	
≤2	250 (44.8)
3	176 (31.5)
4	125 (22.4)
5	7 (1.3)
Lesion size (mm)	8.5 (7-11)
Median (IQR)	
EPE score	
≤2	534 (95.7)

3	22 (3.9)
4	2 (0.4)
5	0 (0)

AS: active surveillance; IQR: interquartile range; PSA: prostate specific antigen; PSAD: prostate specific antigen density; cT: clinical T stage; mpMRI: multiparametric magnetic resonance imaging; ISUP GG: International Society of Urological Pathology grade group; PNBs: previous negative biopsies; PI-RADS: Prostate Imaging Reporting and Data System; EPE: extraprostatic extension.

Table 2. Diagnostic accuracy (sensitivity, specificity, PPV and NPV) of repeated mpMRI scans during follow-up in 364 AS patients enrolled between 2008 and 2020.

ISUP GG≥2 pattern 4>10%	**PI-RADS score increase**	**Lesion size increase**	**EPE score increase**	**Overall mpMRI progression**
Sensitivity	42%	46%	27.5%	61.5%
Specificity	88%	82.5%	96%	78.5%
PPV	33%	37%	50%	28.5%
NPV	91.5%	91.5%	90.5%	93.5%
ISUP GG≥3	**PI-RADS score increase**	**Lesion size increase**	**EPE score increase**	**Overall mpMRI progression**
Sensitivity	52%	62%	33.5%	66.5%
Specificity	85.5%	80%	94%	74.5%
PPV	9.5%	8.5%	14%	7%
NPV	98%	98.5%	98%	99%

AS: active surveillance; mpMRI: multiparametric magnetic resonance imaging; PPV: positive predictive value; NPV: negative predictive value; ISUP GG: International Society of Urological Pathology grade group; PI-RADS: Prostate Imaging Reporting and Data System; EPE: extra-prostatic extension.

Table 3

a Separate multivariable logistic regression models predicting prostate cancer upgrading (ISUP GG≥2 with >10% of pattern 4) at surveillance biopsies in 364 AS patients enrolled between 2008 and 2020 and according to mpMRI progression criteria. All models are adjusted for patient clinical characteristics at surveillance biopsies: age (years), PSAD (ng/ml/ml), cT (cT1 vs. cT2/3), ISUP GG at biopsy (1 vs. 2).

ISUP GG≥2 with >10% of pattern 4 upgrading		
	Odds Ratio (OR) [95% CI]	p value
PI-RADS score		
stable	Ref.	
increase	1.12 (1.04-1.21)	0.002
decrease	0.94 (0.85-1.03)	0.2
Lesion size		
stable	Ref.	
increase	1.06 (1.00-1.14)	0.04
decrease	0.99 (0.93-1.06)	0.9
EPE score		
stable	Ref.	
increase	1.34 (1.22-1.48)	<0.001
decrease	1.22 (1.04-1.43)	0.01
PSAD (ng/ml/ml)	1.21 (1.01-1.50)	0.03
Age (years)	0.99 (0.99-1.00)	0.7
cT stage		
cT1	Ref.	
cT2/3	1.16 (0.91-1.38)	0.1
ISUP GG at biopsy		
I	Ref.	
II	1.05 (0.94-1.16)	0.4
Overall mpMRI progression (yes vs. no)	1.22 (1.16-1.29)	<0.001
PSAD (ng/ml/ml)	1.32 (1.07-1.64)	0.008
Age (years)	0.99 (0.99-1.00)	0.7
cT stage		
cT1	Ref.	
cT2/3	1.18 (0.94-1.46)	0.1
ISUP GG at biopsy		
I	Ref.	

II	1.07 (0.96-1.19)	0.2
N° criteria for mpMRI progression		
0	Ref.	
1	1.12 (1.05-1.20)	<0.001
2	1.34 (1.25-1.43)	<0.001
PSAD (ng/ml/ml)	1.32 (1.07-1.62)	0.009
Age (years)	1.00 (0.99-1.00)	0.9
cT stage		
cT1	Ref.	
cT2/3	1.16 (0.92-1.39)	0.2
ISUP GG at biopsy		
I	Ref.	
II	1.07 (0.97-1.19)	0.2

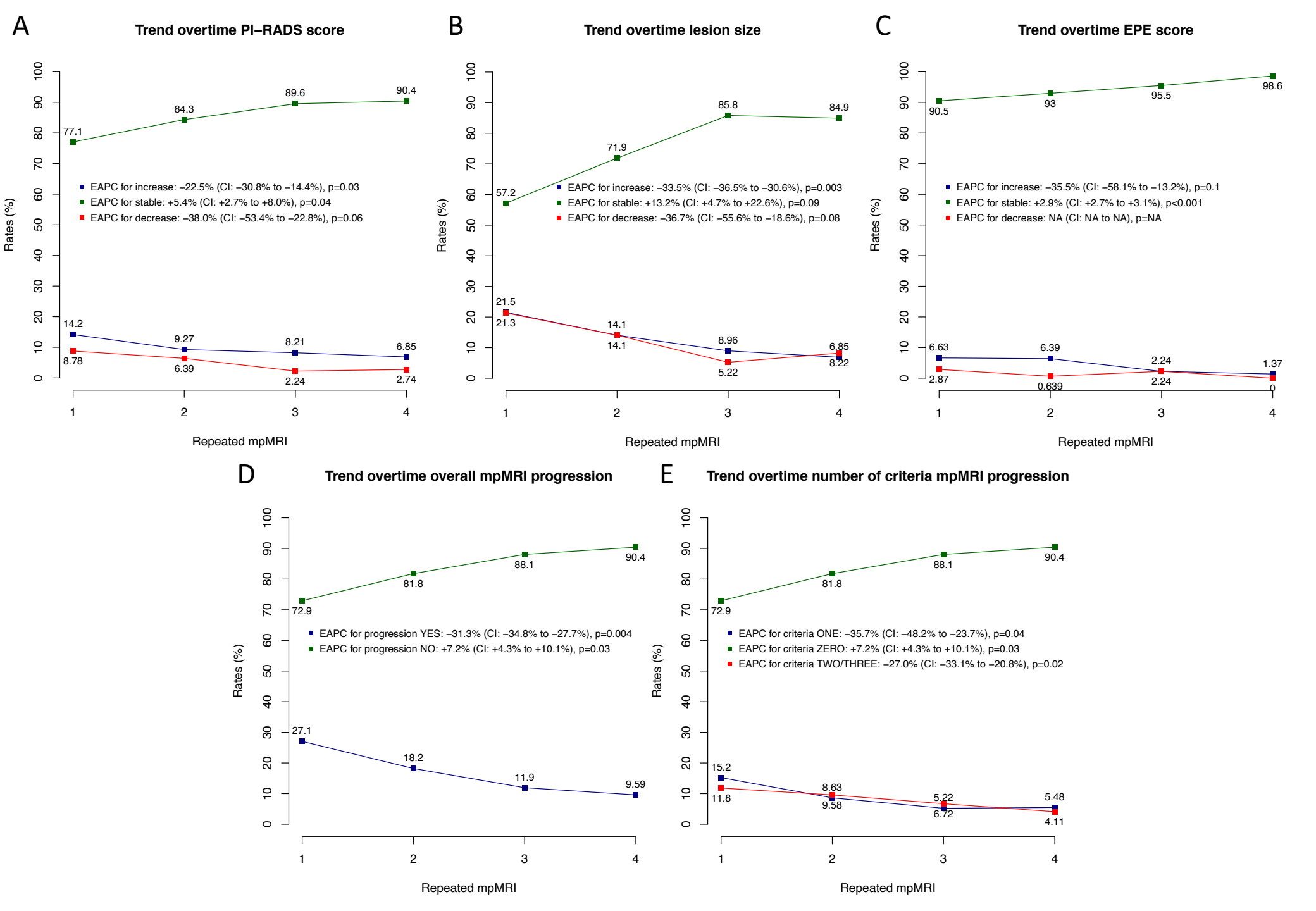
b Separate multivariable logistic regression models predicting prostate cancer upgrading (ISUP GG≥3) at surveillance biopsies in 364 AS patients enrolled between 2008 and 2020 and according to mpMRI progression criteria. All models are adjusted for patient clinical characteristics at surveillance biopsies: age (years), PSAD (ng/ml/ml), cT (cT1 vs. cT2/3), ISUP GG at biopsy (1 vs. 2).

	ISUP GG≥3 upgrading	
	Odds Ratio (OR) [95% CI]	p value
PI-RADS score		
stable	Ref.	
increase	1.04 (1.00-1.08)	0.04
decrease	1.01 (0.96-1.06)	0.5
Lesion size		
stable	Ref.	
increase	1.03 (1.00-1.07)	0.03
decrease	1.00 (0.96-1.03)	0.9
EPE score		
stable	Ref.	
increase	1.07 (1.02-1.13)	0.004
decrease	1.04 (0.95-1.13)	0.3
PSAD (ng/ml/ml)	1.08 (1.00-1.16)	0.05
Age (years)	1.00 (0.99-1.00)	0.4
cT stage		
cT1	Ref.	
cT2/3	1.03 (0.88-1.17)	0.3
ISUP GG at biopsy		
I	Ref.	
II	1.08 (1.02-1.14)	0.005
Overall mpMRI progression (yes vs. no)	1.05 (1.02-1.08)	<0.001
PSAD (ng/ml/ml)	1.07 (0.99-1.19)	0.06
Age (years)	1.00 (0.99-1.00)	0.3
cT stage		
cT1	Ref.	
cT2/3	1.04 (0.90-1.21)	0.3
ISUP GG at biopsy		
I	Ref.	
II	1.08 (1.02-1.14)	0.002

N° criteria for mpMRI progression

0	Ref.	
1	1.00 (0.96-1.03)	0.8
2	1.11 (1.07-1.15)	<0.001
PSAD (ng/ml/ml)	1.07 (1.01-1.17)	0.04
Age (years)	1.00 (0.99-1.00)	0.2
cT stage		
cT1	Ref.	
cT2/3	1.03 (0.88-1.17)	0.2
ISUP GG at biopsy		
I	Ref.	
II	1.08 (1.03-1.14)	0.002

AS: active surveillance; PSAD: prostate specific antigen density; cT: clinical T stage; mpMRI: multiparametric magnetic resonance imaging; ISUP GG: International Society of Urological Pathology grade group; PI-RADS: Prostate Imaging Reporting and Data System; EPE: extra-prostatic extension. CI: confidence interval.


A
Trend overtime PI−RADS score
Rates (%)
Repeated mpMRI
EAPC for increase: −22.5% (CI: −30.8% to −14.4%), p=0.03
EAPC for stable: +5.4% (CI: +2.7% to +8.0%), p=0.04
EAPC for decrease: −38.0% (CI: −53.4% to −22.8%), p=0.06
77.1
84.3
89.6
90.4
14.2
9.27
8.21
6.85
8.78
6.39
2.24
2.74
B
Trend overtime lesion size
Rates (%)
Repeated mpMRI
EAPC for increase: −33.5% (CI: −36.5% to −30.6%), p=0.003
EAPC for stable: +13.2% (CI: +4.7% to +22.6%), p=0.09
EAPC for decrease: −36.7% (CI: −55.6% to −18.6%), p=0.08
57.2
71.9
85.8
84.9
21.5
21.3
14.1
14.1
8.96
5.22
6.85
8.22
C
Trend overtime EPE score
Rates (%)
Repeated mpMRI
EAPC for increase: −35.5% (CI: −58.1% to −13.2%), p=0.1
EAPC for stable: +2.9% (CI: +2.7% to +3.1%), p<0.001
EAPC for decrease: NA (CI: NA to NA), p=NA
90.5
93
95.5
98.6
6.63
6.39
2.24
1.37
2.87
0.639
2.24
0
D
Trend overtime overall mpMRI progression
Rates (%)
Repeated mpMRI
EAPC for progression YES: −31.3% (CI: −34.8% to −27.7%), p=0.004
EAPC for progression NO: +7.2% (CI: +4.3% to +10.1%), p=0.03
72.9
81.8
88.1
90.4
27.1
18.2
11.9
9.59
E
Trend overtime number of criteria mpMRI progression
Rates (%)
Repeated mpMRI
EAPC for criteria ONE: −35.7% (CI: −48.2% to −23.7%), p=0.04
EAPC for criteria ZERO: +7.2% (CI: +4.3% to +10.1%), p=0.03
EAPC for criteria TWO/THREE: −27.0% (CI: −33.1% to −20.8%), p=0.02
72.9
81.8
88.1
90.4
15.2
11.8
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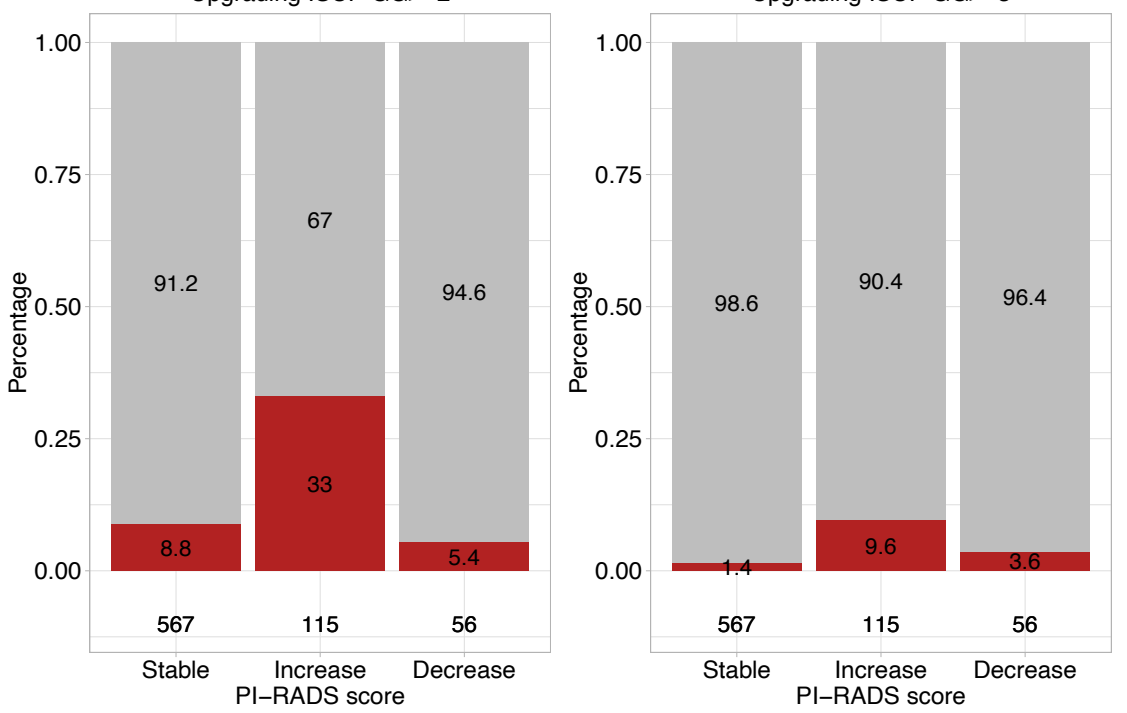
9.58
5.22
6.72
5.48
4.11

A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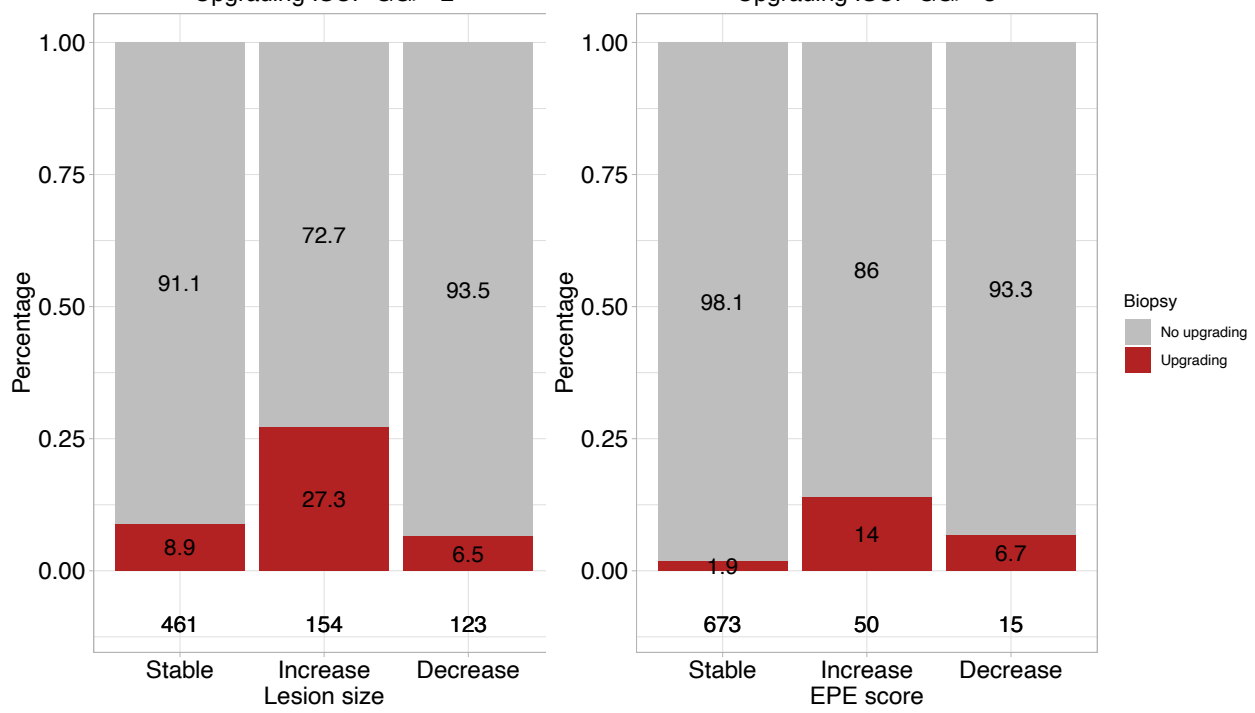
67
33
94.6
5.4
98.6
1.4
90.4
9.6
96.4
3.6
567
115
56
Stable
Increase
Decrease
PI–RADS score
Biopsy
No upgrading
Upgrading

B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0.00
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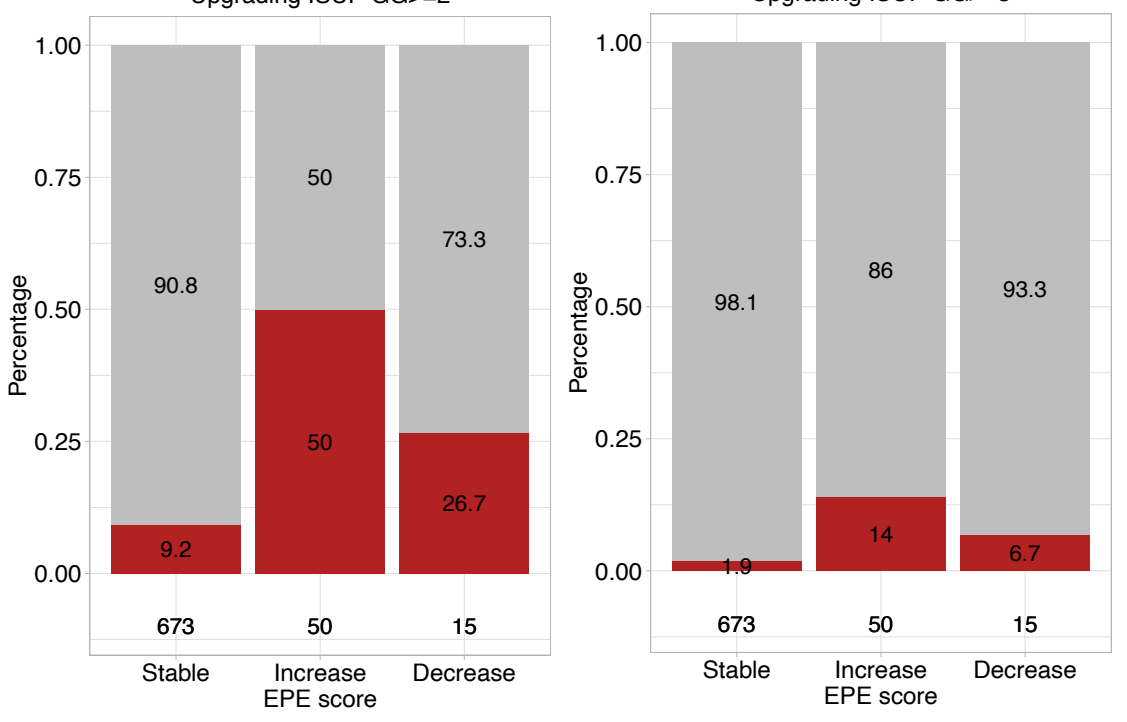
8.9
72.7
27.3
93.5
6.5
98.1
1.9
86
14
93.3
6.7
461
154
123
673
50
15
Stable
Increase
Decrease
Lesion size
EPE score
Biopsy
No upgrading
Upgrading

C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Upgrading ISUP GG>=3
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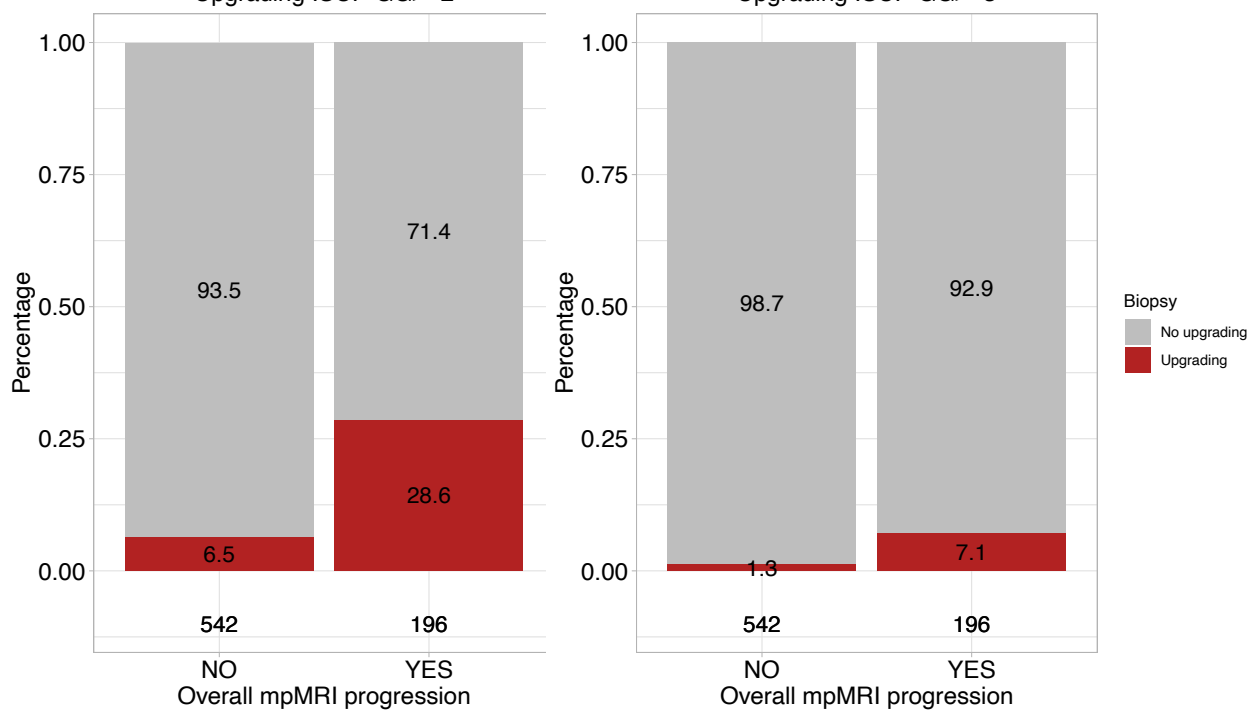
50
50
73.3
26.7
98.1
1.9
86
14
93.3
6.7
673
50
15
Stable
Increase
Decrease
EPE score
Biopsy
No upgrading
Upgrading

D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Upgrading ISUP GG>=3
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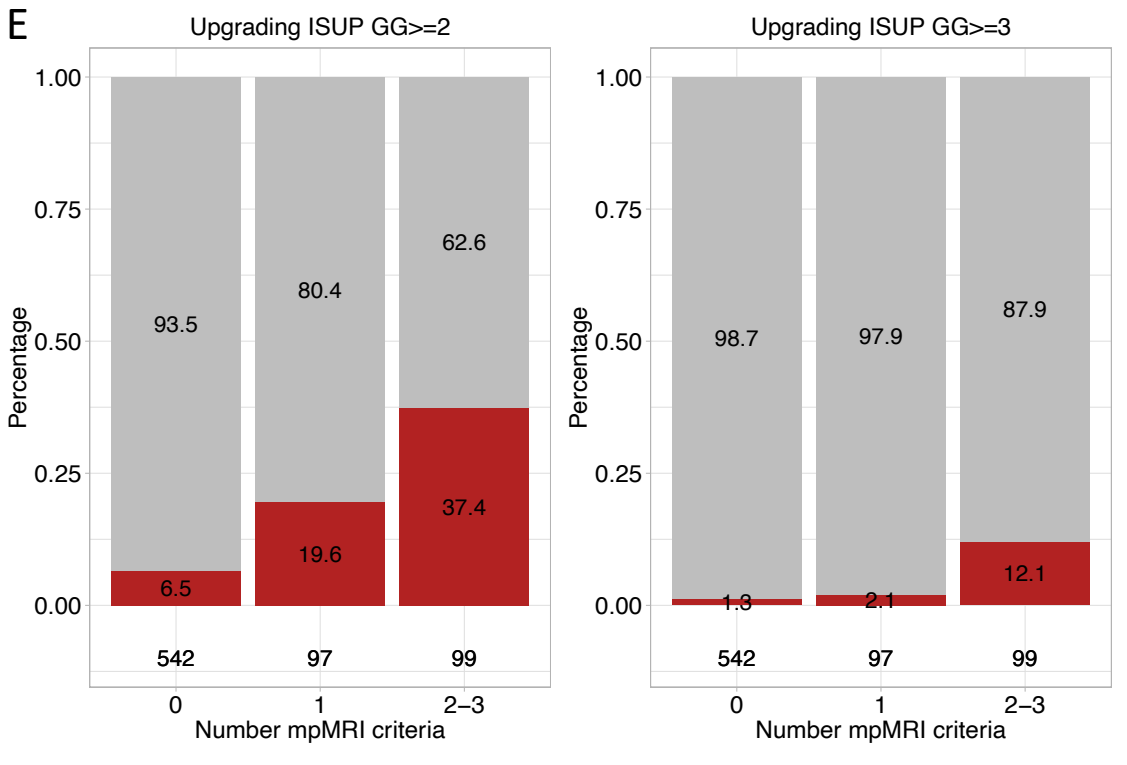
0.50
0.25
0.00
93.5
6.5
71.4
28.6
98.7
1.3
92.9
7.1
542
196
NO
YES
Overall mpMRI progression
Biopsy
No upgrading
Upgrading

E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Upgrading ISUP GG>=3
Percentage
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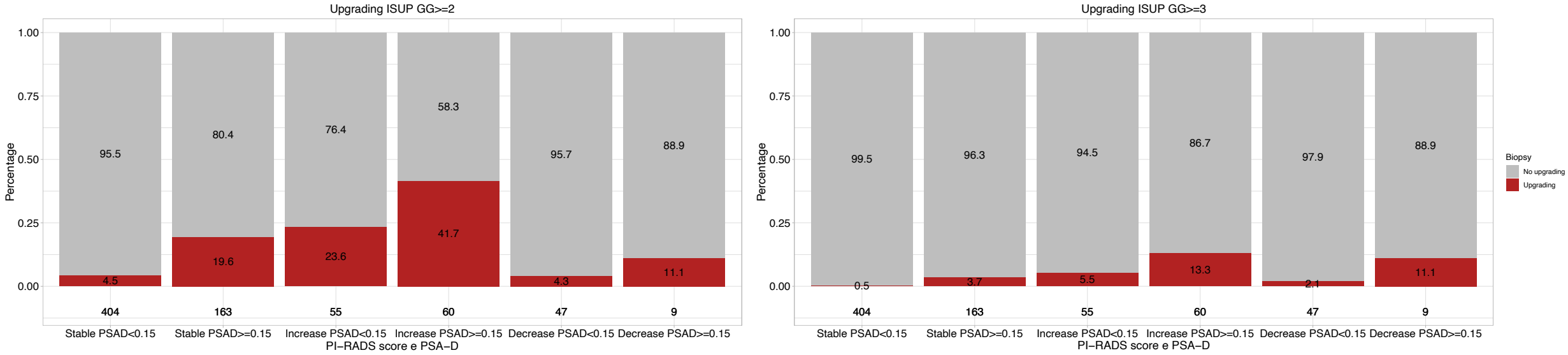
0.50
0.25
0.00
93.5
6.5
80.4
19.6
62.6
37.4
98.7
1.3
97.9
2.1
87.9
12.1
542
97
99
0
1
2–3
Number mpMRI criteria
Biopsy
No upgrading
Upgrading

A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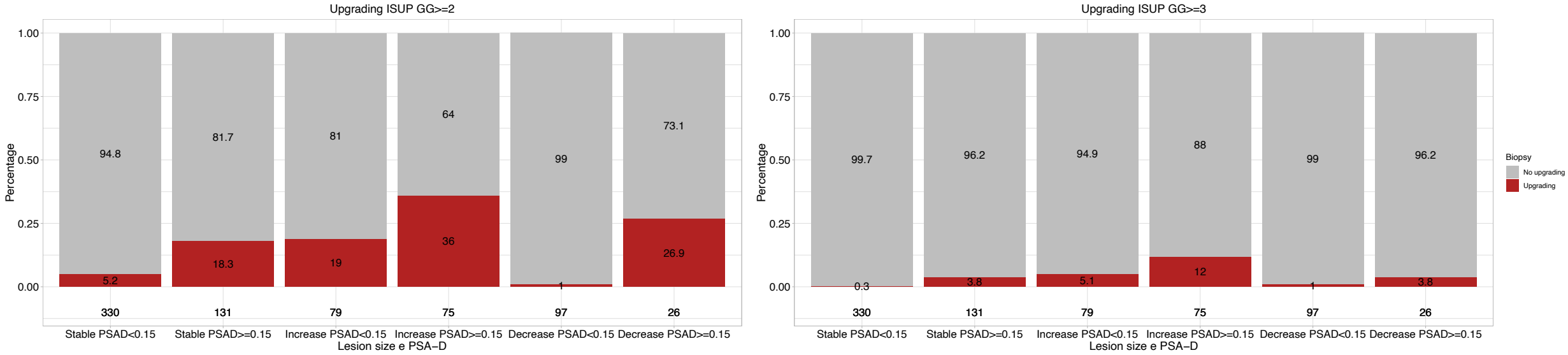
0.50
0.25
0.00
95.5
4.5
80.4
19.6
76.4
23.6
58.3
41.7
95.7
4.3
88.9
11.1
99.5
0.5
96.3
3.7
94.5
5.5
86.7
13.3
97.9
2.1
88.9
11.1
404
163
55
60
47
9
Stable PSAD<0.15
Stable PSAD>=0.15
Increase PSAD<0.15
Increase PSAD>=0.15
Decrease PSAD<0.15
Decrease PSAD>=0.15
PI−RADS score e PSA−D
Biopsy
No upgrading
Upgrading

B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Upgrading ISUP GG>=3
Percentage
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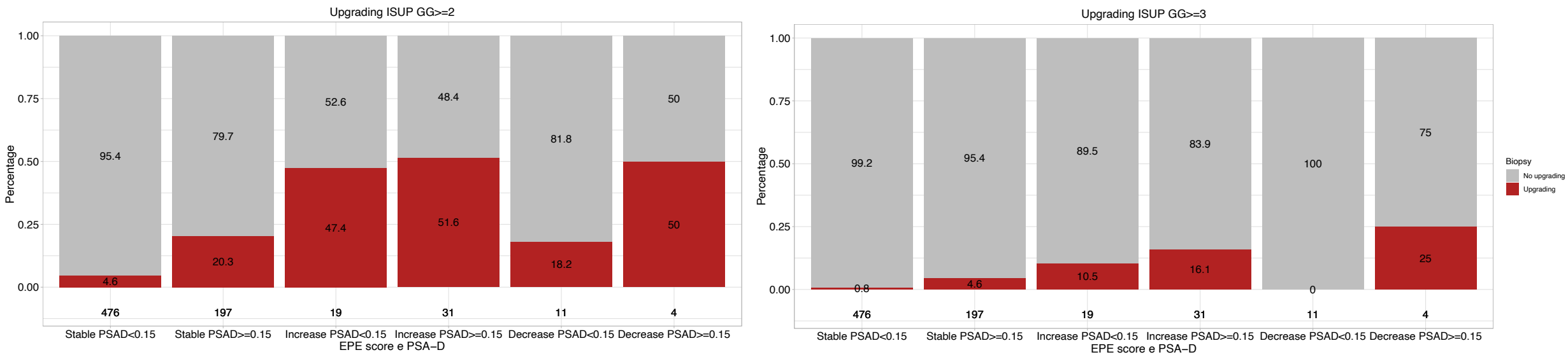
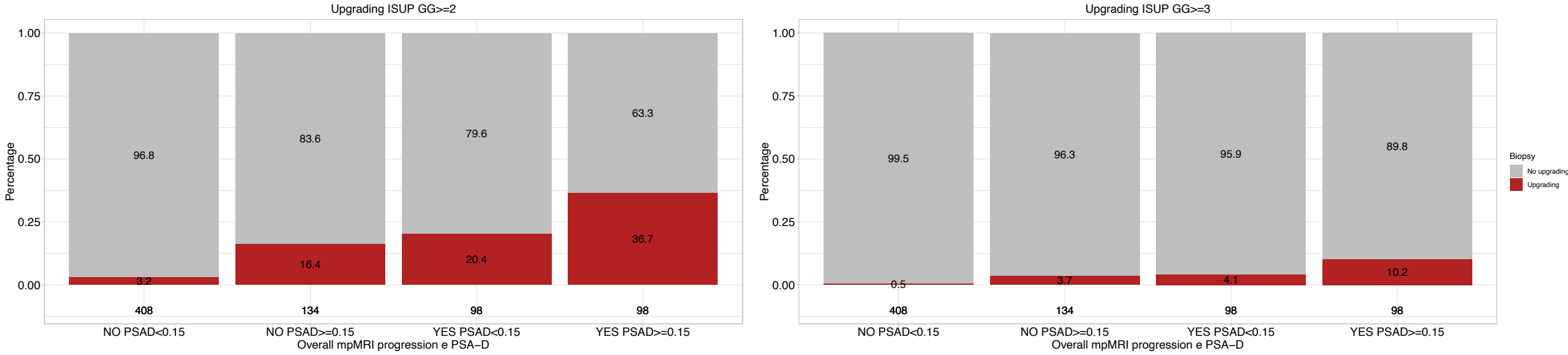
0.75
0.50
0.25
0.00
94.8
5.2
81.7
18.3
81
19
64
36
99
1
73.1
26.9
99.7
0.3
96.2
3.8
94.9
5.1
88
12
99
1
96.2
3.8
330
131
79
75
97
26
Stable PSAD<0.15
Stable PSAD>=0.15
Increase PSAD<0.15
Increase PSAD>=0.15
Decrease PSAD<0.15
Decrease PSAD>=0.15
Lesion size e PSA−D
Biopsy
No upgrading
Upgrading

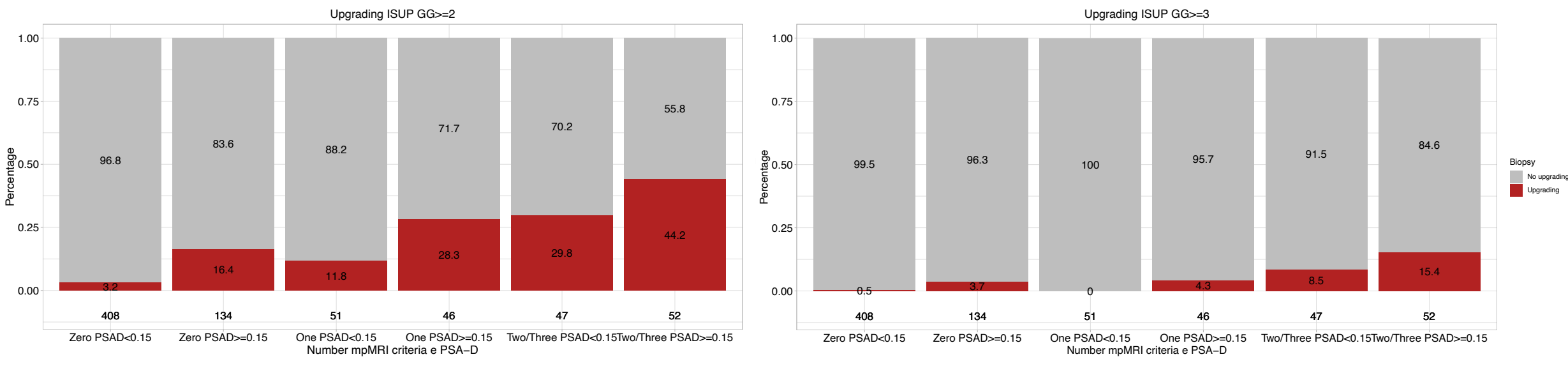
C


Upgrading ISUP GG>=2
Upgrading ISUP GG>=3
Percentage
1.00
0.75
0.50
0.25
0.00
95.4
4.6
79.7
20.3
52.6
47.4
48.4
51.6
81.8
18.2
50
50
99.2
0.8
95.4
4.6
89.5
10.5
83.9
16.1
100
0
75
25
476
197
19
31
11
4
Stable PSAD<0.15
Stable PSAD>=0.15
Increase PSAD<0.15
Increase PSAD>=0.15
Decrease PSAD<0.15
Decrease PSAD>=0.15
EPE score e PSA−D
Biopsy
No upgrading
Upgrading

D


Upgrading ISUP GG>=2
Upgrading ISUP GG>=3
Percentage
1.00
0.75
0.50
0.25
0.00
96.8
3.2
83.6
16.4
79.6
20.4
63.3
36.7
99.5
0.5
96.3
3.7
95.9
4.1
89.8
10.2
408
134
98
98
NO PSAD<0.15
NO PSAD>=0.15
YES PSAD<0.15
YES PSAD>=0.15
Overall mpMRI progression e PSA−D
Biopsy
No upgrading
Upgrading

E


Upgrading ISUP GG>=2
Upgrading ISUP GG>=3
Percentage
1.00
0.75
0.50
0.25
0.00
96.8
3.2
83.6
16.4
88.2
11.8
71.7
28.3
70.2
29.8
55.8
44.2
99.5
0.5
96.3
3.7
100
0
95.7
4.3
91.5
8.5
84.6
15.4
408
134
51
46
47
52
Zero PSAD<0.15
Zero PSAD>=0.15
One PSAD<0.15
One PSAD>=0.15
Two/Three PSAD<0.15
Two/Three PSAD>=0.15
Number mpMRI criteria e PSA−D
Biopsy
No upgrading
Upgrading

Prescribing information and adverse event reporting information can be found at the bottom of this page

PROSTATE CANCER QUESTION HOUR

RCT to RWE: The evolution of non-metastatic castration-resistant prostate cancer treatment

Thursday 2 December 2021
18:00–19:00 GMT

REGISTER HERE FOR THIS PROMOTIONAL WEBINAR

Please join us for what promises to be a highly informative event, featuring a faculty of top international experts:

Professor Heather Payne,
Consultant Clinical Oncologist,
University College Hospital,
London, UK

Dr Thiraviyam Elumalai,
Consultant Clinical Oncologist,
Addenbrooke's Hospital,
Cambridge University Hospitals NHS Foundation Trust,
Cambridge, UK

Professor Karim Fizazi,
Medical Oncologist,
Head of the Department of Cancer Medicine,
Gustave Roussy Institute,
Villejuif, France

Mr William Cross,
Consultant Urological Surgeon,
St James's University Hospital,
Leeds Teaching Hospitals NHS Trust,
Leeds, UK

▼ **NUBEQA® (Darolutamide) 300 mg film-coated tablets Prescribing Information**
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: Each film-coated tablet contains 300 mg of darolutamide. **Indication(s):** NUBEQA is indicated for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease. **Posology & method of administration:** Treatment should be initiated and supervised by a specialist physician experienced in treatment of prostate cancer. Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated. For oral use. The tablets should be taken whole with food. **Adults:** 600 mg darolutamide (two tablets of 300 mg) taken twice daily, equivalent to a total daily dose of 1200 mg. **Children & adolescents:** There is no relevant use of darolutamide in the paediatric population for the indication of treatment of nmCRPC. **Elderly:** No dose adjustment is necessary. **Renal impairment:** No dose adjustment is necessary for patients with mild or moderate renal impairment. For patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m2) not receiving haemodialysis, the recommended starting dose is 300 mg twice daily. **Hepatic impairment:** No dose adjustment is necessary for patients with mild hepatic impairment. The available data on darolutamide pharmacokinetics in moderate hepatic impairment is limited. Darolutamide has not been studied in patients with severe hepatic impairment. For patients with moderate and severe hepatic impairment (Child-Pugh Classes B and C), the recommended starting dose is 300 mg twice daily. **Contra-indications:** Hypersensitivity to the active substance or to any of the excipients. Women who are or may become pregnant. **Warnings & precautions:** The available data in patients with severe renal impairment are limited. As exposure might be increased those patients should be closely monitored for adverse reactions. The available data in patients with moderate hepatic impairment are limited, and darolutamide has not been studied in patients with severe hepatic impairment. As exposure might be increased those patients should be closely monitored for adverse reactions. Patients with clinically significant cardiovascular disease in the past 6 months including stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, and symptomatic congestive heart failure were excluded from the clinical studies. Therefore, the safety of darolutamide in these patients has not been established. Use of strong CYP3A4 and P-gp inducers during treatment with darolutamide may decrease the plasma concentration of darolutamide and is not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product with less potential to induce CYP3A4 or P-gp should be considered. Patients should be monitored for adverse reactions of BCRP, OATP1B1 and OATP1B3 substrates as co-administration with darolutamide may increase the plasma concentrations of these substrates. Co-administration with rosuvastatin should be avoided unless there is no therapeutic alternative. In patients with a history of risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval, physicians should assess the benefit-risk ratio including the potential for Torsade de pointes prior to initiating NUBEQA. NUBEQA 300mg film-coated tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicinal product. **Interactions:** For the effect of other medicinal products on the action darolutamide (e.g CYP3A4, P-gp inducers and CYP3A4, P-gp and BCRP inhibitors and UGT1A9 inhibitors) and the action of darolutamide on other medicinal products (BCRP, OATP1B1, OATP1B3 substrates, P-gp substrates, CYP3A4 substrates and other medicinal products that prolong the QT interval) refer to the SmPC. **Pregnancy & lactation:** Darolutamide is not indicated in women of childbearing potential, and it is not to be used in women who are, or may be, pregnant or breast-feeding. Unknown whether darolutamide or its metabolites are present in semen. If the patient is engaged in sexual activity with a woman of childbearing potential, a highly effective contraceptive method (<1% failure rate per year) should be used during and for 1 week after completion of treatment. Unknown whether darolutamide or its metabolites are excreted in human milk. No studies in animals have been conducted to evaluate the excretion of darolutamide or its metabolites into milk. A risk to the breast-fed child cannot be excluded. There are no human data on the effect of darolutamide on fertility. Based on animal studies, darolutamide may impair fertility in males of reproductive potential. **Effects on ability to drive and use machines:** Darolutamide has no or negligible influence on the ability to drive and use machines. **Undesirable effects:** Very common: fatigue/asthenic conditions (incl. fatigue and asthenia, lethargy and malaise), neutrophil count decreased, bilirubin increased, AST increased. Common: ischaemic heart disease (including arteriosclerosis coronary artery, coronary artery disease, coronary artery occlusion, coronary artery stenosis, acute coronary syndrome, acute myocardial infarction, angina pectoris, angina unstable, myocardial infarction, myocardial ischaemia), heart failure (including cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiogenic shock), rash, pain in extremity, musculoskeletal pain, fractures. Prescribers should consult the SmPC in relation to other side effects. **Overdose:** In the event of intake of a higher than recommended dose, treatment with darolutamide can be continued with the next dose as scheduled. There is no specific antidote for darolutamide and symptoms of overdose are not established. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** Pack of 112 film-coated tablets, £4,040. **MA Number(s):** EU/1/20/1432/001 **Further information available from:** Bayer plc, 400 South Oak Way, Reading RG2 6AD, United Kingdom. Telephone: 0118 206 3000. **Date of preparation:** March 2020

NUBEQA® is a trademark of the Bayer Group

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in Google Play or Apple App Store. Adverse events should also be reported to Bayer plc. Tel.: 0118 206 3500; Fax: 0118 206 3703; Email: pvuk@bayer.com

nmCRPC, non-metastatic castration-resistant prostate cancer; RCT, randomised controlled trial; RWE, real-world evidence.
This promotional meeting has been organised and funded by Bayer and is for healthcare professionals only.

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