Low-risk prostate cancer selected for active surveillance with negative MRI at entry: can repeat biopsies at one year be avoided? A pilot study.

Jonathan Olivier [1,2,3]; Veeru Kasivisvanathan[4,5]; Elodie Drumez[6]; Jean-Christophe Fantoni [3]; Xavier Leroy [2,7]; Philippe Puech[1, 2,8]; Arnauld Villers[1,2,3]

1: INSERM, U1189, ONCO-THAI, F-59037 Lille, France
2: Univ Lille, F-59000 Lille, France
3: Department of Urology, CHRU Lille, Lille university, Lille, France.
4: Division of Surgery and Interventional Science, University College London, UK
5: Department of Urology, University College London Hospital, UK
6: Univ. Lille, CHU Lille, EA 2694 - Santé publique : épidémiologie et qualité des soins, Department of Biostatistics, F-59000 Lille, France
7: Department of Pathology, CHRU Lille, Lille university, Lille, France.
8: Department of Radiology, CHRU Lille, Lille university, Lille, France.

Purpose: In patients considered for active surveillance (AS), the use of MRI and targeted biopsies (TB) at entry challenges the approach of routine "per protocol" repeat systematic biopsies (SB) at one year. This pilot study aimed to assess whether an approach of performing repeat biopsies only if PSA kinetics are abnormal would be safe and sufficient to detect progression.

Methods: Prospective single-centre study of 149 patients on AS with low risk PCa, a negative MRI at entry and followed for a minimum of 12months between 01/2007 and 12/2015. Group1 (n=78) patients had per-protocol 12-mo repeat SB; group2 (n=71) patients did not. Surveillance tests for tumour progression were for both groups: for cause SB and MRI-TB biopsies if PSA velocity (PSA-V)>0.75ng/ml/year, or PSA doubling time (PSADT)<3years. The main objectives are to compare the 2-year rates of tumour progression and AS discontinuation between groups. The secondary objectives are to estimate the diagnostic power of PSA-V and PSA-DT, to predict the risk of tumour progression.

Results: Overall 21 out of 149 patients (14.1%) showed tumour progression, 17.1% for group1 and 12.3% for group2 and 31(21.2%) discontinued AS at 2 years. There was no difference between the 2 groups (p=0.56). The area under the PSA-V and PSADT curves to predict tumour progression was 0.92 and 0.83, respectively.

Conclusions: We did not find any significant difference for progression and AS discontinuation rate between the 2 groups. The PSA kinetic seems accurate as a marker of tumour progression. These results support the conduct of a multi-centre prospective trial to confirm these findings.

Introduction

Active surveillance(AS) reduces the harms of screening and overtreatment of men with a low risk of prostate cancer (PCa) progression(1). This therapeutic strategy concerns about 20% of newly diagnosed PCa. It aims to avoid or delay the use of curative treatments without compromising the long-term survival of patients(2).

Many prospective cohorts have validated AS, but there is no consensus on inclusion or follow-up criteria(3). Selection criteria based on "blind" 12 systematic biopsies(SB) of the posterior part of the prostate are associated with a reclassification rate of 20 to 30% at one year using per protocol" repeat SB. However when selection criteria are based on MRI, targeted biopsies(TB) and the addition of SB, 10% of patients eligible for AS are reclassified at entry, before inclusion(4) and the reclassification/progression rate is only 16% at 2 years(5).

The use of MRI and TB at entry questions the need for routine "per protocol" repeat SB at one year for only 16% of patients. “Per protocol" repeat SB are associated with complications including severe urinary tract infection, sepsis and poor acceptability by patients(6).

To replace "per protocol" repeat SB, it has been suggested to use PSA kinetics(PSAk) followed by “for cause only" repeat SB if the PSA kinetics were abnormal(7,8).

A high PSA velocity (PSA-V) or short PSA doubling time (PSA-DT) are related with an unfavourable outcome and should lead to performing an additional prostate biopsy or to deferred radical treatment during follow-up of men on AS(9). Cooperberg recently validated the role of PSAk as an independent predictor of reclassification/progression in a AS multicentre cohort with PSA data collected at protocol-mandated intervals, relatively long follow-up, and centralized analysis(10).

The question is to assess the value of "per protocol" repeat SB at one year to diagnose progression. One way to answer is to rely only on for cause biopsies, skipping "per protocol" repeat biopsies. However this strategy may be associated with a risk of missing progression for some patients. Our study was designed as a pilot study to look at progression rate in 2 groups (with and without "per protocol" repeat SB) and to assess whether the rate of progression is at least non-inferior in the group without repeat biopsy. If the rate is non-inferior within at least 2 years of follow-up, results may be used as a rational for a cohort or randomised prospective study.

In our series of patients on AS, with baseline MRI and TB assessment and during surveillance we studied 2 consecutive groups with and without "per protocol" repeat 12-mo SB. The main objectives were to compare the 2-year rates of tumour reclassification/progression and AS discontinuation

between groups. Secondary objectives were to estimate the diagnostic power of PSA-V and PSA-DT, to predict the risk of tumour reclassification/progression.

Methods

Study design and population. Prospective cohort study enrolling men on AS at Lille University Hospital (data base protection authorization obtained and patients' consents collected). All consecutive patients between January 2007 and December 2015, who accepted AS were enrolled.

Inclusion criteria were life expectancy>10 years, low risk PCa as determined by trans-rectal ultrasound 12 SB with number of positive biopsies ≤3, Gleason score 6(3 + 3) and maximum cancer core length(MCCL) ≤ 5mm, clinical stage ≤cT2, no abnormality or false positive abnormality for significant cancer at MRI. Mp-MRI were performed as previously described(4) using a 1.5 Tesla system with a pelvic phased array coil and interpreted by a uroradiologist with 15 years of experience in MRI prostate reading. No abnormality on MRI was defined as Likert score ≤ 2 and abnormal MRI suspicious for malignancy as Likert score ≥3. In case of abnormality at MRI suspicious for cancer, negative targeted biopsies were defined as a false positive abnormality. Exclusion criteria were history of 5a-reductase inhibitor(5-ARI) use, absence of pre-biopsy MRI and less than one year of follow-up. Out of 233 patients enrolled on AS, 149 met the inclusion criteria.

Data collection. Clinical data including age and Charlson score, PSA at baseline and every 6-mo, PSA density, PSA kinetics(PSA-V and PSADT) calculated with the MSKCC calculator(https://www.mskcc.org/nomograms/prostate/psa_doubling_time) using at least three measurements over a period of at least 6 mo, pathological data including(number of positive SB, MCCL at baseline and for follow-up biopsies, Gleason score) and prostate volume at ultrasound.

AS follow-up protocol. Visit every year with DRE, PSA every 6-mo, per-protocol MRI and repeat SB at 12 mo for patients enrolled in years 2007-2012(group 1, n=78). Our AS cohort has matured with follow-up. Interim observation in 2012 showing low rate of progression at 12-mo (85%) with calculated PSA-V NPV>95% to predict progression, per-protocol 12-mo repeat SB were removed from AS protocol for patients included in years 2012-2015(group 2, n= 71). During the year 2012, 17/28 patients had 12-mo repeat SB and 11/28 did not. For both groups, other tests including for cause MRI and SB or TB biopsies were indicated for all patients in case of 2 consecutive PSA rises (PSAV > 0.75ng/ml). A for cause MRI plus biopsy were scheduled in addition to a third PSA dosage 3 months later. If PSA kinetics was still suspicious MRI and biopsies indication were confirmed and performed.

Definition of cancer reclassification or progression. Presence of any amount of Gleason grade 4, >3 positive biopsies, MCCL >5mm at 12 SB or MRI-TB with pathological progression criteria in case of newly abnormality at MRI, any pelvic or extra-pelvic metastasis or death due to prostate cancer were defined as reclassification (during first year of follow-up) or progression (after first year of follow-up). Starting from the year 2013 the AS criteria for reclassification or progression were modified and presence of Gleason score 7(3+4) in only 1 core and (MCCL) ≤ 3mm was accepted as non progression. The causes of AS interruption were tumour reclassification/progression, patient choice (anxiety) or physician choice leading to treatment despite the absence of progression), patient decision not to be followed (watchful waiting) and lost to follow up.

Radical prostatectomy assessment. For patients who underwent radical prostatectomy(RP) after AS pathological stage was recorded.

Statistical Analysis

Qualitative variables are expressed as count and percentage. Continuous variables are reported as median and interquartile range (IQR). Normality of continuous variable are checked graphically and by using Shapiro-Wilk test. Main patient's characteristics were compared between groups using Chi-square test for qualitative variables and Mann-Whitney-U test for continuous variables. The 2-year rates of tumour reclassification/progression and active surveillance discontinuation were estimated using Kaplan Meier curves and compared between groups using the log-rank test. To estimate the diagnostic power of PSA-V and PSA-DT, sensitivities, specificities, PPV, NPV, and areas under the curve (AUC) were calculated using patient reclassification/progression as a gold standard. PSA-V threshold values of >0.75ng/ml/year and >0.5ng/ml/year were used (NCCN). PSA-DT threshold value of <3 years was used)(9). All statistical tests were performed at the 2-tailed α level of 0.05. Data were analysed using SAS version 9.4[SAS Institute Inc., Cary, NC 27513, USA].

RESULTS

Population

The clinical, pathological, biological and imaging data for both groups of patients at inclusion are shown in Table I. Patients of group 2 had a shorter follow up (42.5 months (IQR, 26 to 70) vs.32 (IQR, 23 to 49) (p=0.034). No other significant difference was found between the 2 groups.

Follow-up

Of the 78 patients of group 1, 36(46.2%) had negative repeat SB, 33(42.3%) had positive repeat SB but /progression criteria and 9(11.5%) had positive repeat SB with reclassification/progression criteria. Four patients had positive "for cause" biopsies during the first 2 years. For these 13patients, reclassification/progression at 2 years was due to a Gleason grade progression in 4, a size>5mm or >3 positive biopsies in 4 and a progression of size and grade in 5 (Table 2). Overall, 19 patients (24.4%) discontinued AS at 2 years, 13(17.1%) for cancer reclassification/progression, 2(2.8%) for patient choice of treatment (1 negative SB, 1 positive RB without reclassification/progression), 3(3.8%) for physician choice (all 3 had positive SB without reclassification/progression), and 1(1.5%) lost to follow-up. After 2 years, 12 additional patients discontinued AS (7 for tumour progression, 2 for patient choice, 1 for physician choice and 2 lost to FU).

Of the 71 patients of group 2, 10(14.1%) had for cause biopsies during the first 2 years of AS. Two had positive repeat SB but without reclassification/progression criteria and 8 had positive repeat SB with reclassification/progression criteria. For these 8 (12.3%) patients, reclassification/progression at 2 years was due to a Gleason grade progression in 4, a size>5mm or >3 positive biopsies in 3 and a progression of size and grade in 1 (Table 2). Two (3%) patients discontinued for patient choice (with no for cause biopsy indication during their FU) and 2(3%) were lost to follow-up. After 2 years, 2 additional patients discontinued AS 2(3.0%) for cancer reclassification/progression.

Overall, of the 149 patients on AS, 21(14.1%) men were reclassified or progressed at 2 years: 17.1%(95% CI, 10.3% - 27.7%) in group 1 and 12.3%(95% CI, 6.3% - 23.1%) in group 2. There was no statistically significant difference between the 2 groups at 2 years (p=0.56)(Figure 1a) or for the entire follow up period (p=0.19).

At 2 years of FU, 31 patients (21.2% 95%CI,15.4%-28.8%) stopped AS. Nineteen patients in group 1 (24.4%; 95%CI,16.3%-35.5%) and 12 patients in group 2 (17.7%; 95%CI, 10.5%-29.2%) (Figure 1b).

Of these 31 patients, 21 were referred for RP, 2 for radiation therapy, 2 for brachytherapy, 2 for HIFU hemi-ablation, 2 for watchful waiting and 2 were lost to follow-up. No patient had diagnosis of metastasis or death from any cause.

Radical prostatectomy assessment

For 15 patients in group 1, PT specimens showed in 4 (27%) a Gleason score of 6(3+3), in 5 (33%) a Gleason score of 7(3+4) and in 4 (27%) a Gleason score>7(3+5 or 4+4). The pathological stages were pT2 in 10(67%), pT3a in 3(20%). Data are missing for 2 patients (13%). For 6 patients in group 2, PT specimens showed in all of them a Gleason score of 7(3+4). The pathological stages were pT2(83%) in 5 and 1 pT3a(17%) in 1. All patients for both groups were N0 and M0 at imaging. One patient had a detectable PSA during follow-up and had salvage radiation therapy (anteriorly located cancer with stage pT3a, R1).

***PSA-V and PSADT and prediction of* reclassification/progression**

PSA-V. PSA-V>0.75ng/ml/year in the first 2 years, was associated with tumour reclassification during repeat SB in 12/18(66.7%) of cases. Sensitivity of PSA-V for the detection of tumour reclassification was 92% and specificity was 91%. The PPV and NPV of this test were 67% and 98% respectively. The AUC of the PSA-V diagnostic test>0.75ng/ml/year was 0.92 (95% CI, 0.83 - 1.00]). The accuracy of PSA-V for tumour progression is shown in Figure 2a. For PSA-V threshold value of >0.5ng/ml/year sensitivity, specificity, PPV, NPV were respectively: 92%, 86%, 57% and 98%

In case of PSA-V >1 ng/ml/year sensitivity, specificity, PPV, NPV were respectively: 92.3%, 93.8%, 75% and 98.4%.

PS-DT. PSADT<3 years in the first 2 years, was associated with tumour reclassification in 81.8% of cases (9/11). The sensitivity of PSADT for detection of tumour progression was 69% and its specificity was 97%. The VPP and VPN for this test were 82% and 94%, respectively. The AUC for PSADT diagnostic test <3 years was 0.83 (95%CI, 0.70-0.96). The accuracy of PSADT for tumour progression is shown in Figure 2b.

DISCUSSION

In this retrospective pilot study, we evaluated the approach of "per protocol" RB at one year for patients on AS with negative MRI at entry. We did not find any significant difference for reclassification/progression rate between 2 groups in which the only difference for follow up was the use of "per protocol" RB at one year. We also did not demonstrate difference for AS interruption rate at 2 years. This is the first study to report reclassification/progression rates without per-protocol RB at 12-mo. Our results are encouraging since they open the door to obviate unnecessary biopsies, without hampering the possibility of diagnosis to tumour progression to a clinically significant stage.

Our reclassification/progression rate of 14.1% is similar to the 16 % rate at a median follow up of 39 months observed in the Cambridge cohort who receive MRI at inclusion (5). These rates reflect in part tumours with rapid growth and in part tumours that were missed by the diagnostic tests used for selection criteria. Hence, if MRI accuracy is high to eliminate significant tumours, its NPV was ranges from 63% to 98% (11,12), explaining that there are still some significant tumours that are missed at entry. In some of our cases, MRI during surveillance showed a new abnormality suspicious for cancer (confirmed by TB), and which was actually retrospectively seen when reviewing previous MRI. In this case, tumour progression was associated with suspicious PSA-V.

These results, which need to be confirmed in larger series, could have clinical important implications. Indeed, "per protocol" RB are often not accepted by some patients who prefer not to enter AS or to leave AS by choice. In fact, 2 patients of group 1 chose to undergo RP treatment in another institution, following RB, which showed no progression. These choices can be explained, by patient reluctance about the frequent per-protocol based multiple repeated prostate biopsies indications (13). No longer performing "per protocol" RB would therefore improve the comfort of 86% of patients of our series and reduce the risk of choosing radical treatments in patients who may not benefit from radical treatment.

Controversy exists for the use of PSAk to predict PCa progression for patients on AS. PSADT and PSA-V were initially used in AS follow-up protocols but some papers described their inaccuracy. As Van den Bergh et al, described in 2008, the evidence concerning the prognostic value of the PSA-V and PSA DT is sparse, especially in active surveillance (9). Cooperberg recently validated the role of PSAk as an independent predictor of reclassification/progression in a AS multicentre cohort with PSA data collected at protocol-mandated intervals, relatively long follow-up, and centralized analysis (10).

These encouraging data suggest that PSAk or similar assessments of kinetics should be considered in future multivariable models of AS outcomes and must be validated in other surveillance cohorts. Hence, important limitation of their study is the reliability of the end point. Their reclassification itself was imperfect end point, as it may reflect undersampling due to the lack of MRI and targeted biopsies at entry and during follow-up. MRI were only performed at the clinicians' discretion and, as enrolment started in 2008, the majority of men did not undergo this imaging test.

In our series, we found an excellent NPV of PSA-V and PSADT. The PSADT, originally described to predict the biological recurrence of radiotherapy-treated PCa (14), has been found in several studies to be predictive of progression on AS (15,16). Similarly, PSA-V has been tested by many authors as predictors of progression in AS (17,18) but few studies have shown significant results. Iremashvili et al. showed an association between PSA-V and progression only after 4 sets of biopsies (19). Patel et al. showed that the number of times the PSA-V increased above 0.4ng / ml / year predicted PCa progression in AS (20). Differences in populations chosen for the studies and biopsy protocols may explain differences in findings. We did not use PSA density at inclusion or during follow-up and cannot retrospectively assess its role as a risk factor for progression.

Our study has several limitations: The retrospective mono-centric nature of the study leads to a probable selection bias. The medium duration of follow-up can lead to interpretation bias. Time to assess progression without per-protocol based biopsy is unknown. Longer follow-up in group 2 may show additional progressions which could have been detected by per-protocol 12-mo SB. The lack of power of our study because of the small size in each group could lead to interpretation bias. Finally our centre is a regional tertiary reference centre. That can cause a recruitment bias. Imaging and pathology analyses were performed by radiologists and pathologists dedicated to urology. This may lead to a difficulty in the generalization of our results.

Conclusion. We did not find significantly less reclassification/progression and AS discontinuation rate in the group without "per protocol" RB at one year. These results support the safety and the need to conduct of a multi-centre prospective trial to confirm these findings.

Table I: Clinical, pathological, biological and imaging data for both groups of patients at inclusion

	Group 1(n=78) With per protocol 12-mo SB	Group 2 (n=71) Without per protocol 12-mo SB
Age	63 (59 - 67)	65 (60 - 70)
Charlson score	2 (2 - 4)	2 (2 - 4)
Total PSA (ng/ml)	6.62 (5.45 - 8.30)	6.21 (4.55 - 8.60)
PSA density (ng/ml/cm^3)	0.13 (0.09 - 0.18)	0.10 (0.07 - 0.16)
Number of positive SB	1 (1 - 1)	1 (1 - 2)
MCCL (mm)	1 (1 - 2)	1 (1 - 2)
Follow-up (mo)	42.5 (26 - 70)	32 (23 - 49)

Values are median (interquartile range). SB: 12 cores systematic biopsies. MCCL: Maximal cancer core length

Table 2: Progression causes at 2 years and pathological results after radical prostatectomy

Patient	Group	Time to progression (mo)	Number of positive SB n,(size)	Number of positive MRI-TB n,(size)	Gleason sum at biopsy	Cause of progression	Treatment	pT-Stage (RP)
P63	1	24	1(8mm)	0	3+4	Grade + Size	BT	
P65	1	11	2 (?)	0	4+3	Grade	RT	
P75	1	24	4 (1-1-1-4mm)	2 (1-3mm)	3+3	Size	RP	T2c
P90	1	9	4 (1-1-3-7mm)	0	3+3	Size	RP	T2c
P94	1	10	0	1 (3mm)	4+3	Grade	RP	T2c
P100	1	12	1 (1mm)	2 (1-9mm)	3+5	Grade + Size	RP	T2c
P102	1	12	0	2 (4-5mm)	4+3	Grade	RP	T3a
P108	1	12	4 (1-1-3-4mm)	0	3+3	Size	RP	T2c
P113	1	14	0	3 (2-2-4mm)	3+4	Grade + Size	RP	T3a
P115	1	13	0	2 (2-8mm)	4+3	Grade + Size	RP	T3a
P130	1	11	1 (1mm)	2 (1-2mm)	4+3	Grade	HIFU	
P135	1	24	3 (1-1-2mm)	1(1mm)	3+3	Size	RP	T2c
P140	1	19	3 (1-2-2mm)	2 (5-7mm)	3+4	Grade + Size	RP	T2c
P2	2	23	4 (2-2-2-2)	0	3+3	Size	HIFU	
P6	2	14	1 (5mm)	0	3+4	Grade	RP	T2c
P7	2	24	2 (2-3mm)	0	3+5	Grade	RP	T3a
P11	2	19	2 (1-5mm)	1 (1mm)	4+3	Grade	RT	
P57	2	18	2 (1-1mm)	2 (2-4mm)	3+3	Size	RP	T2c
P107	2	4	0	2 (1-5mm)	3+4	Grade	RP	T2c
P110	2	5	4 (1-2-2-4mm)	2 (2-6mm)	3+3	Size	BT	
P133	2	8	0	1 (6mm)	3+4	Grade + Size	RP	T2c

BT: Brachytherapy; RT: Radiotherapy; RP: Radical prostatectomy; HIFU: High Intensity Focus Ultrasound.

Figure 1a: Tumour progression free-survival curves according to groups

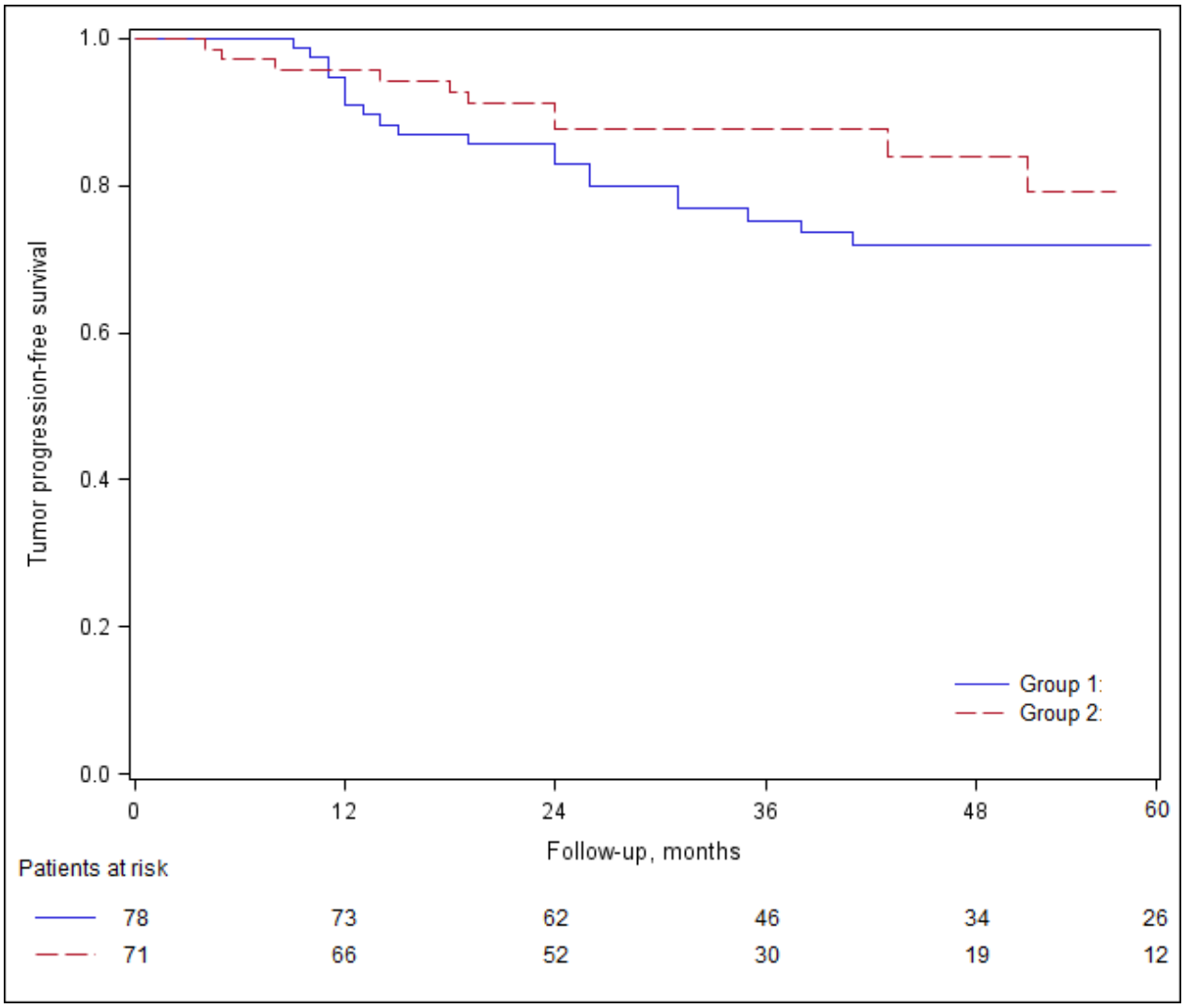


Figure 1b : AS discontinuation free survival curves according to groups.

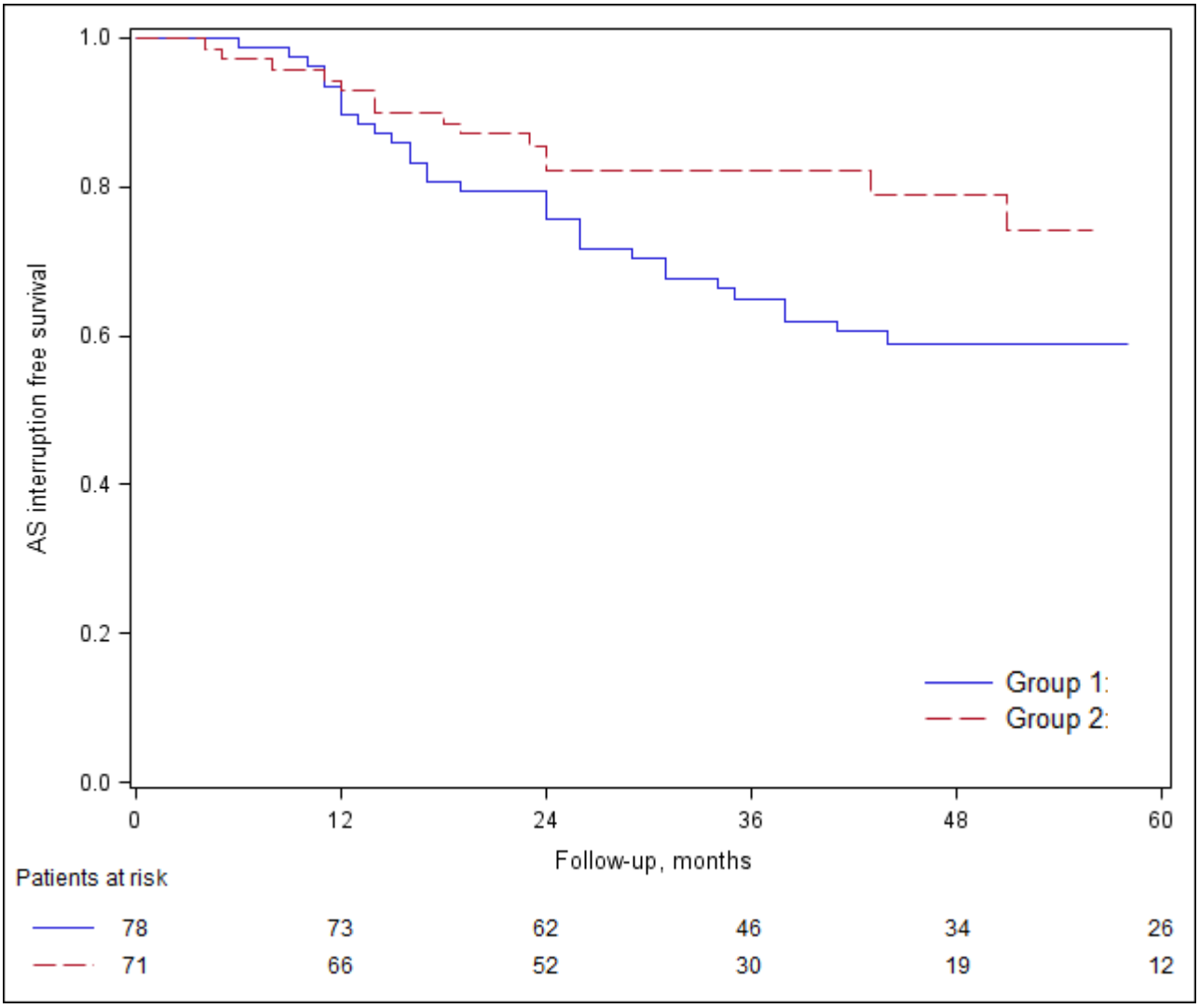
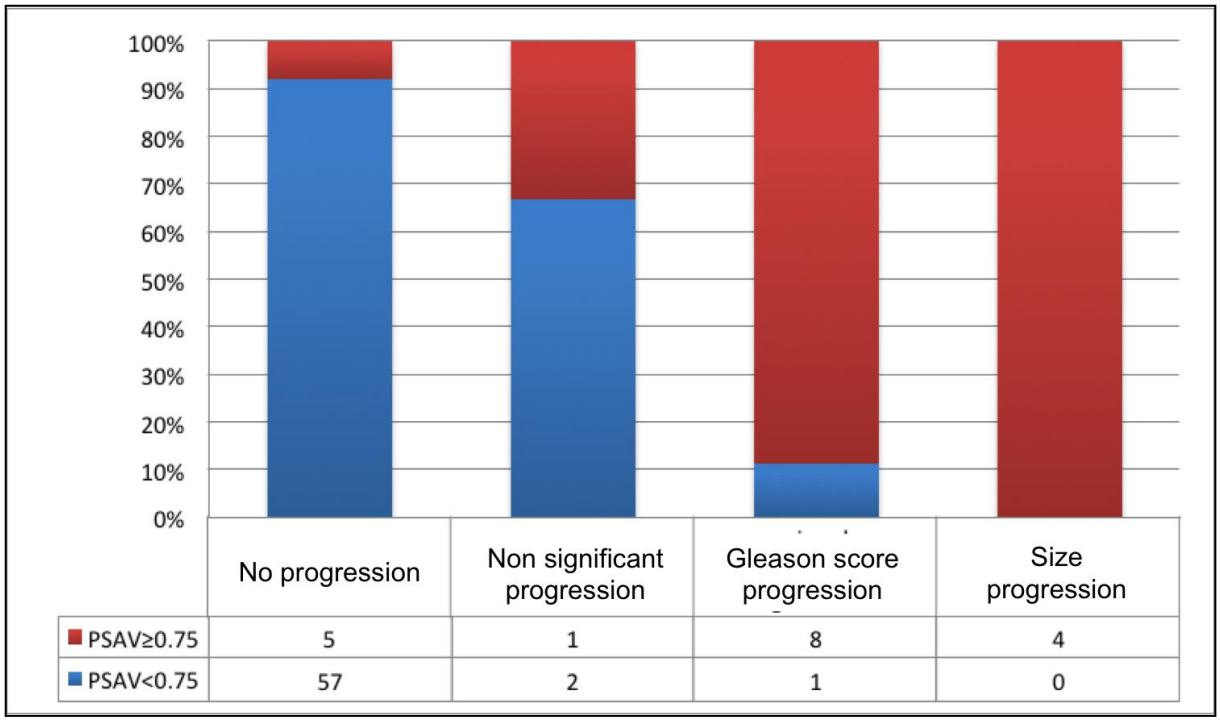
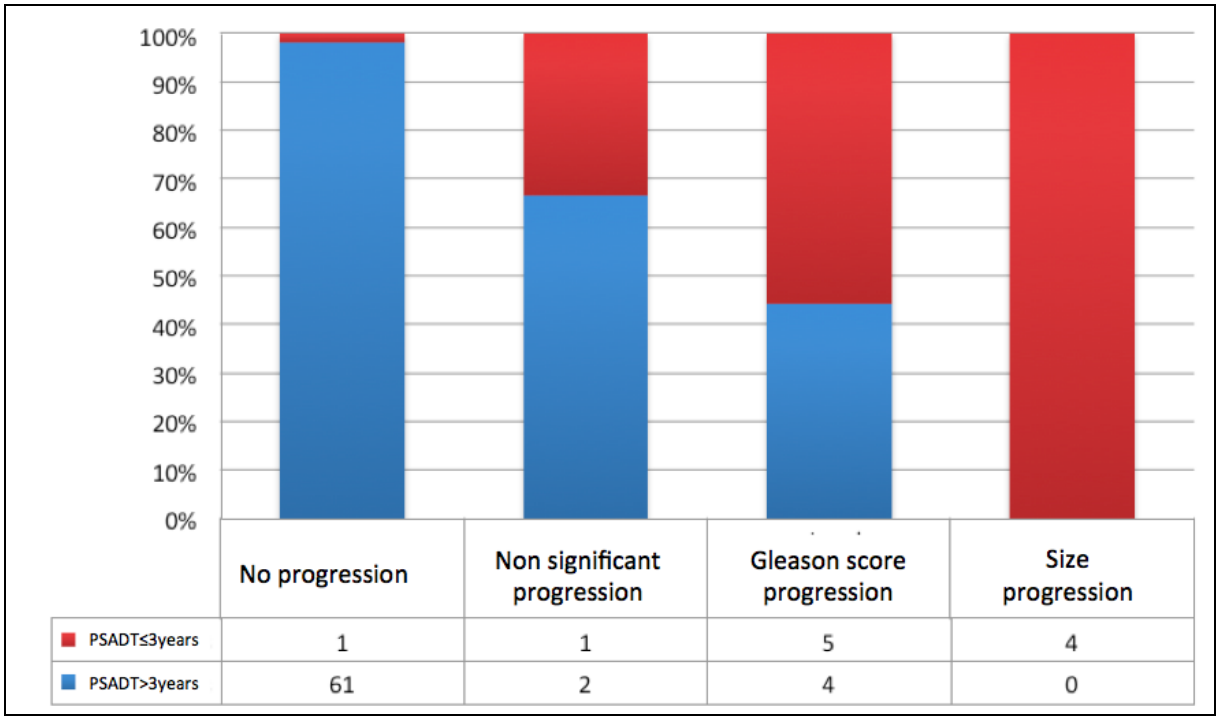


Figure 2a: PSA velocity and progression at repeat biopsies at 1 year



	No progression	Non significant progression	Gleason score progression	Size progression
PSAV≥0.75	5	1	8	4
PSAV<0.75	57	2	1	0

Figure 2b: PSA doubling time and progression at repeat biopsies at 1 year.



	No progression	Non significant progression	Gleason score progression	Size progression
PSADT≤3years	1	1	5	4
PSADT>3years	61	2	4	0

1. Bul M, Zhu X, Valdagni R, Pickles T, Kakehi Y, Rannikko A, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. Eur Urol. 2013 Apr;63(4):597–603.

2. Klotz L. Active surveillance for prostate cancer: patient selection and management. Curr Oncol Tor Ont. 2010 Sep;17 Suppl 2:S11-17.

3. Bruinsma SM, Bangma CH, Carroll PR, Leapman MS, Rannikko A, Petrides N, et al. Active surveillance for prostate cancer: a narrative review of clinical guidelines. Nat Rev Urol. 2016 Mar;13(3):151–67.

4. Ouzzane A, Renard-Penna R, Marliere F, Mozer P, Olivier J, Barkatz J, 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 Aug;194(2):350–6.

5. Thurtle D, Barrett T, Thankappan-Nair V, Koo B, Warren A, Kastner C, 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 Feb 13;

6. Thoma C. Prostate cancer: Avoiding excess confirmatory biopsies. Nat Rev Urol. 2015 Sep;12(9):476.

7. Bruinsma SM, Roobol MJ, Carroll PR, Klotz L, Pickles T, Moore CM, 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 Mar 14;

8. McLaren DB, McKenzie M, Duncan G, Pickles T. Watchful waiting or watchful progression?: Prostate specific antigen doubling times and clinical behavior in patients with early untreated prostate carcinoma. Cancer. 1998 Jan 15;82(2):342–8.

9. van den Bergh RCN, Roemeling S, Roobol MJ, Aus G, Hugosson J, Rannikko AS, et al. Outcomes of men with screen-detected prostate cancer eligible for active surveillance who were managed expectantly. Eur Urol. 2009 Jan;55(1):1–8.

10. Cooperberg MR, Brooks JD, Faino AV, Newcomb LF, Kearns JT, Carroll PR, et al. Refined Analysis of Prostate-specific Antigen Kinetics to Predict Prostate Cancer Active Surveillance Outcomes. Eur Urol. 2018 Feb 9;

11. Vargas HA, Akin O, Afaq A, Goldman D, Zheng J, Moskowitz CS, et al. Magnetic resonance imaging for predicting prostate biopsy findings in patients considered for active surveillance of clinically low risk prostate cancer. J Urol. 2012 Nov;188(5):1732–8.

12. Fütterer JJ, Briganti A, De Visschere P, Emberton M, Giannarini G, Kirkham A, et al. Can Clinically Significant Prostate Cancer Be Detected with Multiparametric

Magnetic Resonance Imaging? A Systematic Review of the Literature. Eur Urol. 2015 Dec;68(6):1045–53.

13. Bruinsma SM, Bokhorst LP, Roobol MJ, Bangma CH. How Often is Biopsy Necessary in Patients with Prostate Cancer on Active Surveillance? J Urol. 2016 Jan;195(1):11–2.

14. D'amico AV, Hanks GE. Linear regressive analysis using prostate-specific antigen doubling time for predicting tumor biology and clinical outcome in prostate cancer. Cancer. 1993 Nov 1;72(9):2638–43.

15. Soloway MS, Soloway CT, Williams S, Ayyathurai R, Kava B, Manoharan M. Active surveillance; a reasonable management alternative for patients with prostate cancer: the Miami experience. BJU Int. 2008 Jan;101(2):165–9.

16. Khatami A, Ali K, Aus G, Gunnar A, Damber J-E, Jan-Erik D, et al. PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. Int J Cancer. 2007 Jan 1;120(1):170–4.

17. Venkitaraman R, Norman A, Woode-Amissah R, Fisher C, Dearnaley D, Horwich A, et al. Predictors of histological disease progression in untreated, localized prostate cancer. J Urol. 2007 Sep;178(3 Pt 1):833–7.

18. Iremashvili V, Manoharan M, Lokeshwar SD, Rosenberg DL, Pan D, Soloway MS. Comprehensive analysis of post-diagnostic prostate-specific antigen kinetics as predictor of a prostate cancer progression in active surveillance patients. BJU Int. 2013 Mar;111(3):396–403.

19. Iremashvili V, Kava BR, Manoharan M, Parekh DJ, Punnen S. Is It Time to Revisit the Role of Prostate-specific Antigen Kinetics in Active Surveillance for Prostate Cancer? Urology. 2016 Sep;95:139–44.

20. Patel HD, Feng Z, Landis P, Trock BJ, Epstein JI, Carter HB. Prostate specific antigen velocity risk count predicts biopsy reclassification for men with very low risk prostate cancer. J Urol. 2014 Mar;191(3):629–37.