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Characterization of a “low-risk” cohort of grade group 2 prostate cancer patients: Results from the Shared Equal Access Regional Cancer Hospital database

Kathleen F McGinley^{1,2}, Xizi Sun^{2,3}, Lauren E Howard^{2,3}, William J Aronson^{4,5}, Martha K Terris^{6,7}, Christopher J Kane⁸, Christopher L Amling⁹, Matthew R Cooperberg¹⁰, Stephen J Freedland^{2,11}

¹Division of Urology, Department of Surgery, Duke University, Durham, North Carolina, USA

²Division of Urology, Veterans Affairs Medical Center, Durham, North Carolina, USA

³Department of Biostatistics and Bioinformatics, Duke University, Durham, North Carolina, USA

⁴Urology Section, Department of Surgery, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, California, USA

⁵Department of Urology, UCLA School of Medicine, Los Angeles, California, USA

⁶Section of Urology, Veterans Affairs Medical Center, Augusta, Georgia, USA

⁷Department of Urology, Georgia Regents University, Augusta, Georgia, USA

⁸Urology Department, University of California San Diego Health System, San Diego, California, USA

⁹Department of Urology, Oregon Health Sciences University, Portland, Oregon, USA

¹⁰Department of Urology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA

¹¹Division of Urology, Department of Surgery, Samuel Oschin Comprehensive Cancer Center, Cedars-Sinai Medical Center, Los Angeles, California, USA

Abstract

Objectives: To examine if there is a subset of men with grade group 2 prostate cancer who could be potential candidates for active surveillance.

Methods: We used the Shared Equal Access Regional Cancer Hospital database to identify 776 men undergoing radical prostatectomy from 2006 to 2015 with >8 biopsy cores obtained and complete information. We compared men who fulfilled low-risk disease criteria (clinical stage T1c/T2a; grade group 1; prostate-specific antigen <10 ng/mL) with the exception of grade group 2

Correspondence: Stephen J Freedland M.D., Cedars-Sinai Medical Center, 8635 West 3rd Street, Suite 1070W, Los Angeles, CA 90048, USA. stephen.freedland@cshs.org.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Conflict of interest

None declared.

versus men who met all three low-risk criteria. Logistic regression was used to test the association between grade group and radical prostatectomy pathological features. Biochemical recurrence was examined using Cox models. To examine whether there was a subset of men with low-volume grade group 2 with comparable outcomes to low-risk men, we repeated all analyses limiting the percentage of positive cores in the grade group 2 group to $\leq 33\%$, and positive cores to ≤ 4 , ≤ 3 or ≤ 2 .

Results: Grade group 2 low-risk men had increased risk of pathological grade group 3 or higher ($P = 0.001$), extraprostatic extension ($P = 0.001$), seminal vesicle invasion ($P = 0.001$) and higher risk of biochemical recurrence (hazard ratio = 1.76, $P = 0.006$). Using increasingly strict definitions of low-volume disease, at ≤ 2 positive cores there was no difference in adverse pathology between groups (all $P > 0.2$), except higher pathological grade group ($P = 0.006$). Biochemical recurrence was similar in men in grade group 1 and grade group 2 (hazard ratio = 1.24; $P = 0.529$).

Conclusions: Among men with prostate-specific antigen ≤ 10 ng/mL and clinical stage T1c/T2a, those in grade group 2 with ≤ 2 total positive cores have similar rates of adverse pathology and biochemical recurrence as men with grade group 1.

Keywords

biopsy; neoplasm grading; neoplasm recurrence; prostate cancer; prostatectomy

Introduction

AS is an attractive option to avoid overtreatment for men with low-risk disease typically defined as GG1, PSA ≤ 10 ng/mL, clinical stage $\leq$ T2a,¹ low disease volume on biopsy (limited by percentage or total number of positive cores)^{2–5} and low PSAD.^{6–8} Among men meeting these criteria, PC-specific mortality is low and radical treatment is avoided.⁹ Limited data exist on the inclusion of men with intermediate-risk PC, including GG2, into AS protocols.¹⁰ In the University of Toronto's AS cohort, 72 (17%) men were in GG2. Relative to men in GG1, those in GG2 were 1.8-fold more likely to undergo radical treatment.¹ Conversely, Cooperberg *et al* reported that among 90 men with intermediate-risk disease undergoing AS at UCSF, there was no difference in progression-free survival or the proportion of men undergoing treatment within a 4-year period versus men with low-risk disease.¹¹ Most recently, Musunuru *et al* released a study reporting lower overall survival and cause-specific survival in 213 patients aged greater than 70 years with clinical stage T2c or PSA ≤ 15 ng/mL or GG1–2 followed on AS at a single institution.¹²

As Gleason 7 is now the most common score on biopsy, we examined whether there was a subset of men in GG2 who would be reasonable candidates for AS.¹³ We hypothesized that by defining PSA, clinical stage and volume criteria on biopsy, we could identify a group of men in GG2 who would be candidates for AS, thereby further reducing PC overtreatment.

Methods

Study population

After obtaining institutional review board approval, data from patients at Veterans Administration Medical Centers (Palo Alto, CA, USA; West Los Angeles, CA, USA; San Diego, CA, USA; Durham, NC, USA; Augusta, GA, USA) were combined into the SEARCH database. As few men treated before 2001 had adequate prostate sampling (defined as >8 cores) and ISUP grading changed in 2005, we limited analyses to men treated in 2006 or later ($n = 2095$). We excluded men with missing data on race ($n = 22$), PSA ($n = 4$), GG ($n = 6$), pathological GG ($n = 7$), clinical stage ($n = 8$), number of cores taken ($n = 156$), number of positive cores ($n = 54$), PM ($n = 10$), EPE ($n = 17$), SVI ($n = 2$) and surgical technique ($n = 8$). Of the remaining 1801 men, 776 met our study criteria of PSA ≤ 10 ng/mL, GG2 or GG1, clinical stage T1c or T2a and >8 cores on biopsy. In a subset analysis, we further excluded men with missing PSAD data ($n = 80$). In this subset, 696 men met the study inclusion criteria.

We compared men who fulfilled the criteria of D'Amico low-risk disease (clinical stage T1c/T2a, GG1 and PSA ≤ 10 ng/mL) with the exception of GG2 (henceforth "GG2 low-risk") versus men who met all three criteria for D'Amico low-risk disease.¹⁴ We used this definition of low-risk disease for comparison, because AS is a recommended treatment option for men meeting these criteria in the NCCN Guide-lines.¹⁵

Statistical analysis

Differences in demographic and clinicopathological features between the GG2 low-risk and D'Amico low-risk group were examined using *t*-tests for normally distributed continuous variables, Wilcoxon rank-sum tests for non-normally distributed continuous variables, χ^2 -tests for categorical variables and Fisher's exact test for categorical variables with any expected cell count ≤ 5 .

Crude and adjusted logistic regression models were used to test the association between risk group (GG2 low-risk vs D'Amico low-risk) and RP pathological features (pathological GG1–2 vs 3–5, PM, EPE and SVI). Models were adjusted for age at surgery (continuous), surgery year (continuous), race (white vs black vs other), number of biopsy cores (continuous), surgical center, surgical technique, clinical stage (T1c vs T2a) and PSA (log-transformed, continuous).

On average, men were evaluated every 3 months in the first year postoperatively, every 6 months in years 2–3 and annually thereafter. BCR was defined as a single PSA >0.2 ng/mL, two consecutive PSAs of 0.2 ng/mL or secondary treatment for elevated PSA in the postoperative period.¹⁶ HRs for time to BCR between GG2 low-risk and D'Amico low-risk disease were analyzed using Cox proportional hazards analysis, adjusting for age at surgery (continuous), surgery year (continuous), race (white vs black vs other), surgical center, surgical technique, clinical stage (T1c vs T2a), PSA (log-transformed, continuous) and biopsy cores taken (continuous). Time to BCR was examined using the Kaplan–Meier method, and comparisons between the groups were carried out using the log-rank test.

All analyses were repeated, restricting the percentage or number of positive biopsy cores in the GG2 low-risk group, including positive cores 33%, 4 positive cores, 3 positive cores and 2 positive cores. A similar analysis was carried out, but matching the number or percentage of positive cores in the D'Amico low-risk and GG2 low-risk group.

In a subset analysis including men with PSAD data, all analyses were repeated limiting the PSAD threshold of the GG2 low-risk at 0.30, 0.25, 0.20, 0.15 and 0.10 ng/mL/g. To account for the possibility of late adoption of ISUP guidelines, we repeated the main analysis, but limited the cohort to patients with surgery in 2008 or more recently.

Statistical analyses were carried out using Stata 14.1 (StataCorp, College Station, TX, USA). Statistical significance was two-sided with $P < 0.05$.

Results

D'Amico low-risk patients versus GG2 low-risk patients

Baseline characteristics of the 776 men who met inclusion criteria are shown in Table 1. Median days from biopsy to RP was 113 days (IQR 83–159). Among all patients, 371 (48%) had D'Amico low-risk disease, and 405 (52%) had GG2 low-risk disease. The GG2 low-risk group was older (61.5 vs 60.5 years; $P = 0.026$), had a more recent median surgery year versus the D'Amico low-risk group (2012 vs 2010; $P < 0.001$), were more likely to have a robotic prostatectomy (60% vs 40%; $P < 0.001$) and undergo a PLND (65% vs 30%; $P < 0.001$). Among men whose cancer did not recur, median postoperative follow up was significantly shorter in the GG2 low-risk group (23.4 months vs 40.1 months; $P < 0.001$). As expected, GG2 low-risk men had more positive cores (4 vs 3; $P < 0.001$), greater percentage of positive cores (33% vs 25%; $P < 0.001$), and higher rates of EPE (14% vs 5%; $P < 0.001$), SVI (8% vs 2%; $P < 0.001$) and positive lymph nodes (1% vs <1%; $P = 0.024$) vs D'Amico low-risk men. Consistent with Gleason grading on prostate biopsy, GG2 low-risk men were more likely to be higher pathological GG versus D'Amico low-risk men (12% vs 27% GG1; 63% vs 51% GG2; 25% vs 11% GG3–5; $P < 0.001$). There were no significant differences in race, PSA, PSAD, clinical stage, days from biopsy to RP or PM.

The GG2 low-risk group had higher pathological GG, more EPE and more SVI, in both crude and adjusted models (all $P < 0.002$; Table 2). The risk of PM was not significantly different between groups. GG2 low-risk men had a higher risk of BCR than D'Amico low-risk men (log-rank, $P < 0.001$; Fig. 1a).

In order to identify if there were subsets of men with GG2 low-risk disease with outcomes similar to D'Amico low-risk men, we assessed the impact of limiting the analysis to men with low-volume GG2 low-risk disease, using varying definitions of “low-volume.” As the definition of low-volume became increasingly strict (i.e. fewer cores positive), the HR for BCR between the GG2 low-risk group and the D'Amico -risk group became increasingly smaller (i.e. closer to 1; Table 3). At 2 positive cores, the difference in time to BCR between the GG2 low-risk and the D'Amico low-risk group was not statistically significant (HR = 1.24, $P = 0.529$). When matching the definition of low-volume disease in both groups, men with GG2 low-risk disease and 2 positive cores had similar time to BCR

compared with men with D'Amico low-risk disease and ≥ 2 positive cores (HR = 1.47, $P = 0.315$; Tables S1–S3 and Fig. S1).

Analysis of GG2 low-risk patients versus D'Amico low-risk patients with ≥ 2 total positive cores

As time to BCR was comparable between the GG2 low-risk and D'Amico low-risk group when restricted to men with ≥ 2 total positive cores, we repeated the analysis comparing baseline characteristics (Table 4), risk of adverse pathology (Table 5) and BCR risk (Fig. 1b) between these groups. There were 371 men (81%) with D'Amico low-risk disease and 88 men (19%) with GG2 low-risk disease and ≥ 2 positive biopsy cores. Consistent with the larger cohort of men previously reviewed, the GG2 low-risk group with ≥ 2 total positive cores had a more recent median year of surgery than the D'Amico low-risk group (2011 vs 2010; $P = 0.001$). Median postoperative follow up was significantly shorter in the GG2 low-risk group compared with the D'Amico low-risk group (30.2 months vs 40.1 months; $P = 0.003$). While limiting the number of positive cores in the GG2 low-risk group to ≤ 2 , men in the GG2 low-risk group were more likely to have two positive cores versus the D'Amico low-risk group ($P = 0.004$), and a greater percentage of positive cores (17% vs 10%; $P = 0.018$). Consistent with biopsy GG, pathological GG was higher in the GG2 low-risk group compared with the D'Amico low-risk group (22% vs 38% GG1; 51% vs 51% GG2; 27% vs 11% GG3–5; $P < 0.001$). There were no significant differences in race, PSA at diagnosis, PSAD, clinical stage, number of biopsy cores, surgical technique, or rates of EPE, SVI or PM between groups.

The likelihood of the GG2 low-risk group having a pathological GG3–5 remained statistically greater than the D'Amico low-risk group ($P = 0.006$; Table 5). However, the risk of PM, EPE, and SVI were similar between the GG2 low-risk and the D'Amico low-risk group. There was no significant difference in time to BCR between the two groups (log-rank, $P = 0.528$; Fig. 1b).

Table S4 shows the stratification of D'Amico low-risk and GG2 low-risk men by year of surgery. Over time, the number of GG2 low-risk men undergoing surgery is increasing.

Subset analysis: D'Amico low-risk patients versus GG2 low-risk patients with PSAD data

An alternative means to select “low-risk” men in GG2 is to limit to men with low PSAD. To address this, we evaluated progressively lower PSAD thresholds in the GG2 low-risk group, and found that on univariable analysis men with GG2 low-risk had significantly higher BCR risk than the D'Amico low-risk group, until the PSAD was ≤ 0.10 ng/mL/g, when results were similar (HR = 1.10, $P = 0.819$; Table S5).

Sensitivity analysis: D'Amico low-risk patients versus GG2 low-risk patients in 2008–2015

To account for the possibility of late adoption of ISUP guidelines, we repeated the main analysis, but limited the cohort to 658 patients who underwent surgery between 2008 and 2015. The results were similar to the main analysis in that the GG2 low-risk group had higher pathological GG, more EPE and more SVI, in both crude and adjusted models (Table S6).

Discussion

As GG2 disease is now the most common score on biopsy, we examined if a subset of GG2 PC patients had similar outcomes to low-risk patients, and thus could be reasonable potential AS candidates.¹³ Using the SEARCH database of men undergoing RP, we compared men who fulfilled the D'Amico low-risk disease criteria versus men with GG2 low-risk PC, but who otherwise fulfilled the D'Amico low-risk disease criteria. We explored associations between risk group, RP pathological features and BCR, restricting PSAD (subset analysis) and the percentage or number of positive cores between the GG2 low-risk and the D'Amico low-risk group. We found that among men with PSA ≤ 10 ng/mL and clinical stage T1c/T2a, those with GG2 PC and a PSAD ≤ 0.10 ng/mL/g had similar rates of adverse pathology and BCR as men with GG1. The number of men meeting this PSAD threshold was ~15% of GG2 low-risk patients. We found that among men with PSA ≤ 10 ng/mL and clinical stage T1c/T2a, those with GG2 PC in ≤ 2 positive cores had similar rates of adverse pathology and BCR as men with GG1. The number of men meeting this cut-off was ~37% of SEARCH. Additional studies are required to assess the safety of including these men on AS protocols to reduce PC overtreatment.

Previous studies established higher rates of BCR, metastases and cancer-specific death in men with GG2 versus those with GG1.^{17–19} The heterogeneity of PC outcomes in men with Gleason 7 disease is recognized to strongly correlate with primary Gleason grade (3 vs 4).^{20,21} Although AS for low-risk disease has made progressive in-roads to mitigate PC overtreatment, a decrease in non-curative initial management among men with intermediate-risk PC has been observed in USA population-level datasets.²²

Our interest in the possible expansion of AS to a defined population of men with intermediate-risk PC is shared. In a European multi-institutional dataset, Gandaglia *et al.* reported no significant BCR difference between 564 men with GG2 organ-confined disease and 926 men with GG1 organ-confined disease who preoperatively met PRIAS criteria for AS.²³ In a single-institution RP dataset, Kwon *et al.* identified 217 men with GG2 disease who otherwise fulfilled at least one common AS protocol criteria (Hopkins,⁶ Memorial Sloan Kettering Cancer Center,³ PRIAS,²⁴ Miami,⁴ UCSF²⁵ or Toronto¹). They found the rate of pathologically aggressive disease would not significantly increase with expansion of AS criteria to include GG2 under most contemporary protocols.²⁶ Another single-institution study of 1190 men with GG2, but otherwise low-risk disease, found that men with low PSA and low stage might be suitable for AS.²⁷ Other tools for differentiating AS patients versus those who should be treated include multiparametric magnetic resonance imaging,²⁸ molecular markers²⁹ and possibly testosterone levels.³⁰

In a retrospective review of 2323 men who underwent RP for GG2 at six European institutions, Ploussard *et al.* determined that 46% had unfavorable disease at final pathology. However, by narrowing their selection criteria to men with PSA ≤ 10 ng/mL, PSAD ≤ 0.15 ng/mL/g, clinical stage T1c and ≤ 2 positive cores, the rate of adverse disease was 19%, leading the authors to conclude that expanding AS to these men might be acceptable provided strict adherence to selection criteria.³¹

Similar to Ploussard's analysis, we explored a PSAD of ≥ 0.15 ng/mL/g and ≥ 2 positive cores as cut-points. Although pathological outcomes and BCR were similar between the GG2 low-risk group with ≥ 2 positive cores and D'Amico low-risk group in our cohort, we found a threshold PSAD of ≥ 0.10 ng/mL/g was required to achieve similar outcomes between the groups. In SEARCH, 4.2% of men had GG2 low-risk disease and ≥ 2 positive cores on biopsy.

Including men with GG2, PSA ≤ 10 ng/mL, clinical stage T1c/T2a and ≥ 2 total positive cores would considerably expand the population eligible for AS. In the present study, among men with GG2 low-risk disease, 22% had ≥ 2 total positive cores on biopsy. Men meeting our GG2 low-risk disease criteria with ≥ 2 total positive cores comprised 5% of the entire SEARCH population between 2013 and 2015.

The present study had the inherent limitations of all retrospective analyses. Although our dataset included men from five Veterans Administration centers, central pathology review was not completed. Changes in Gleason grading during our study period might limit study validity. Specifically, grade migration resulting from changing ISUP guidelines could impact risk and outcomes over time. However, a sensitivity analysis restricting to men with surgery in more recent years showed similar results. We were unable to quantify the amount of Gleason 4 on pathology reports to distinguish a "large" GG2 from a "small" GG3, which might have similar prognosis. Furthermore, we did not examine more specific pathological characteristics, such as cribriform architecture, which is associated with tumor upstaging in GG2 patients.^{32,33} While a commonly used criterion for AS selection is $\geq 50\%$ tumor involvement in each core, this metric was not available in our data.³⁴ Pathological findings serve as intermediate end-points for aggressive disease, and might not predict disease-specific or overall survival; overall survival was not included, as few prostate cancer deaths occurred in the cohort. Year of surgery and follow-up length between our D'Amico low-risk and GG2 low-risk groups were significantly different, and introduce possible bias. As SEARCH is a RP database, an inherent selection bias exists. Towards this end, we noted more low-risk GG2 treated more recently and fewer GG1. Whether this reflects increased use of AS for GG1, changing PSA screening guidelines, or changing criteria for surgery or differences in grading is unknown without knowing the full spectrum of all men diagnosed with PC at all centers within SEARCH. The rate of upgrading in our low-risk patients was higher than in other studies, possibly related to our cohort including a large percentage of black men and not being limited by other AS criteria (i.e. no limits on the number of cores, PSAD or amount of any core involvement). How this could have affected the present results is unclear. Although we adjusted for known con-founders of adverse pathology, we had no way to account for unmeasured confounding. We chose pathological GG3 as our definition of aggressive disease, as the goal was not to understand factors predicting any upgrading, but rather upgrading to an aggressive disease. This definition has been used by others, and as these men are generally not considered AS candidates, this is a reasonable end-point.³⁵ As all men with GG2 low-risk disease in our dataset underwent RP, it is unknown if their outcomes with intervention reflect the natural history of GG2 low-risk disease monitored on AS. Furthermore, the time from biopsy to surgery was short, and thus we presume that all upgrading in the present study was as a result of sampling and not progression. As such, we are unable to account for differences in grade progression, which can occur over time in a

group not treated surgically. This further argues that validation of the present results in AS-managed patients is essential.

Among men with PSA ≤ 10 ng/mL and clinical stage T1c/T2a, those with GG2 PC in ≥ 2 total positive cores have similar rates of adverse pathology and BCR as men with GG1 disease. This finding, if confirmed in additional cohorts of AS patients, might expand AS protocol inclusion criteria to further reduce PC overtreatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations & Acronyms

AS	active surveillance
BCR	biochemical recurrence
EPE	extraprostatic extension
GG	grade group
HR	hazard ratio
ISUP	International Society of Urological Pathology
NCCN	National Comprehensive Cancer Network
PC	prostate cancer
PLND	pelvic lymph node dissection
PM	positive margins
PRIAS	Prostate Cancer Research International Active Surveillance
PSA	prostate-specific antigen
PSAD	prostate-specific antigen density
RARP	robotic-assisted radical prostatectomy
RP	radical prostatectomy
RRP	radical retropubic prostatectomy
SEARCH	Shared Equal Access Regional Cancer Hospital
SVI	seminal vesicle invasion

UCSF

University of California, San Francisco

References

1. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J. Clin. Oncol.* 2010; 28: 126–31. [PubMed: 19917860]
2. Cooperberg MR, Carroll PR, Klotz L. Active surveillance for prostate cancer: progress and promise. *J. Clin. Oncol.* 2011; 29: 3669–76. [PubMed: 21825257]
3. Berglund RK, Masterson TA, Vora KC, Eggener SE, Eastham JA, Guillonneau BD. Pathological upgrading and up staging with immediate repeat biopsy in patients eligible for active surveillance. *J. Urol.* 2008; 180: 1964–7. [PubMed: 18801515]
4. Soloway MS, Soloway CT, Eldefrawy A, Acosta K, Kava B, Manoharan M. Careful selection and close monitoring of low-risk prostate cancer patients on active surveillance minimizes the need for treatment. *Eur. Urol.* 2010; 58: 831–5. [PubMed: 20800964]
5. Selvadurai ED, Singhera M, Thomas K et al. Medium-term outcomes of active surveillance for localised prostate cancer. *Eur. Urol.* 2013; 64: 981–7. [PubMed: 23473579]
6. Tosoian JJ, Trock BJ, Landis P et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J. Clin. Oncol.* 2011; 29: 2185–90. [PubMed: 21464416]
7. van den Bergh RC, Vasarainen H, van der Poel HG et al. Short-term outcomes of the prospective multicentre “Prostate Cancer Research International: Active Surveillance” study. *BJU Int.* 2010; 105: 956–62. [PubMed: 19817747]
8. van den Bergh RC, Roemeling S, Roobol MJ et al. Gleason score 7 screen- detected prostate cancers initially managed expectantly: outcomes in 50 men. *BJU Int.* 2009; 103: 1472–7. [PubMed: 19154509]
9. Dall’Era MA, Klotz L. Active surveillance for intermediate-risk prostate cancer. *Prostate Cancer Prostatic Dis.* 2017; 20: 1–6. [PubMed: 27801900]
10. Dall’Era MA, Albertsen PC, Bangma C et al. Active surveillance for prostate cancer: a systematic review of the literature. *Eur. Urol.* 2012; 62: 976–83. [PubMed: 22698574]
11. Cooperberg MR, Cowan JE, Hilton JF et al. Outcomes of active surveillance for men with intermediate-risk prostate cancer. *J. Clin. Oncol.* 2011; 29: 228–34. [PubMed: 21115873]
12. Musunuru HB, Yamamoto T, Klotz L et al. Active surveillance for intermediate risk prostate cancer: survival outcomes in the Sunnybrook experience. *J. Urol.* 2016; 196: 1651–8. [PubMed: 27569437]
13. Fine SW, Amin MB, Berney DM et al. A contemporary update on pathology reporting for prostate cancer: biopsy and radical prostatectomy specimens. *Eur. Urol.* 2012; 62: 20–39. [PubMed: 22421083]
14. D’Amico AV, Whittington R, Malkowicz SB et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998; 280: 969–74. [PubMed: 9749478]
15. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Prostate Cancer, version 1.2015 Available from URL: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp
16. Cookson MS, Aus G, Burnett AL et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *J. Urol.* 2007; 177: 540–5. [PubMed: 17222629]
17. Bianco FJ Jr, Wood DP Jr, Cher ML, Powell IJ, Souza JW, Pontes JE. Tenyear survival after radical prostatectomy: specimen Gleason score is the predictor in organ-confined prostate cancer. *Clin. Prostate Cancer* 2003; 1: 242–7. [PubMed: 15040883]
18. Cuzick J, Fisher G, Kattan MW et al. Long-term outcome among men with conservatively treated localised prostate cancer. *Br. J. Cancer* 2006; 95: 1186–94. [PubMed: 17077805]

19. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* 2005; 293: 2095–101. [PubMed: 15870412]
20. Rastiah KK, Stricker PD, Haynes AM et al. Prognostic significance of Gleason pattern in patients with Gleason score 7 prostate carcinoma. *Cancer* 2003; 98: 2560–5. [PubMed: 14669274]
21. Wright JL, Salinas CA, Lin DW et al. Prostate cancer specific mortality and Gleason 7 disease differences in prostate cancer outcomes between cases with Gleason 4 + 3 and Gleason 3 + 4 tumors in a population based cohort. *J. Urol.* 2009; 182: 2702–7. [PubMed: 19836772]
22. Weiner AB, Patel SG, Etzioni R, Eggener SE. National trends in the management of low and intermediate risk prostate cancer in the United States. *J. Urol.* 2015; 193: 95–102. [PubMed: 25106900]
23. Gandaglia G, Ploussard G, Isbarn H et al. What is the optimal definition of misclassification in patients with very low-risk prostate cancer eligible for active surveillance? Results from a multi-institutional series. *Urol. Oncol.* 2015; 33: 164.e1–9.
24. 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]
25. Whitson JM, Porten SP, Hilton JF et al. The relationship between prostate specific antigen change and biopsy progression in patients on active surveillance for prostate cancer. *J. Urol.* 2011; 185: 1656–60. [PubMed: 21419438]
26. Kwon O, Kim TJ, Lee IJ, Byun SS, Lee SE, Hong SK. Can contemporary patients with biopsy Gleason score 3 + 4 be eligible for active surveillance? *PLoS ONE* 2014; 9: e109031.
27. Morlacco A, Chevillet JC, Rangel LJ, Gearman DJ, Jeffrey Karnes R. Adverse disease features in Gleason Score 3 + 4 “favorable intermediate-risk” prostate cancer: implications for active surveillance. *Eur. Urol.* 2016; doi: 10.1016/j.eururo.2016.08.043.
28. de Cobelli O, Terracciano D, Tagliabue E et al. Predicting pathological features at radical prostatectomy in patients with prostate cancer eligible for active surveillance by multiparametric magnetic resonance imaging. *PLoS ONE* 2015; 10: e0139696.
29. Ross AE, D’Amico AV, Freedland SJ. Which, when and why? Rational use of tissue-based molecular testing in localized prostate cancer. *Prostate Cancer Prostatic Dis.* 2016; 19: 1–6. [PubMed: 26123120]
30. Ferro M, Lucarelli G, Bruzzese D et al. Low serum total testosterone level as a predictor of upstaging and upgrading in low-risk prostate cancer patients meeting the inclusion criteria for active surveillance. *Oncotarget* 2017; 8: 18424–34. [PubMed: 27793023]
31. Ploussard G, Isbarn H, Briganti A et al. Can we expand active surveillance criteria to include biopsy Gleason 3 + 4 prostate cancer? A multi-institutional study of 2,323 patients. *Urol. Oncol.* 2015; 33: 71.e1–9.
32. Keefe DT, Schieda N, El HS et al. Cribriform morphology predicts upstaging after radical prostatectomy in patients with Gleason score 3 + 4 = 7 prostate cancer at transrectal ultrasound (TRUS)-guided needle biopsy. *Virchows Arch.* 2015; 467: 437–42. [PubMed: 26229020]
33. Flood TA, Schieda N, Keefe DT et al. Utility of Gleason pattern 4 morphologies detected on transrectal ultrasound (TRUS)-guided biopsies for prediction of upgrading or upstaging in Gleason score 3 + 4 = 7 prostate cancer. *Virchows Arch.* 2016; 469: 313–9. [PubMed: 27394432]
34. Russo GI, Cimino S, Castelli T et al. Percentage of cancer involvement in positive cores can predict unfavorable disease in men with low-risk prostate cancer but eligible for the prostate cancer international: active surveillance criteria. *Urol. Oncol.* 2014; 32: 291–6. [PubMed: 24184119]
35. Klein EA, Cooperberg MR, Magi-Galluzzi C et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur. Urol.* 2014; 66: 550–60. [PubMed: 24836057]

Fig. 1. Kaplan–Meier curves for risk of BCR in (a) all patients in the cohort and (b) patients with GG1 or GG2 and 2 positive biopsy cores.

Table 1Baseline characteristics between D'Amico low-risk^{††} and GG2 low-risk patients

	D'Amico low-risk <i>n</i> = 371 (48%)	Grade group 2 low-risk <i>n</i> = 405 (52%)	<i>P</i>-value
Age (mean ± SD)	60.5 ± 5.7	61.5 ± 6.1	0.026 [†]
Year of surgery	2010 (2008, 2012)	2012 (2010, 2013)	0.001 [‡]
Race, <i>n</i> (%)			0.800 [§]
White	195 (53)	204 (50)	
Black	165 (44)	187 (46)	
Other	11 (3)	14 (3)	
PSA (ng/mL)	5.3 (4.4, 6.9)	5.5 (4.6, 6.8)	0.363 [‡]
PSA density (ng/mL/cc)	0.16 (0.10, 0.23)	0.16 (0.12, 0.23)	0.092 [‡]
Clinical stage (%)			0.009 [§]
T1c	311 (84)	309 (76)	
T2a	60 (16)	96 (24)	
No. cores	12 (12, 12)	12 (12, 12)	0.002 [‡]
Positive cores	3 (2, 4)	4 (3, 6)	<0.001 [‡]
% Positive cores	25 (11, 36)	33 (23, 50)	<0.001 [‡]
Follow up (months)	40.1 (21.3, 63.1)	23.4 (12.0, 43.4)	<0.001 [‡]
Surgical technique, <i>n</i> (%)			0.010 [§]
Open RRP	159 (43)	147 (36)	
Perineal prostatectomy	12 (3)	5 (1)	
Laparoscopic prostatectomy	18 (5)	12 (3)	
RARP	182 (49)	241 (60)	
Pathological GG, <i>n</i> (%)			<0.001 [§]
1	139 (37)	49 (12)	
2	190 (51)	254 (63)	
3–5	42 (11)	102 (25)	
Extracapsular extension, <i>n</i> (%)	18 (5)	57 (14)	<0.001 [§]
Seminal vesicle invasion, <i>n</i> (%)	6 (2)	31 (8)	<0.001 [§]
Positive margins, <i>n</i> (%)	127 (34)	160 (40)	0.128 [§]
PLND performed, <i>n</i> (%)	109 (30)	263 (65)	<0.001 [§]
Positive lymph nodes, <i>n</i> (%)	2 (<1)	6 (1)	<0.001 [¶]
Days from biopsy to RP	111 (82, 169)	116 (86, 150)	0.943

P-value calculated using[†]
t-test[‡]
rank-sum test

^{\$} χ^2 -test or

[¶]Fisher's exact test. D'Amico low-risk patients had PSA ≤ 10 , clinical stage T1c–T2a, GG1 and ≥ 8 cores taken on biopsy. PSA density was available for 696 men. Cells show median (25th percentile, 75th percentile) unless otherwise noted. GG2 low-risk patients had PSA ≤ 10 , clinical stage T1c–T2a, GG2 and ≥ 8 cores taken on biopsy.

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Table 2

Odds ratios for risk group predicting pathological features between D'Amico low-risk and GG2 low-risk patients

	OR (95% CI)	P-value
Pathological GG3–5		
Crude	2.64 (1.78–3.90)	<0.001
Adjusted [†]	2.02 (1.32–3.08)	0.001
Positive margins		
Crude	1.25 (0.94–1.68)	0.129
Adjusted [†]	1.31 (0.95–1.82)	0.100
Extraprostatic extension		
Crude	3.21 (1.85–5.57)	<0.001
Adjusted [†]	3.30 (1.81–6.02)	<0.001
Seminal vesicle invasion		
Crude	5.04 (2.08–12.23)	<0.001
Adjusted [†]	4.32 (1.70–10.96)	0.002

[†] Adjusted for age, year, race, surgical center, surgical technique, clinical stage, number of biopsy cores taken and PSA.

Table 3

Hazard ratios for risk of biochemical recurrence for GG2 low-risk group relative to D'Amico low-risk group stratified by the number of positive biopsy cores

Entry criteria	No. D'Amico low-risk patients	No. GG2 low-risk patients	HR (95% CI)	P-value
Univariable				
All	371	405	1.92 (1.31–2.79)	0.001
<33% positive cores	371	177	1.72 (1.08–2.76)	0.023
4 positive cores	371	214	1.68 (1.08–2.62)	0.023
3 positive cores	371	163	1.73 (1.07–2.81)	0.025
2 positive cores	371	88	1.24 (0.64–2.40)	0.529
Multivariable				
All	371	405	1.77 (1.18–2.65)	0.006
<33% positive cores	371	177	1.77 (1.05–2.94)	0.033
4 positive cores	371	214	1.77 (1.09–2.87)	0.020
3 positive cores	371	163	1.76 (1.05–2.97)	0.033
2 positive cores	371	88	1.33 (0.66–2.67)	0.425

D'Amico low-risk patients had PSA <10, clinical stage T1c–T2a, GG1 and >8 cores taken on biopsy. GG2 low-risk patients had PSA <10, clinical stage T1c–T2a, GG2 and >8 cores taken on biopsy.

Table 4

Baseline characteristics between D'Amico low-risk and GG2 low-risk patients with 2 total positive biopsy cores

	D'Amico low-risk <i>n</i> = 371 (81%)	Grade group 2 low-risk <i>n</i> = 88 (19%)	<i>P</i>-value
Age (mean $\pm$ SD)	60.5 $\pm$ 5.7	62.3 $\pm$ 5.6	0.009 [†]
Year of surgery	2010 (2008, 2012)	2011 (2009, 2013)	<0.001 [†]
Race, <i>n</i> (%)			0.788 [¶]
White	195 (53)	43 (49)	
Black	165 (44)	42 (48)	
Other	11 (3)	3 (3)	
PSA (ng/mL)	5.3 (4.4, 6.9)	5.4 (4.4, 6.9)	0.993 [‡]
PSA density (ng/mL/cc)*	0.16 (0.10, 0.23)	0.14 (0.09, 0.19)	0.085 [‡]
Clinical stage (%)			0.145 [§]
T1c	311 (84)	68 (77)	
T2a	60 (16)	20 (23)	
No. cores	12 (12, 12)	12 (11, 12)	0.656 [‡]
Positive cores	3 (2, 4)	2 (1, 2)	<0.001 [‡]
% Positive cores	25 (11, 36)	17 (8, 17)	<0.001 [‡]
Follow up (months)	40.1 (21.3, 63.1)	30.2 (12.9, 48.8)	0.003 [‡]
Surgical technique, <i>n</i> (%)			0.68 [¶]
Open RRP	159 (43)	35 (40)	
Perineal prostatectomy	12 (3)	3 (3)	
Laparoscopic prostatectomy	18 (5)	2 (2)	
RARP	182 (49)	48 (55)	
Pathological GG, <i>n</i> (%)			<0.001 [§]
1	139 (38)	19 (22)	
2	190 (51)	45 (51)	
3–5	42 (11)	24 (27)	
Extracapsular extension, <i>n</i> (%)	18 (5)	4 (5)	0.999 [¶]
Seminal vesicle invasion, <i>n</i> (%)	6 (2)	2 (2)	0.653 [¶]
Positive margins, <i>n</i> (%)	127 (34)	24 (27)	0.212 [§]
PLND performed, <i>n</i> (%)	109 (30)	47 (53)	<0.001 [§]
Positive lymph nodes, <i>n</i> (%)	2 (<1)	0	<0.001 [¶]
Days from biopsy to RP	111 (82, 169)	110 (80, 141)	0.274

P-value calculated using

[†] t-test

[‡]rank-sum test

^{\$} χ^2 -test or

[¶]Fisher's exact test. D'Amico low-risk patients had PSA ≤ 10 , clinical stage T1c–T2a, GG1, and ≥ 8 cores taken on biopsy. PSA density was available for 408 men. Cells show median (25th percentile, 75th percentile) unless otherwise noted. GG2 low-risk patients had PSA ≤ 10 , clinical stage T1c–T2a, GG2 and ≥ 8 cores taken on biopsy.

Table 5

Odds ratios for risk group predicting pathological features between D'Amico low-risk and GG2 low-risk patients with 2 total positive biopsy cores

	OR (95% CI)	P-value
Pathological GG3–5		
Crude	2.94 (1.66–5.19)	<0.001
Adjusted [†]	2.38 (1.28–4.44)	0.006
Positive margins		
Crude	0.72 (0.43–1.21)	0.213
Adjusted [†]	0.82 (0.47–1.43)	0.486
Extraprostatic extension		
Crude	0.93 (0.31–2.83)	0.904
Adjusted [†]	1.04 (0.32–3.42)	0.946
Seminal vesicle invasion		
Crude	1.41 (0.28–7.13)	0.674
Adjusted [†]	1.92 (0.29–12.6)	0.496

[†] Adjusted for age, year, race, surgical center, surgical technique, clinical stage, number of biopsy cores taken and PSA.