Title

Precision Medicine in Active Surveillance for Prostate Cancer: Development of the Canary–Early Detection Research Network Active Surveillance Biopsy Risk Calculator

Journal

European Urology, 68(6)

ISSN

0302-2838

Authors

Ankerst, Donna P
Xia, Jing
Thompson, Ian M
et al.

Publication Date

2015-12-01

DOI

10.1016/j.eururo.2015.03.023

Peer reviewed

HHS Public Access

Author manuscript

Eur Urol. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Eur Urol. 2015 December ; 68(6): 1083–1088. doi:10.1016/j.eururo.2015.03.023.

PRECISION MEDICINE IN ACTIVE SURVEILLANCE FOR PROSTATE CANCER: DEVELOPMENT OF THE CANARY-EDRN ACTIVE SURVEILLANCE BIOPSY RISK CALCULATOR (ABC)

Donna P. Ankerst[1,2], **Jing Xia**[3], **Ian M. Thompson Jr**[1], **Josef Hoefler**[4], **Lisa F. Newcomb**[4], **James D. Brooks**[5], **Peter R. Carroll**[6], **William J. Ellis**[4], **Martin E. Gleave**[7], **Raymond S. Lance**[8], **Peter S. Nelson**[9], **Andrew A. Wagner**[10], **John T. Wei**[11], **Ruth Etzioni**[3], and **Daniel W. Lin**[4]

[1]Department of Urology University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

[2]Life Sciences Mathematics Unit, Technische Universitaet Muenchen, Munich, Germany

[3]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[4]Department of Urology, University of Washington, Seattle, WA, USA

[5]Department of Urology, Stanford University School of Medicine, Stanford CA

[6]Department of Urology, Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco, San Francisco, CA

[7]Department of Urologic Sciences, The Vancouver Prostate Centre, University of British Columbia, Vancouver, British Columbia

[8]Departments of Microbiology and Molecular Cell Biology and Urology, Eastern Virginia Medical School, Norfolk, VA

[9]Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, WA

[10]Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

[11]Department of Urology, University of Michigan, Ann Arbor, MI

Abstract

BACKGROUND—Men on active surveillance (AS) face repeated biopsies. Most biopsies will not show disease progression nor change management; such biopsies do not contribute to patient management, are potentially morbid, and costly.

Corresponding Author: Prof. Donna P. Ankerst, Zentrum Mathematik, M12, Technische Universitaet Muenchen, Boltzmannstr 3, 85747 Garching, Tel: +49 89 289 18388, Fax: +49 89 289 18435, ankerst@tum.de.

OBJECTIVE—To use a contemporary AS prospective trial to develop a tool to predict AS biopsy outcomes.

DESIGN, SETTING AND PARTICIPANTS—Biopsies (median 2, range 2 to 9 per patient) from 859 men participating in the Canary Prostate Active Surveillance Study with Gleason grade 6 prostate cancer (median follow-up: 35.8 [range 3.0–148.7] months) were analyzed.

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS—Logistic regression was used to predict progression, defined as Gleason score increase from ≤ 6 to ≥ 7 or increase in percent of cores positive for cancer from < 34% to ≥ 34%. 5-fold internal cross-validation was performed to evaluate the Area-Underneath-the-receiver-operating-characteristic-Curve (AUC).

RESULTS AND LIMITATIONS—Statistically significant risk factors for progression on biopsy were prostate-specific antigen (PSA), (odds ratio [OR] 1.045, 95% confidence interval [CI], 1.028 to 1.063), percent cores positive for cancer on most recent biopsy, (OR 1.401, 95% CI=1.301–1.508), and history of at least one prior negative biopsy (OR 0.524, 95% CI=0.417–0.659). A multivariable predictive model incorporating these factors, age, and number of months since last biopsy achieved an AUC of 72.4%.

CONCLUSIONS—A combination of readily-available clinical measures risk-stratify patients considering active surveillance prostate biopsy. Risk of progression or upgrading can be estimated and incorporated in clinical practice.

PATIENT SUMMARY—The Canary-EDRN Active Surveillance Biopsy Risk Calculator, an online tool, can be used to guide patient decision-making regarding follow-up prostate biopsy.

Keywords

active surveillance; biopsy; progression; prostate-specific antigen

INTRODUCTION

Although the increase in prostate-specific antigen (PSA) testing and resulting treatment of prostate cancer is likely responsible for some of the 44% fall in prostate cancer mortality witnessed in the United States since 1992, the increased testing has dramatically increased the detection of low-grade, low-volume tumors, particularly among older men [1], [2], and [3]. In the U.S. randomized study of prostate cancer screening, low-grade/low-risk cancers comprised 63% of cancers detected; in the more contemporary ProtecT study in the U.K., this rate was 77% [4] and [5]. Over-detection of cancer and the subsequent overtreatment with radical radiation or surgical therapies and the attendant gastrointestinal, urinary, and sexual side effects, was a primary reason for the U.S. Preventive Services Task Force recommendation *against* PSA testing for prostate cancer detection [6].

An appealing management plan for men with these low-grade, low-volume prostate cancers is Active Surveillance (AS). With this management strategy, patients with low-risk tumors are followed with periodic PSA tests (every 3–6 months), digital rectal examinations (DRE every 6–12 months), and ‘surveillance’ biopsies (every 1–3 years). The optimal frequency of repeat tests and biopsies has not yet been established. Conceptually, however, the goal of AS is clear: to spare the majority of men the morbidity of treatment while identifying those men

who harbor or develop more aggressive tumors, detecting such tumors sufficiently early to allow treatment. However, as prostate biopsy is painful, anxiety-provoking, expensive, and potentially-morbid (2–4% of patients will develop a fever or sepsis [7]), AS prostate biopsies revealing no cancer or no progression of cancer (according to grade or volume) are unnecessary and harmful; methods to reduce the number of AS biopsies could have substantial clinical utility.

Previous studies have examined variables associated with risk of upgrading of biopsy Gleason 6 disease at the time of radical prostatectomy [8] and [9]. In a study of 431 patients with Gleason 6 cancer who underwent radical prostatectomy, PSA density, obesity, number of positive biopsy cores and maximum core involvement were independently associated with the risk of upgrading [10]. Unfortunately, the standards for Gleason grading at biopsy and radical prostatectomy are fundamentally different so these measures may not be predictive of subsequent finding of higher grade disease on surveillance biopsy.

Herein, we have employed data from a large ongoing AS study in the U.S. to identify predictors of disease progression on surveillance biopsy. This analysis leverages data from over 800 AS cases in the Canary Prostate Active Surveillance Study (PASS) with a median of three years of follow-up to identify predictors of the outcome of biopsy on AS, including clinical, biomarker and pathologic data from previous visits and biopsies. To translate a summary of these data and results to community providers and their patients, a user-friendly tool is made available online.

MATERIALS AND METHODS

The Canary PASS is an ongoing multicenter, prospective AS study with Institutional Review Board approval and participants at Stanford University, University of California at San Francisco, University of British Columbia, University of Washington, University of Texas Health Science Center at San Antonio, Beth Israel Deaconess Medical Center, Eastern Virginia Medical School, and the University of Michigan. Since 2008, the study has recruited patients with previously untreated, early stage prostate cancer who elected AS for prostate cancer. While there was no eligibility restriction on time since initial diagnosis, over 75% of participants have been diagnosed within 18 months of study enrollment. Serum PSA measurements are performed every three months from the time of study entry, and DRE, at entry and every 6 months. Patients diagnosed within one year prior to study entry undergo repeat biopsy at the baseline visit if a biopsy with at least 10 cores was not available, at 6–12 months from diagnosis, at 2 years, and then every 2 years thereafter. Patients diagnosed greater than one year prior to the baseline visit undergo repeat biopsy at the baseline visit if only one prior biopsy or if the most recent biopsy was greater than 2 years prior to the baseline visit, and then every 2 years from the most recent biopsy [11]. Biopsies on study are specified to be a minimum of 10–12 cores, though deviations occur due to medical necessity or as part of the diagnostic biopsy performed prior to study start.

For this study participants with Gleason 6 or less cancer who enrolled in PASS from August 2008 until March 2013 and had at least one post-diagnostic biopsy performed were studied. Biopsy results with no PSA value within 12 months prior to diagnosis and PSA values

greater than 20 ng/ml that were spuriously high (with lower values before and after) were excluded from analysis. The primary outcome of progression (or disease reclassification), defined as either Gleason score upgrade from 6 or less to 7 or greater, or percent cancer cores positive for cancer increase from less than 34% to greater than or equal to 34%, was assessed using logistic regression. All biopsies per patient were used, excluding the diagnostic biopsy and biopsies performed after progression. Generalized estimating equations (GEEs) were used to fit the models in order to account for correlation among multiple biopsies performed on the same patients. These models essentially yield the same mean predictions as maximum likelihood, which assumes independent biopsies, but result in inflated standard errors, wider confidence intervals, and diminished statistical significance that more accurately reflect the amount of uncertainty in the data. Risk factors used in the models were age at biopsy, time in months since the most recent prior biopsy, most recent PSA value, PSA change (current PSA minus baseline PSA divided by months between), history of at least one prior negative biopsy (i.e., showing no cancer), and the percent of positive cores (< 34% vs. ≥ 34 %) obtained on the most recent prior biopsy. The optimal model for prediction was chosen as that which minimized the Bayesian Information Criterion (BIC) and internally validated using 5-fold cross-validation with reporting of the Area Underneath the Receiver Operating Characteristic curve (AUC).

All statistical tests were performed at the two-sided 0.05 significance level and all analyses were performed in the freeware R statistical package.

RESULTS

The study cohort comprised 859 PASS participants diagnosed with Gleason grade 6 prostate cancer and clinical characteristics listed in Table 1. The median follow-up was 35.8 months and ranged from 3.0 to 148.7 months. The median number of on-study biopsies per patient, including the biopsy at diagnosis, was 2 and ranged from 2 to 9; sequential biopsy and associated clinical results are shown in Table 2. The median number of cores taken on biopsy was 12 and higher for later visits, though a minority deviated. Most patients had stable disease, or no cancer detected, at their on-study biopsies. The percent progressing ranged from 10 to 30 percent across biopsy number (1st, 2nd, 3rd, etc.) on study, whereas upwards of 36% of biopsies at each visit showed no cancer (0 percent of cores positive for cancer).

Statistically significant risk factors for progression on biopsy were most recent prostate-specific antigen (PSA) value, odds ratio (OR) 1.045, 95% confidence interval (CI), 1.028 to 1.063 per 1 ng/mL, higher percent cores positive on the prior biopsy, OR = 1.401, 95% CI = 1.301 to 1.508 per 10%, and a history of one or more prior biopsies negative for prostate cancer, OR = 0.524, 95% CI 0.417 to 0.659. PSA change since baseline was not associated with progression ($p > 0.05$). Age of patient and months since the previous biopsy were also not associated with progression, but did contribute to improved validation so were left in the model; a multivariable model containing the predictors in Table 2 obtained a cross-validated AUC of 72.4%.

A potential artefact in terms of higher detection associated with more biopsy cores performed on the current biopsy was assessed by including as an additional predictor, the number of biopsy cores. This factor was not statistically significant ($p > 0.05$). To facilitate external validation, comparison with other published series, and physician-patient use, the calculator is posted online with a descriptive interface at prostate-cancer-risk-calculator.org.

DISCUSSION

There is a growing consensus that a substantial proportion of prostate cancers diagnosed through screening should be successfully managed with AS [12] and [13]. Multiple intermediate- and long-term studies have demonstrated that with this management strategy, treatment may be avoided in the majority of patients while achieving very high rates of disease-specific survival [14]. This was demonstrated even in the pre-PSA era in series managed conservatively [15] and [16]. The National Comprehensive Cancer Network includes AS as an option for low-risk localized prostate cancer and *recommends* AS for very low risk prostate cancer in men with 10–20-year life expectancy [17].

Increasingly-evident at centers with large numbers of men on AS is that, with the remarkably low risk of cancer progression or mortality among many contemporary cancers, the schedule for AS may be too intense for most patients. If, for example, a 52-year-old man is found to have 2% of one biopsy core with Gleason 3+3 disease and opts for an AS strategy with quarterly PSAs, semi-annual examinations, and biannual biopsies, and if he remains on surveillance and healthy until age 75, then, in the intervening 23 years, he will undergo 92 PSA tests, 46 DREs, and 11 prostate biopsies, each of which is costly, anxiety-provoking, and potentially-morbid, as in the case of biopsy with its risk of infection and bleeding. For some men, this management strategy may be a greater burden than simply proceeding to surgery or radiation. Of major concern is that some men may abandon AS (and undergo treatment) due to fatigue with repeated biopsies.

There are to date, several AS series reporting a multivariable model for prediction of reclassification of varying sample size/median follow-up compared to ours (n = 859/3.0 years). Ross et al (n = 290/2.9 years) focused on the utility of PSA kinetics (doubling time versus velocity) for monitoring men on AS, and found that neither predicted progression [18]. This agrees with our finding that change in PSA since baseline did not provide independent predictive power in determining risk of progression. Another smaller series but with longer follow-up compared to ours (205 patients/4.6 years) also found number of positive cores found in prior biopsies to be a significant predictor, in addition to PSA-density [19]. In our experience, prostate volume, included in the estimation of PSA-density, is often either missing or measured with error, but nonetheless we are currently investigating this marker in the PASS cohort. Interestingly, early results from the large Prostate cancer Research International Active Surveillance study (PRIAS) (n = 1480/1.6 years) have additionally isolated PSA density and number of prior cores as key predictors for progression [20]. Finally, the longest ongoing AS series, which included Gleason score 7 patients in AS (n = 993/6.4 years), also reported only two risk factors for biopsy reclassification: Gleason score at baseline and PSA at baseline [21]. None of these prior

studies provides an accessible predictive tool to our knowledge though undoubtedly more will appear in an increasingly patient-focused information age.

In this study, we have identified predictors that are easily measurable and contribute independently to predict the outcome of a surveillance biopsy: age of the patient, number of months since the last biopsy, most recent PSA value, percent of cores positive on the patient's last biopsy, and number of prior negative biopsies. The latter risk factor is one that has received little attention, or even awareness of, in the AS literature. A biopsy negative of cancer is not uncommon in AS men, and indeed was the case in more than 36% of the biopsies in this series. We found that this more detailed specification of the nature of the past biopsies to be more predictive than just knowing that a prior biopsy was performed (this risk factor was not significant in our model). Future AS studies should devote more attention to the findings of the grade as well as absence of tumor on biopsy.

A limitation of this study is the relatively short follow-up, with approximately 50% of patients having only 2 biopsies (Table 2). We have recently shown the need for clinical risk models to move away from static concepts and be dynamically updated over time as new data become available, as is standard practice in other fields [22]. We too plan future regular updates to the model and online tool. Another limitation of our study is that despite achieving statistical significance, the odds ratios associated with many of the identified risk factors for progression represent rather minor effects in terms of effect size. However, since predictions assimilate the effects of multiple predictors, overall accuracy as measured by the internally validated AUC shows good performance exceeding 70%. An internally validated AUC does not remove the need for external validation since it can be over-optimistic; this is another reason why the tool has been posted online at prostate-cancer-risk-calculator.org.

The online tool based on our analysis represents the first risk calculator for decision making among men on AS. We previously used a similar strategy to develop a tool for prediction of biopsy outcomes in men in whom cancer is suspected; this tool is now widely used [23]. We anticipate updating our AS calculator in the future. Planned updates will include adding new PASS patients and longer follow-up which will bring greater precision to the tool. Additionally, some specific aims of PASS incorporate the testing of novel markers that can be later added to the tool to enhance precision [24]. We have previously demonstrated how such markers can be incorporated into existing risk tools, even when the markers are measured on separate patient populations [25]. Such new markers are needed across the board for all progression tools. In conclusion, our AS calculator has the potential of reducing the burden of active surveillance – morbidity, cost, anxiety – while maintaining the very high rate of cancer-specific survival expected from a low-risk cohort. It brings us closer to developing an individualized protocol for determining surveillance biopsy frequency and establishes a baseline against which other predictive models, potentially incorporating novel markers or diagnostic tests, can be compared. With this tool, physicians may now have a conversation with patients on AS as to the potential outcomes of their surveillance biopsy, ideally, tailoring the intensity of AS (including biopsy frequency) to the patient's risk of disease progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Support: Canary Foundation, U01 CA086402, P30 CA054174, R01 CA183570

References

1. Etzioni R, Tsodikov A, Mariotto A, et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. Cancer Causes and Control. 2008; 19:175–181. [PubMed: 18027095]
2. Moul JW, Mouraviev V, Sun L, et al. Prostate cancer: the new landscape. Curr Opin Urol. 2009; 19:154–160. [PubMed: 19195129]
3. Cooperberg MR, Lubeck DP, Meng MV, et al. The changing face of low-risk prostate cancer; trends in clinical presentation and primary management. J Clin Oncol. 2004; 22:2141–2149. [PubMed: 15169800]
4. Andriole GL, Crawford ED, Grubb RL, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian cancer screening trial: mortality results after 13 years of follow-up. J Natl Cancer Inst. 2012; 104:125–132. [PubMed: 22228146]
5. Lane JA, Donovan JL, Davis M, et al. Active monitoring, radical prostatectomy, or radiotherapy for localized prostate cancer; study design and diagnostic and baseline results of the ProtecT randomized phase 3 trial. Lancet Oncol. 2014; 15:1109–1118. [PubMed: 25163905]
6. Moyer VA. Screening for prostate cancer. US Preventive Services Task Force recommendation statement. Ann Intern Med. 2012; 157:120–134. [PubMed: 22801674]
7. Loeb S, van den Heuvel S, Zhu X, et al. Infectious complications and hospital admissions after prostate biopsy in a European randomized trial. Eur Urol. 2012; 61:1110–1114. [PubMed: 22244150]
8. Epstein JI, Feng Z, Trock BJ, et al. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factor in in tertiary grades. Eur Urol. 2012; 61:1019–1024. [PubMed: 22336380]
9. Moussa AS, Li J, Soriano M, et al. Prostate biopsy clinical and pathological variables that predict significant grading changes in patients with intermediate and high grade prostate cancer. BJU Int. 2009; 103:43–48. [PubMed: 18782303]
10. Truong M, Slezak JA, Lin CP, et al. Development and multi-institutional validation of an upgrading risk tool for Gleason 6 prostate cancer. Cancer. 2013; 119:3992–4002. [PubMed: 24006289]
11. Newcomb LF, Brooks JD, Carroll PR PR, et al. Canary Prostate Active Surveillance Study: design of a multi-institutional active surveillance cohort and biorepository. Urology. 2010; 75:407–413. [PubMed: 19758683]
12. Mohler J, Bahnson RR, Boston B, et al. NCCN clinical practice guidelines in oncology: prostate cancer. J Natl Compr Canc Netw. 2010; 8:162–200. [PubMed: 20141676]
13. Cooperberg MR, Broering J, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol. 2010; 28:1117–1123. [PubMed: 20124165]
14. Klotz L, Zhang L, Lam A, et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol. 2010; 28:126–131. [PubMed: 19917860]
15. Whitmore WF Jr, Warner JA, Thompson IM Jr. Expectant management of localized prostate cancer. Cancer. 1991; 67:1091–1096. [PubMed: 1991257]
16. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA. 2005; 293:2095–2101. [PubMed: 15870412]
17. National Comprehensive Cancer Network. Guideline Version 1.2015. Prostate Cancer Update. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

18. Ross AE, Loeb S, Landis P, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. J Clin Oncol. 2010; 28:2810–2816. [PubMed: 20439642]
19. Iremashvili V, Burdick-Will J, Soloway MS. Improving risk stratification in patients with prostate cancer by active surveillance: a nomogram predicting the risk of biopsy progression. BJU Int. 2013; 112:39–44. [PubMed: 23551868]
20. Bul M, Zhu X, Valdagni R, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. Eur Urol. 2013; 63:597–603. [PubMed: 23159452]
21. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. JCO. 2015; 33:272–277.
22. Strobl A, Thompson IM, Vickers A, Ankerst DP. The next generation of clinical decision-making tools: development of a real-time prediction tool for outcome of prostate biopsy in response to a continuously evolving prostate cancer landscape. J Urol. 2015 to appear.
23. Ankerst DP, Hoefler J, Bock S, et al. Prostate Cancer Prevention Trial risk calculator 2.0 for the prediction of low- vs high-grade prostate cancer. Urology. 2014; 98:529–534.
24. Lin DW, Newcomb LF, Brown EC, et al. Urinary TMPRSS2:ERG and PCA3 in an active surveillance cohort: results from a baseline analysis in the Canary Prostate Active Surveillance Study. Clin Cancer Res. 2013; 19:2442–2450. [PubMed: 23515404]
25. Ankerst DP, Koniarski T, Liang Y, et al. Updating risk prediction tools: a case study in prostate cancer. Biom J. 2012; 54:127–142. [PubMed: 22095849]

Take Home Message

Urologists may now offer a customized approach to active surveillance to patients, allowing them to individualize their surveillance biopsy schedule, using the Active surveillance Biopsy Calculator (ABC). This approach may be more attractive to many patients and increase their participation in joint decision-making during follow-up.

Table 1

Participant characteristics at diagnosis.

Characteristic	PASS cohort (n=859)
Age at diagnosis	
≤ 49	40 (4.7%)
50–59	251 (29.2%)
60–69	461 (53.7%)
70–79	106 (12.3%)
≥ 80	1 (0.1%)
Race	
White	783 (91.2%)
Black	43 (5.0%)
Other	33 (3.8%)
PSA at diagnosis (ng/mL)	
0–2.5	104(12.1%)
2.5–4	148(17.2%)
4–6	352(41.0%)
6–10	192[(22.4%)
> 10	53(6.2%)
NA	10(1.2%)
T stage	
T1a, c	763(88.8%)
T2a	92(10.7%)
T2b, c	4 (0.5%)

Table 2

Biopsy characteristics at diagnosis and then at each sequential surveillance biopsy; not shown are 3 8th biopsy cases and 2 9th biopsy cases.

Characteristics	Diagnosis biopsy	First biopsy	Second biopsy	Third biopsy	Fourth biopsy	Fifth biopsy	Sixth biopsy	Seventh biopsy
# of patients	979	859	458	211	75	26	14	6
Mean (SD) age at biopsy (years)	62.0 (6.9)	63.0 (7.0)	64.4 (6.9)	65.5 (6.9)	65.5 (7.2)	67.5 (6.8)	66.5 (5.7)	65.1 (6.1)
Mean (SD) number of months since last biopsy	0 (0)	12.8 (8.8)	19.7 (8.3)	21.1 (7.9)	20.1 (7.8)	20.4 (5.7)	20.6 (5.5)	20.1 (5.8)
Mean (SD) of most recent PSA	5.5 (3.0)	5.0 (3.3)	5.2 (3.6)	5.4 (3.6)	5.5 (3.9)	5.0 (3.8)	5.3 (3.3)	5.0 (4.8)
Median (range) of number of biopsy cores	12 (4, 60)*	12 (4, 60)#	12 (4, 46)	12 (4, 46)	12 (4, 34)	15 (12, 18)	16 (12, 18)	17 (14, 20)
Percent of cores positive for cancer								
0	0 (0.0%)	312 (36.3%)	190 (41.5%)	88 (41.7%)	30 (40.0%)	11 (42.3%)	6 (42.9%)	3 (50%)
> 0 and < 34%	860 (87.8%)	465 (54.1%)	224 (48.9%)	104 (49.3%)	41 (54.7%)	14 (53.9%)	8 (57.1%)	3 (50%)
≥ 34%	37 (3.8%)	66 (7.7%)	37 (8.1%)	18 (8.85%)	4 (5.3%)	1 (3.9%)	0 (0.0%)	0 (0.0%)
NA	82 (8.4%)	16 (1.9%)	7 (1.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gleason score								
≤ 6	979 (100%)	732 (85.2%)	384 (83.8%)	166 (78.7%)	63 (84.0%)	23 (88.5%)	11 (78.6%)	6 (100.0%)
7	0 (0.0%)	123 (14.3%)	70 (15.3%)	43 (20.4%)	10 (13.3%)	3 (11.5%)	2 (14.3%)	0 (0.0%)
≥ 8	0 (0.0%)	4 (0.5%)	4 (0.9%)	2 (1.0%)	2 (2.7%)	0 (0.0%)	1 (7.1%)	0 (0.0%)
Outcome								

Characteristics	Diagnosis biopsy	First biopsy	Second biopsy	Third biopsy	Fourth biopsy	Fifth biopsy	Sixth biopsy	Seventh biopsy
Progression	0 (0.0%)	163 (0.0%)	104 (22.7%)	61 (28.9%)	19 (25.3%)	3 (11.5%)	3 (21.4%)	1 (16.7%)
Stable	897 (91.6%)	684 (79.6%)	347 (75.8%)	149 (70.6%)	56 (74.6%)	23 (88.5%)	11 (78.6%)	5 (83.3%)
NA	82 (8.4%)	12 (1.4%)	7 (1.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[*] 5 patients with number of cores below 4; 2 patients with number of cores above 60;

[#] 1 patient with a missing number of cores; 19 patients with more than 60 cores.

Eur Urol. Author manuscript; available in PMC 2016 December 01.

Table 3

Results of a logistic regression model for progression.

Covariates	Log odds ratio	Odds ratio	95% CI of odds ratio	P value
Intercept	−3.543	0.029	(0.014, 0.059)	<0.001
Age at biopsy	0.017	1.017	(1.006, 1.029)	0.127
Months since last biopsy	0.016	1.016	(1.008, 1.025)	0.053
Last PSA (ng/mL)	0.044	1.045	(1.028, 1.063)	0.008
Percent cores positive for cancer on last biopsy/10	0.337	1.401	(1.301, 1.508)	<0.001
Number of prior negative biopsies				
0	Ref			
1 or more	−0.646	0.524	(0.417, 0.659)	0.005