Title

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Journal

Investigative Urology, 207(4)

ISSN

0021-0005

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Publication Date

2022-04-01

DOI

10.1097/ju.0000000000002354

Peer reviewed

HHS Public Access

Author manuscript

J Urol. Author manuscript; available in PMC 2023 April 01.

Published in final edited form as:

J Urol. 2022 April ; 207(4): 805–813. doi:10.1097/JU.0000000000002354.

Evaluating the outcomes of active surveillance in Grade Group 2 prostate cancer: Prospective results from the Canary PASS Cohort

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Abstract

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CONFLICTS OF INTEREST: None

Presented at the 115th American Urologic Association Annual Meeting, Washington, DC.

Introduction: Active Surveillance (AS) for grade group 2 (GG2) patients is not yet well-defined. We sought to compare clinical outcomes of men with GG1 and GG2 prostate cancer undergoing AS in a large prospective North American cohort.

Methods: Participants were prospectively enrolled in an AS study with protocol-directed follow up at 10 centers in the US and Canada. We evaluated time from diagnosis to biopsy grade reclassification and time to treatment. In men treated after initial surveillance, adverse pathology (AP) and recurrence were also analyzed.

Results: At diagnosis, 154 (9%) had GG2 and 1574 (91%) had GG1. Five-year reclassification rates were similar between GG2 or GG1 (30% vs 37%, p=0.11). However, more patients with GG2 were treated at 5 years (58% vs 34%, p<0.001) and GG at diagnosis was associated with time to treatment (HR = 1.41; p=0.01). Treatment rates were similar in patients who reclassified during AS, but in patients who did not reclassify, those diagnosed with GG2 underwent definitive treatment more often than GG1 (5-year treatment rates 52% and 12%, p<0.0001). In participants who underwent RP after initial surveillance, the adjusted risk of AP was similar (HR = 1.26; p=0.4). Biochemical recurrence (BCR) within 3 years of treatment for GG2 and GG1 patients was 6% for both groups.

Conclusions: In patients on active surveillance, the rate of definitive treatment is higher after an initial diagnosis of GG2 than GG1. Adverse pathology after RP and short-term BCR after definitive treatment were similar between GG2 and GG1.

Keywords

Prostatic Neoplasms; Active Surveillance; Gleason Score

Introduction:

Active Surveillance (AS), in which cancer is carefully monitored with repeat evaluations including prostate specific antigen (PSA) measurements and repeat biopsy, is endorsed as the preferred management strategy for low risk prostate cancer (PCa).[1] Randomized trials have not demonstrated a significant survival benefit for immediate treatment of low-risk PCa.[2-5] Indeed, long-term studies of carefully selected men diagnosed with Grade Group (GG1) prostate cancer managed by AS have shown very favorable outcomes.[5] However, these same randomized trials suggest that some patients diagnosed with GG2 cancer may have a survival benefit from immediate curative treatment.[4]

Guidelines include AS as one option for management in select patients diagnosed with GG2, in particular men with low volume GG2 and no other intermediate risk factors, e.g. PSA > 10 ng/mL. Outcomes in GG2 patients undergoing AS are largely confined to single institutional series from tertiary care centers with some studies suggesting that active surveillance may not be appropriate for GG2 cancers while others promoting the use of AS only in men with one core of GG2 disease.[6,7] Whether GG2 cancers should be routinely monitored using AS remains a matter of debate.

We sought to evaluate the impact of GG at diagnosis on clinical outcomes of men undergoing AS in the large multicenter Canary Prostate Active Surveillance Study (PASS)

cohort. We specifically evaluated reclassification and treatment rates, as well as adverse clinical outcomes in men receiving treatment after initial surveillance, to help inform decisions about monitoring GG2 cancers by active surveillance.

Methods:

Study population:

Canary PASS is a multicenter, prospective cohort enrolling AS patients at 10 sites. Patients who are eligible for AS provide informed consent under institutional review board supervision (clinicaltrials.gov NCT00756665). The majority of patients enroll in PASS prior to the first surveillance biopsy (e.g. confirmatory biopsy), but they may enroll any time during AS and clinical and pathologic data are collected for the previous five years. In PASS, patients are followed using a standardized protocol in which PSA is measured every 3 months; clinic visits occur every 6 months, and ultrasound-guided biopsies are 6-12 and 24 months after diagnosis, then every 2 years. Other studies, including magnetic resonance image (MRI) and biomarker tests, have been performed at the clinicians' discretion as they came into clinical use and data are collected.[8,9] Biopsies are read by GU pathologists at study sites.

In this analysis we included patients enrolled in PASS between August 2008 and April 2020. We excluded patients with GG3 at diagnosis, no follow-up biopsy, those diagnosed with PCa more than 5 years before enrollment, and those who had treatment within 6 months after diagnosis.

Study outcomes and Statistical analysis:

The primary outcome was time from cancer diagnosis to PCa treatment during AS. Secondary outcomes included time to biopsy reclassification, adverse pathology (AP) in men treated by radical prostatectomy (RP) after initial surveillance, and biochemical recurrence (BCR) in men treated after initial surveillance. Reclassification was defined as increase in Gleason GG at follow-up biopsy. Adverse pathology at RP was defined as GG ≥3, ≥pT3a, or pN1.[10] BCR after RP was defined as two PSA values >0.2 ng/mL or secondary treatment with detectable PSA ≥0.02 ng/mL. BCR after radiation therapy was defined as PSA greater than nadir+2 ng/mL or secondary treatment >6 months after radiation with evidence of rising PSA or positive prostate biopsy. Metastasis was determined by independent review of the PASS Endpoints Committee using the AJCC definition of disease in non-regional lymph nodes, soft tissue, or bones.

Overall cumulative incidence of treatment, stratified by GG at diagnosis and reclassification status during AS, was estimated using the Kaplan-Meier (KM) method and plotted as (1-KM estimator). Time zero was time of diagnosis. Participants without treatment were censored at date of last study contact. Overall cumulative incidence of reclassification, stratified by GG at diagnosis, was estimated using the Aalen-Johansen estimator. Participants without reclassification were censored at date of last study contact, treatment, or 2 years after their last biopsy, whichever came first. Cox proportional hazards (PH) models were used to estimate the unadjusted and covariate-adjusted hazards ratios for the association between

GG at diagnosis and risk of treatment or reclassification. Besides diagnostic GG, which was the variable of interest, the covariates in the model were based on previously published work and included age, BMI, percent of positive cores (cores containing cancer/total cores), prostate size, and PSA.[11] The association between GG and AP at RP was analyzed using parametric survival models for interval-censored data with Weibull distribution and inverse probability of censoring weighting applied to adjust for informative censoring.[12] Based on prior work, we included prostate size and PSA in multivariable modeling.[12] Time from definitive treatment to BCR was evaluated using the Kaplan-Meier method. All analyses were 2-tailed with alpha set at 0.05 and were performed using R version 3.3.0.

Results:

Between August 2008 and April 2020, 2003 participants were enrolled in the Canary PASS. For this analysis, we excluded 8 participants diagnosed with GG3, 181 who have not undergone a follow-up biopsy, 62 who enrolled greater than 5 years after diagnosis, 6 who underwent treatment less than 6 months after diagnosis, and 18 diagnosed by method other than prostate needle biopsy, resulting in 1728 participants. At diagnosis, 1574 (91%) patients had GG1 and 154 (9%) had GG2, of which 113 (73%) presented with a single core of GG2. Participants diagnosed with GG1 were enrolled earlier than those with GG2, and thus had a longer median follow-up [6.3 (IQR: 3.1,8.9) vs. 4.1 (IQR: 2.3,7.3) years] (Table 1). Biopsy rates were comparable in both groups (Supplementary Table 1).

The rate of reclassification after a diagnosis of GG2 was slightly lower than after a diagnosis of GG1, but the difference was not statistically significant; the 5-year reclassification rate was 30% (95% CI: 21-38%) for GG2 and 37% (95% CI: 34-39%) for GG1 (Figure 1). In multivariable modeling, when adjusted for age, BMI, % of cores positive for cancer, prostate size and PSA, all of which have previously been shown to be associated with reclassification,[11] diagnostic GG was significantly associated with time to reclassification such that GG2 at diagnosis was protective (HR = 0.63, 95% CI: 0.46-0.87, p = 0.01; Table 2).

Proportionally more patients diagnosed with GG2 were treated at 5 years compared to patients diagnosed with GG1 [58% (95% CI: 47-67%) vs 34% (95% CI: 31-36%), respectively; Figure 2A]. When further stratified by reclassification during surveillance, rates of definitive treatment were similar for both GG2 and GG1 participants who reclassified at a follow-up biopsy; the 5-year treatment rate was 74% (95% CI: 55-85%) and 79% (95% CI: 75-83%) respectively (Figure 2B). Participants diagnosed with GG2 who did not undergo grade reclassification were treated at a higher rate than GG1 participants who did not have reclassification; the 5-year treatment rates were 52% (95% CI: 37-63%) and 12% (95% CI: 10-14%) respectively. In multivariable modeling, the association between GG at diagnosis and time to treatment remained (HR = 1.41, 95% CI: 1.09-1.83, p = 0.01; Table 3).

There were 361 men who underwent RP after initial AS, 30 after an initial diagnosis of GG2 and 331 after a diagnosis of GG1. Adverse pathology was found in 16 (53%) of patients diagnosed with GG2 and 151 (46%) of the patients diagnosed with GG1 (Supplemental

Table 2). A diagnosis of GG2 was not significantly associated with AP either in univariate analysis (HR = 1.22; 95% CI: 0.64-2.16, p = 0.5) or after adjustment for diagnostic PSA and prostate size (HR = 1.26 95% CI: 0.65-2.26, p = 0.4; Table 4). In total, there were 616 men treated by either RP or radiation, with median follow-up after treatment of 3.2 (IQR: 1.3-5.5) years. Of these, 70 had an initial diagnosis of GG2 and 546 had an initial diagnosis of GG1. Rates of BCR within 3 years of treatment were similar in patients diagnosed initially with GG2 or GG1 (6% each) (Supplemental Figure 1). To date, no patients initially diagnosed with GG2 developed confirmed metastasis after treatment, and 6 patients (1%) diagnosed with GG1 developed distant metastasis after treatment.

Discussion

In this analysis, we evaluated clinical outcomes of men diagnosed with GG1 and GG2 prostate cancer and enrolled in a multi-institutional cohort of men following protocol-directed active surveillance. We found that the rate of biopsy reclassification was similar after diagnosis of GG2 or GG1 cancer. However, the rate of treatment was substantially higher in men diagnosed with GG2 cancer. This higher treatment rate was primarily because GG2 participants who did not reclassify at surveillance biopsy were treated at much higher rates than GG1 patients who did not reclassify. Reclassification led to similar treatment rates regardless of whether the patient was initially diagnosed with GG1 or GG2. In men who had curative treatment after initial surveillance, adverse pathology at RP and short-term BCR after treatment were apparently similar in patients diagnosed with GG1 and GG2 cancers.

Controversy still exists surrounding the recommendation of routine AS in men initially diagnosed with GG2 disease, even low volume GG2 who fulfill the favorable intermediate risk group criteria. In large randomized control trials of immediate treatment to watchful waiting, the only subgroup of participants who benefited from immediate definitive surgery were classified in the intermediate risk group with no available substratification of favorable versus unfavorable intermediate.[3,4] Indeed, all clinical guidelines promote equipoise between AS and definitive curative therapy in favorable intermediate risk disease, however some studies suggest that even two cores of GG2 should not undergo AS or that AS should not be considered outside of a clinical trial for GG2 disease.[6,13]

In the present study, we found that the 5-year treatment rate for patients diagnosed with GG2 was significantly higher than for patients diagnosed with GG1 (58% vs 34% respectively, p<0.001) and similar to other groups who have reported on GG2 patients undergoing AS[12]. After adjustment for age, BMI, positive biopsy cores, prostate size, and PSA, diagnostic GG2 remained significantly associated with time to treatment. Despite a similar treatment rate in GG1 and GG2 patients who had grade reclassification, GG2 patients who did not experience grade reclassification during active surveillance had a 4-fold increased rate of definitive treatment. Reasons for treatment in the absence of reclassification are likely multifactorial, and we have found married men and those with worse urinary quality of life more often elect treatment without reclassification.[14] Unadjusted rates of biopsy reclassification appeared similar between the two groups, but after adjustment, a diagnosis of GG2 cancer was protective of reclassification. These findings are consistent with earlier results from our group[15] and others,[13] and is likely explained in part by

higher withdrawal from AS in men diagnosed with GG2 before they undergo biopsy reclassification. Importantly, comparison of reclassification rates between GG1 and GG2 patients should be interpreted with caution as they are inherently different clinical scenarios. However, appreciating the reclassification and treatment rates for each presenting scenario is of utmost importance in framing a shared decision-making conversation. Causes of treatment in GG2 appear to be multifactorial and include an increase in the number of cores with pattern 4, an increase in percentage of pattern 4, and possibly the finding of adverse pathological subtypes such as cribriform pattern 4.

We also evaluated other clinical endpoints of AP, BCR, and metastasis in GG2 compared to GG1 patients. Perhaps surprisingly, we found no significant association, in either univariate or multivariable analysis, between diagnostic GG and AP. Furthermore, we did not observe a difference in recurrence after treatment or metastases in men diagnosed with GG2 versus GG1 cancer, although follow-up time is short and hampers definitive conclusions regarding the safety of managing GG2 cancers with AS.

Various strategies are available for incorporation into AS that may help to improve risk prediction in GG2 patients and aid in the decision to choose initial AS. For example, the percentage of Gleason pattern 4 has been shown to be associated with AP and BCR and may be used to further stratify GG2 disease in AS.[16,17] The presence of cribriform Gleason pattern 4 morphologies is also an important marker for aggressiveness in GG2 disease, and future studies in AS should address this parameter with relevant clinical outcomes.[18,19]

This study has limitations that merit mention. First, this study does not specifically ascertain the patient reported reasons for pursuing treatment, with or without grade reclassification. Centralized pathologic review was also not used in this study, although all the centers in PASS have genitourinary pathologists reviewing biopsies regularly and central pathology review within the Canary program is in progress. Finally, as previously mentioned, follow-up is relatively short, especially when assessing the clinical outcomes of BCR and metastasis-free survival. Despite these limitations, this study is strengthened by it being a prospective multicenter evaluation of AS in GG2 patients which includes a heterogeneous population treated by multiple different providers across institutions. Continued increased enrollment of GG2 patients is ongoing focus in PASS and will provide additional clarity as follow-up time matures.

Conclusions:

Patients diagnosed with low volume GG2 prostate cancer and enrolled in a multi-center, protocol-directed, active surveillance study received treatment at a higher rate than those diagnosed with GG1 cancer. In men treated after initial surveillance, we found no evidence that diagnostic GG was associated with adverse pathology in radical prostatectomies, or recurrence after treatment. These combined results can be used during a shared decision-making visit to fully inform GG2 patients about their likelihood of reclassification and eventual treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

FUNDING

Canary Foundation

Institute for Prostate Cancer Research

NIH R01CA184712

NIH U01CA113913

Key Definitions and Abbreviations

AS	active surveillance
AP	adverse pathology
BCR	biochemical recurrence
BMI	body mass index
GG	grade group
HR	hazard ratio
IQR	interquartile range
KM	Kaplan-Meier
MRI	magnetic resonance imaging
PASS	Prostate Cancer Active Surveillance Study
PCa	prostate cancer
PH	proportional hazard
PSA	Prostate-Specific Antigen
RP	radical prostatectomy

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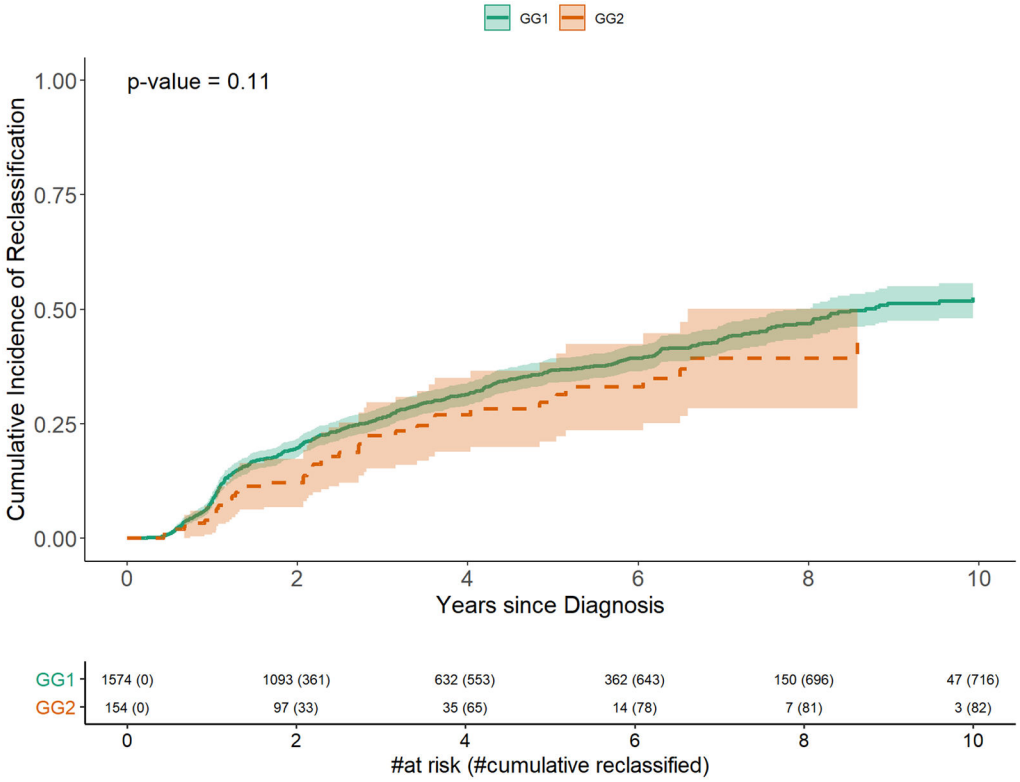

Figure 1.

Time to reclassification stratified by Gleason GG at diagnosis. Shaded area represents 95% CI.

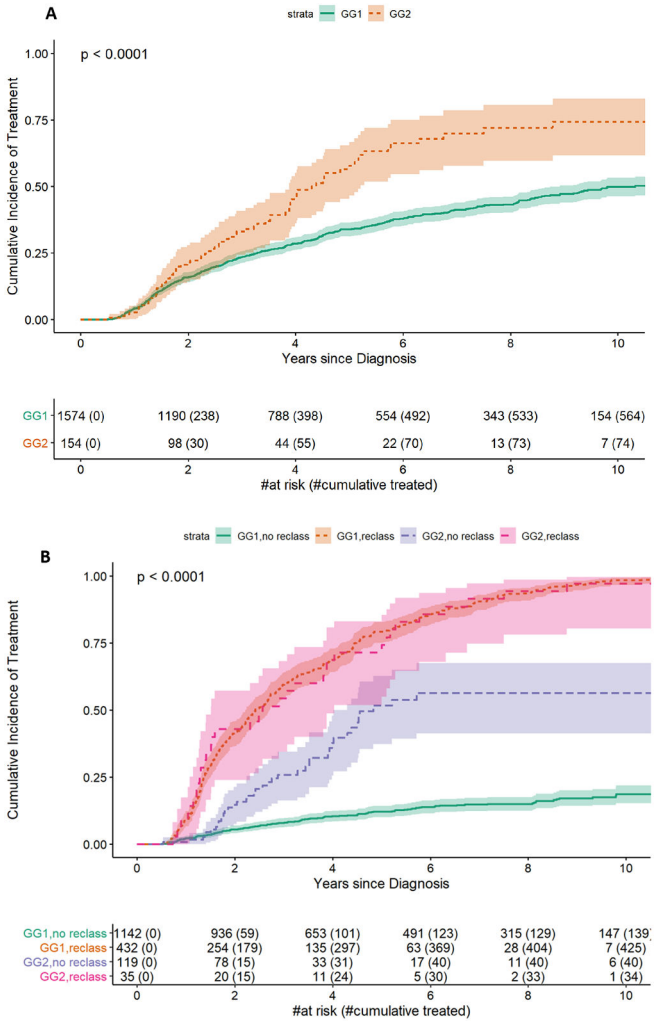

Figure 2.

Time to treatment stratified by (A) Gleason GG at diagnosis and (B) Gleason GG at diagnosis and biopsy grade reclassification before treatment. Shaded areas represent 95% CI.

Table 1:

Participant characteristics at diagnosis and during follow-up, reported either as median (IQR) or n (%).

	GG1 (N=1574)	**GG2 (N=154)**	**Overall (N=1728)**
Age (years)	63 (58,67)	66 (62,70)	63 (58,67)
Year of Diagnosis	2012 (2010, 2016)	2014 (2012, 2017)	2012 (2010, 2016)
Race			
Black	105 (6.7 %)	14 (9.1 %)	119 (6.9 %)
White	1387 (88 %)	133 (86 %)	1520 (88 %)
Other	67 (4.3 %)	6 (3.9 %)	73 (4.2 %)
Unknown	15 (1.0 %)	1 (0.6 %)	16 (0.9 %)
Clinical T-stage			
T1c	1402 (89 %)	126 (82 %)	1528 (88 %)
T2a	162 (10 %)	25 (16 %)	187 (11 %)
T2b-c	10 (0.6 %)	3 (1.9 %)	13 (0.8 %)
BMI (kg/m^2)	27 (25,30)	28 (26,32)	27 (25,31)
Prostate Size (cm^3)	44 (32,59)	41 (34,53)	43 (32,59)
PSA (ng/ml)	5.1 (4.0,6.6)	5.4 (4.3,7.0)	5.1 (4.0,6.7)
PSA Density	0.11 (0.08,0.16)	0.14 (0.09,0.17)	0.11 (0.08,0.16)
% Positive cores[1]	10 (8.3,17)	17 (10,30)	10 (8.3,17)
Total Follow-up[2] (years)	6.3 (3.1,8.9)	4.1 (2.3,7.3)	6.2 (3.0,8.8)
Follow-up for participants with no treatment (years)	5.4 (2.8, 8.5)	2.8 (1.7, 5.2)	5.2 (2.6,8.4)
Grade reclassification	585	43	628
Treatment	573	75	648
Radical Prostatectomy	331 (58 %)	30 (40 %)	361 (57 %)
Radiation	215 (38 %)	40 (53 %)	255 (39 %)
ADT	9 (1.6 %)	2 (2.7 %)	11 (1.7 %)
Other[3]	18 (3.1 %)	3 (4.0 %)	21 (3.2 %)

[1] Positive cores is defined as # cores positive for cancer/total # cores collected

[2] Follow-up is defined as time from diagnosis to last study contact

[3] Includes 5 GG1 and 1 GG2 RP for which pathology data was not available

Table 2.

Cox Proportional Hazards models for association of diagnostic characteristics and biopsy reclassification.

	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Diagnostic GG (2 vs 1)	0.90 (0.66 - 1.24)	0.5	0.63 (0.46 - 0.87)	0.01
Age	1.02 (1.01 - 1.03)	< 0.01	1.03 (1.02 - 1.04)	< 0.01
BMI	1.02 (1.00 - 1.03)	0.08	1.03 (1.02 - 1.05)	< 0.01
% positive cores (10% increase)	1.31 (1.23 - 1.39)	< 0.01	1.27 (1.19 - 1.35)	< 0.01
Prostate size[1]	0.99 (0.98 - 0.99)	< 0.01	0.98 (0.98 - 0.98)	< 0.01
PSA[1]	1.32 (1.15 - 1.53)	< 0.01	1.59 (1.36 - 1.85)	< 0.01

[1]Log transformed

Table 3.

Cox Proportional Hazards models for association of diagnostic characteristics and treatment during active surveillance.

	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Diagnostic GG (2 vs 1)	1.91 (1.49 - 2.45)	< 0.01	1.41 (1.09 - 1.83)	0.01
Age	1.01 (1.00 - 1.02)	0.16	1.01 (1.00 - 1.02)	0.08
BMI	1.00 (0.99 - 1.02)	0.7	1.02 (1.01 - 1.04)	0.01
% positive cores (10% increase)	1.37 (1.29 - 1.45)	< 0.01	1.28 (1.20 - 1.36)	< 0.01
Prostate size[1]	0.98 (0.98 - 0.99)	< 0.01	0.97 (0.97 - 0.98)	< 0.01
PSA[1]	1.34 (1.17 - 1.54)	< 0.01	1.72 (1.48 - 1.99)	< 0.01

[1]Log transformed

Table 4.

Weibull regression models for association of diagnostic characteristics and adverse pathology in men who underwent RP after initial surveillance.

Univariate modelling		
Variable	**HR (95% CI)**	**P value**
GG2	1.22 (0.64, 2.16)	0.5
Age	1.01 (0.98, 1.03)	0.7
BMI	1.04 (0.99, 1.08)	0.10
% positive cores	1.00 (0.99, 1.02)	> 0.9
Prostate size[1]	0.50 (0.32, 0.72)	< 0.001
PSA[1]	0.99 (0.93, 1.06)	0.7
PSA Density[1]	1.39 (0.95, 2.08)	0.10
Multivariate modelling		
Variable	**HR (95% CI)**	**P value**
GG2	1.26 (0.65, 2.26)	0.4
Prostate size[1]	0.49 (0.29, 0.71)	0.001
PSA[1]	1.00 (0.96, 1.11)	0.9

[1]Log transformed