NIH-PA Author Manuscript

Predictive models for worsening prognosis in potential candidates for active surveillance of presumed low-risk prostate cancer

Prasanna Sooriakumaran,
Department of Urology, Lefrak Center of Robotic Surgery & Institute of Prostate Cancer, Weill Cornell Medical College, James Buchanan Brady Foundation, New York, NY 10065, USA

Abhishek Srivastava,
Department of Urology, Lefrak Center of Robotic Surgery & Institute of Prostate Cancer, Weill Cornell Medical College, James Buchanan Brady Foundation, New York, NY 10065, USA

Paul Christos,
Department of Statistics & Public Health, Weill Cornell Medical College, New York, NY, USA

Sonal Grover,
Department of Urology, Lefrak Center of Robotic Surgery & Institute of Prostate Cancer, Weill Cornell Medical College, James Buchanan Brady Foundation, New York, NY 10065, USA

Maria Shevchuk, and
Department of Pathology, Weill Cornell Medical College, New York, NY, USA

Ashutosh Tewari
Department of Urology, Lefrak Center of Robotic Surgery & Institute of Prostate Cancer, Weill Cornell Medical College, James Buchanan Brady Foundation, New York, NY 10065, USA

Ashutosh Tewari: akt2002@med.cornell.edu

Abstract

Purpose—Low-risk prostate cancer patients clinically eligible for active surveillance can also be managed surgically. We evaluated the pathologic outcomes for this cohort that was treated by radical prostatectomy and devised nomograms to predict patients at risk of upgrading and/or upstaging.

Materials and methods—Seven hundred and fifty patients treated by radical prostatectomy from Jan 2005 to the present fulfilled conventional active surveillance criteria and formed the study cohort. Preoperative data on standard clinicopathologic parameters were available. The radical prostatectomy specimens were graded and staged, and any upgrading to Gleason sum >6 or upstaging to ≥pT3 ('worsening prognosis') were noted. Multivariable logistic regression models were used to develop predictive nomograms.

Results—Of the 750 patients, 303 (40.4%) patients were either upgraded or upstaged. Multivariable analysis found that preoperative PSA, number of positive cores, and prostate volume were significantly predictive of worsening prognosis and formed the nomogram criteria.

Conclusions—Of patients deemed eligible for active surveillance based on conventional criteria, 40.4% have worse prognostic factors after radical prostatectomy. Current active surveillance criteria may be too relaxed, and the use of nomograms which we have devised, may aid in counseling primary prostate cancer patients considering active surveillance as their therapy of choice.

Keywords

Active surveillance; Nomograms; Prostate cancer

Introduction

Prostate cancer is the commonest nondermatologic cancer in Western men [1]. In recent years, increased public awareness and prostate-specific antigen (PSA) screening have led to more men being diagnosed earlier with prostate cancer that is deemed to be low risk disease, defined as PSA 10 ng/ml, biopsy Gleason score 6, and clinical stage T2a [2]. For these patients, active surveillance (AS) with selective delayed intervention is becoming an increasingly popular alternative to upfront extirpative surgery or radiotherapy. It seeks to avoid the morbidity associated with overtreatment of indolent prostate cancer and delay treatment for disease until it becomes clinically significant. Current selection protocols into AS programs [3, 4] comprise variations of the criteria first proposed by Epstein et al. [5] in 1994 in which men with a PSA density 0.15 ng/ml/g, Gleason grade 6, 2 positive biopsy cores, and no biopsy core with more than 50% involvement are eligible. These selection criteria have been reported to accurately predict for clinically insignificant disease with a positive predictive value of up to 95% and a negative predictive value of 66% [5].

However, recent studies have raised the concern of inappropriate treatment being recommended based on inaccurate reporting of the Gleason sum (GS) on initial needle biopsy report [6–8]. Hence, it appears that current AS criteria may include patients with higher Gleason sums than thought at clinical diagnosis. These patients may be at increased risk of worse prognosis should they be considered erroneously as suitable for AS strategies. Upstaging from biopsy to radical prostatectomy histology can also occur and again worsen the prognosis of potentially eligible AS candidates. Predicting upstaging from cT2a disease relies on the definition of upstaging: disease on final pathology encompassing more than half of one lobe or bilateral disease is pT2b/c, but this may simply be due to better sampling of the cancer and not due to clinically significantly increased tumor bulk beyond that predicted by clinical stage. Hence, in agreement with other investigators, we consider upstaging to pT3 (disease no longer confined to the prostate) as our staging criterion of worsening prognosis. Herein, we report our experience in predicting upgrading to Gleason sum 7 and/or upstaging to pT3 at final pathology in a cohort of AS-eligible men who underwent robotic-assisted radical prostatectomy by a single surgeon (AT) at a single institution.

Materials and methods

Patient selection

This is an institutional review board-approved, retrospective cohort study from a prospective database on patients undergoing robotic-assisted laparoscopic radical prostatectomy for prostate cancer. Data from 2,476 patients, from January 2005 to September 2010, were analyzed.Of these patients, 750 were classified as patients that fulfilled standard active surveillance (AS) criteria: PSA 10, clinical stage 2a, Gleason 6, 2 cores positive, and less than 50% cancer present in any one core. Preoperative data including PSA, biopsy Gleason score, number of cores taken, number of positive cores, maximal percentage of

cancer on biopsy core, clinical stage, presence of HGPIN, and prostate volume were recorded.

Pathologic examination of prostate specimens

All biopsy and prostate specimens were reviewed at our institution by the surgical pathology department. Prostate specimens were serially sectioned from apex to base. Histologic examination reported standard diagnostic criteria including Gleason grading and pathologic stage. To ameliorate interobserver variability of Gleason sum and pathologic stage reporting, 182 consecutive radical prostatectomy specimens were externally reviewed by an experienced offsite genitourinary pathologist. After establishing a concordance rate of 89% between our in-house and offsite pathologists' reports, external validation was discontinued for financial prudence.

Statistical analysis

Patients were defined into two groups: one cohort that remained low risk and suitable for AS, and a second group that was deemed "worsening prognosis" due to Gleason upgrading to 7 and/or upstaging to pT3. Descriptive statistics (including mean, standard deviation, median, range, frequency, and percent) were calculated for the study cohort. Univariable analyses using t-tests, Wilcoxon rank-sum tests, and chi-square tests were performed to determine predictors of worsening prognosis from the list of preoperative variables. Multivariable logistic regression modeling was used to evaluate a priori defined variables (PSA, number of cores taken, number of positive cores, maximal percentage of cancer on biopsy core, clinical stage, presence of HGPIN, and prostate volume) for predicting upgrading, upstaging, and either upgrading or upstaging (worsening prognosis) (i.e., three separate models). Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated from the univariable and multivariable models. The area under the curve (AUC) method was used to quantify the predictive accuracy (PA) of (1) each variable on univariable analysis and (2) the final multivariable models (via the concordance index [c-index] from the univariable and multivariable logistic regression models). All PA estimates were internally validated using 200 boostrap samples. Nomograms were created to predict upgrading, upstaging, and worsening prognosis, using variables from the multivariable models with associated *P* values less than 0.20 or large effect estimates (regardless of *P* value) [9]. Finally, calibration plots were fitted to evaluate the extent of over-or-under-estimation of the observed upgrading, upstaging, and worsening prognosis rates. All *P* values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in SAS Version 9.2 (SAS Institute Inc., Cary, NC). The nomograms and calibration plots were constructed in R Version 2.10.1 (The R Foundation for Statistical Computing, 2009).

Results

Out of a cohort of 2,476 men undergoing robotic radical prostatectomy, 750 patients fulfilled all the following preoperative selection criteria for active surveillance: PSA <10 ng/ dl; clinical stage T2a, Gleason 6; 2 positive cores; and 50% cancer present in any one core. Review of these 750 radical prostatectomy specimens showed that 297 demonstrated Gleason upgrading on final pathology (39.6%), while 453 were not upgraded (60.4%). Of the 750 patients 29 (3.9%) patients were upstaged to at least pT3, and 303/750 (40.4%) were either upgraded or upstaged. Patients with Gleason upgrading at final pathology had significantly higher BMI (*P* = 0.004), higher preoperative PSA (*P* < 0.001), higher number of positive cores, higher maximum percentage of cancer in biopsy (*P* = 0.02), smaller prostates (*P* = 0.08), higher Gleason pathology score (*P* < 0.0001), higher percentage with pT3–4 disease (*P* < 0.0001), and higher positive margin rate (*P* < 0.0001) compared with patients who did not display GS upgrading (Table 1). Both cohorts had similar age, number

of biopsy cores taken, HGPIN on biopsy, preoperative Gleason biopsy score, and clinical stage (Tables 2, 3).

In an effort to determine variables that correlated with upgrading, upstaging, or either upgrading or upstaging (worsening prognosis), univariable and multivariable analyses were performed. Preoperative PSA, number of positive cores, and maximum percentage of cancer in biopsy cores were predictive of upgrading at $P < 0.05$ on univariable analysis with odds ratios of 1.17, 2.08, and 1.44, respectively (Table 4). Based on multivariable analysis, preoperative PSA, number of positive cores, and lower prostate volume were statistically significant contributors to upgrading at $P < 0.20$ with odds ratios of 1.24, 1.94, and 0.99, respectively (Table 5), and were entered into the upgrading nomogram. This nomogram (Fig. 1) was reasonably discriminatory at differentiating between patients deemed clinically eligible for AS based on current conventional criteria who remained eligible from those that would be upgraded were they to have undergone surgery (bootstrap corrected c-index 0.65). The nomogram was also well calibrated internally though did slightly underpredict the risk of upgrading in those at <30% and >50% actual risk (data not shown).

None of the variables were predictive of upstaging at $P < 0.05$ on univariable analysis (Table 6). However, based on a restricted multivariable analysis (i.e., due to the small number of outcome events only four variables could be explored in the model), preoperative PSA, number of positive cores, and lower prostate volume were statistically significant contributors to upstaging at $P < 0.20$ with odds ratios of 1.21, 1.95, and 0.98, respectively (Table 7), and were entered into the upstaging nomogram. Clinical stage was also entered into the upstaging nomogram as its effect estimate was large (OR 1.94) and the lack of significance was likely the result of the low number of outcome events ($n = 29$). This nomogram (Fig. 2) was also reasonably discriminatory at differentiating between patients deemed clinically eligible for AS based on current conventional criteria who remained eligible from those that would be upstaged were they to have undergone surgery (bootstrap corrected c-index 0.65). The nomogram was also well calibrated internally though the probability of upstaging was < 20% in our patients (data not shown).

Preoperative PSA, number of positive cores, and maximum percentage of cancer in biopsy cores were predictive of either upgrading or upstaging (worsening prognosis) at $P < 0.05$ on univariable analysis with odds ratios of 1.17, 2.08, and 1.44, respectively (Table 8). Based on multivariable analysis, preoperative PSA, number of positive cores, and lower prostate volume were statistically significant contributors to worsening prognosis at $P < 0.20$ with odds ratio of 1.24, 1.93, and 0.99, respectively (Table 9), and were entered into the worsening prognosis nomogram. This nomogram (Fig. 3) was also reasonably discriminatory at differentiating between patients deemed clinically eligible for AS based on current conventional criteria who remained eligible from those that would be upgraded or upstaged were they to have undergone surgery (bootstrap corrected c-index 0.64). The nomogram was also well calibrated internally though did slightly underpredict the risk of worsening prognosis in those at <30% and >50% actual risk (data not shown).

Discussion

The proportion of men having low-risk prostate cancer at diagnosis has doubled in the past decade, largely as a result of screening, accounting for almost half of all men being diagnosed with prostate cancer in 2000–2001 in the CaPSURE registry [2]. The European Randomized Study of Screening for Prostate Cancer reported that although PSA-based screening reduced the rate of prostate cancer mortality by 20%, this was associated with a high risk of overdiagnosis [10]. Hence, AS with selective delayed intervention has become an increasingly attractive option for patients diagnosed with low-risk prostate cancer, who

wish to avoid the myriad of complications from overtreatment for otherwise indolent disease. Emerging evidence from single- and multiinstitutional studies now suggest that AS is safe, is associated with a low risk of disease progression, and does not significantly compromise disease-specific outcomes [3, 11, 12]. However, underestimation of disease severity in AS-eligible men remains a primary concern, with the incidence of Gleason upgrading at final pathology varying from 18 to 50% in various series [6, 8, 13]. Also, the pT3 rate in such AS-eligible patients is 10–15% [14, 15]. Taken together, these findings suggest a significant percentage of men thought to be low risk and suitable for AS strategies may actually harbor more sinister disease.

Our analyses demonstrate that PSA, number of positive cores, and lower prostate volume are significant predictors of upgrading or upstaging in patients deemed eligible for AS by conventional criteria. Freedland et al. [16] and Briganti et al. [17] both demonstrated that smaller prostate glands were associated with more high-grade cancers, a higher likelihood of extracapsular extension, seminal vesicle invasion, and earlier biochemical progression after surgery. In 1999, D'Amico and colleagues first reported the significant association between prostate gland volume 75 cm^3 and PSA >20 ng/dL with Gleason upgrading [6], which has been confirmed by other investigators [13, 18, 19]. However, Kulkarni et al. [20] failed to demonstrate an association between small prostate volumes and upgrading or upstaging, and the small effect estimate in our study of 0.99 suggests that prostate volume may not be very clinically significant. It may be that it is not prostate volume but rather more thorough preoperative needle sampling in a smaller gland that accounts for some studies showing worsening prognosis in men with small glands. Previous studies have indeed reported a lower likelihood of GS discordance with extended biopsy schemes [21, 22]. Turley et al. [23] recently reported that the association between smaller prostate volume and upgrading was significant only in men who had an extended-core biopsy ($P < 0.001$), but not in men with a sextant biopsy ($P = 0.22$). Other investigators, however, failed to confirm this finding or correlate number of cores taken with upstaging [7, 13]. In our study, the number of biopsy cores taken was not significant for predicting worsening prognosis in a multivariable model. However, number of positive cores (2 vs. 1) almost doubled the risk of worsening prognosis on multivariable analysis (OR 1.93).

Several studies have already documented that a higher baseline PSA as being associated with adverse pathologic features at radical prostatectomy [8, 22]. Baseline PSA density, which is a composite of PSA and prostate volume has been previously reported to be a significant predictor for adverse pathologic features and disease progression in men undergoing radical prostatectomy after AS [24]. In their series of men with prostate cancer managed with AS, Dall'Era et al. [25] reported that those with baseline PSA density >0.15 ng/ml/cm^3 were five times more likely to receive active treatment than men with a lower PSA density. In their series of men undergoing robotic-assisted radical prostatectomies who had Gleason 6 microfocal prostate cancer on biopsy (who would be deemed to have low risk disease), Thong et al. [26] also reported that PSA density >0.20 ng/ml/cm^3 was a significant predictor of both upgrading and upstaging. This is consistent with our study results showing that elevated PSA and lower prostate volume are significantly associated with upgrading and/or upstaging.

Interobserver variability has also been previously cited as a cause for upgrading or upstaging [27]. To ameliorate this possible confounder, 182 consecutive radical prostatectomy specimens were reviewed by an experienced external uropathologist after the specimens had been processed and reported by two dedicated in-house uropathologists according to our institutional protocols. An 89% concordance rate was achieved between both in-house and external pathologists, following which external validation was discontinued for financial

prudence. Nonetheless, not being able to externally validate all of our radical prostatectomy specimens constitutes a limitation of this study.

Using the models of best fit from the multivariable analyses, we created nomograms to aid in the prediction of Gleason upgrading, pathologic upstaging, and either upgrading or upstaging (worsening prognosis). PSA density was not used in the nomogram derivation as this is a function of PSA and prostate volume, which are usually measured separately by most clinicians. These two variables were therefore separately used in the statistical modeling. Our nomograms should aid the practicing urologist, oncologist, and general practitioner who see patients with low-risk prostate cancer to adequately counsel them regarding their appropriateness for active surveillance. Rather than selecting arbitrary cut-offs, these nomograms enable the prediction of risk of worsening prognosis in clinically low risk patients deemed suitable for AS strategies. However, the models of best fit used in the derivation of the nomograms have concordance indexes (or area under the curve) of 0.64–0.65, making them only fairly discriminatory. In other words, there is a 64–65% chance that a pair of AS conventionally eligible individuals, one who is upgraded and/or upstaged on final histology and one who is not, will be correctly classified as such by the nomograms. The nomograms were also found to be well calibrated, especially in the middle range, meaning that the physician can give a reasonably accurate prediction of the probability that an AS conventionally eligible patient will be upgraded and/or upstaged were he to have surgery, assuming the patient was not deemed to be at the extremes of risk.

This work has a number of limitations. For one, the nomograms have not yet been validated by other surgical cohorts, and thus, the generalizability of their use remains in question. Other limitations of this study are its retrospective nature and inclusion of patients who did not have routine repeat restaging biopsy. In their cohort of 104 men who were eligible for AS but underwent immediate repeat biopsy, Berglund et al. [28] reported that 27% demonstrated GS upgrading or upstaging on repeat biopsy. These men with upgraded or upstaged disease were more likely to have higher pathologic stage and grade at radical prostatectomy than those who were not, suggesting that early repeat biopsy helps better select patients with low risk disease who would derive the most benefit from AS protocols [12]. Also, whether this upgrading and/or upstaging will result in differences in prostate cancer specific and/or overall survival will require longer follow-up of these patients, which is ongoing. Nevertheless, this study represents the largest study to date looking at predictors for upgrading and/or upstaging in AS-eligible men who chose to undergo radical prostatectomy.

Conclusions

Increasing evidence is emerging that contemporary selection criteria used for enrollment into active surveillance programs may be inadequate for keeping out those men with high risk of upgrading or upstaging at final pathology, with the attendant risks of delayed treatment, adverse pathologic features and biochemical progression. In our series, 40.4% of patients deemed eligible for AS by conventional criteria were upgraded and/or upstaged. Preoperative PSA, number of positive cores (2 vs. 1), and lower prostate volume are significant independent predictors for worsening prognosis. Until advances in proteomics, gene studies, and cancer biomarkers allow us to accurately distinguish aggressive from indolent prostate cancer, collaborative efforts using large multi-institutional databases to assess the true predictive value of these aforementioned predictors of worsening prognosis remain the best surrogate means of discriminating those men with true indolent disease who would derive the most benefit from active surveillance regimes. We suggest the use of nomograms, advocating caution in interpretation, to help clinicians and patients make decisions regarding enrollment into active surveillance protocols.

Acknowledgments

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009; 59(4):225–249. [PubMed: 19474385]

2. Cooperberg MR, Broering JM, Kantoff PW, Carroll PR. Contemporary trends in low risk prostate cancer: risk assessment and treatment. J Urol. 2007; 178(3 Pt 2):S14–S19. [PubMed: 17644125]

3. Klotz L. Active surveillance for favorable risk prostate cancer: rationale, risks, and results. Urol Oncol. 2007; 25(6):505–509. [PubMed: 18047961]

4. Carter HB, Kettermann A, Warlick C, Metter EJ, Landis P, Walsh PC, et al. Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. J Urol. 2007; 178(6):2359–2364. discussion 2364–2355. [PubMed: 17936806]

5. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA. 1994; 271(5):368–374. [PubMed: 7506797]

6. D'Amico AV, Renshaw AA, Arsenault L, Schultz D, Richie JP. Clinical predictors of upgrading to Gleason grade 4 or 5 disease at radical prostatectomy: potential implications for patient selection for radiation and androgen suppression therapy. Int J Radiat Oncol Biol Phys. 1999; 45(4):841–846. [PubMed: 10571187]

7. Fukagai T, Namiki T, Namiki H, Carlile RG, Shimada M, Yoshida H. Discrepancies between Gleason scores of needle biopsy and radical prostatectomy specimens. Pathol Int. 2001; 51(5):364–370. [PubMed: 11422794]

8. Pinthus JH, Witkos M, Fleshner NE, Sweet J, Evans A, Jewett MA, et al. Prostate cancers scored as Gleason-6 on prostate biopsy are frequently Gleason 7 tumors at radical prostatectomy: implication on outcome. J Urol. 2006; 176(3):979–984. discussion 984. [PubMed: 16890675]

9. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996; 15(4):361–387. [PubMed: 8668867]

10. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009; 360(13):1320–1328. [PubMed: 19297566]

11. Patel MI, DeConcini DT, Lopez-Corona E, Ohori M, Wheeler T, Scardino PT. An analysis of men with clinically localized prostate cancer who deferred definitive therapy. J Urol. 2004; 171(4):1520–1524. [PubMed: 15017211]

12. Eggener SE, Mueller A, Berglund RK, Ayyathurai R, Soloway C, Soloway MS, et al. A multi-institutional evaluation of active surveillance for low risk prostate cancer. J Urol. 2009; 181(4):1635–1641. discussion 1641. [PubMed: 19233410]

13. Dong F, Jones JS, Stephenson AJ, Magi-Galluzzi C, Reuther AM, Klein EA. Prostate cancer volume at biopsy predicts clinically significant upgrading. J Urol. 2008; 179(3):896–900. discussion 900. [PubMed: 18207180]

14. Conti SL, Dall'era M, Fradet V, Cowan JE, Simko J, Carroll PR. Pathological outcomes of candidates for active surveillance of prostate cancer. J Urol. 2009; 181(4):1628–1633. discussion 1633–1624. [PubMed: 19233388]

15. Smaldone MC, Cowan JE, Carroll PR, Davies BJ. Eligibility for active surveillance and pathological outcomes for men undergoing radical prostatectomy in a large, community based cohort. J Urol. 2010; 183(1):138–143. [PubMed: 19913808]

16. Freedland SJ, Isaacs WB, Platz EA, Terris MK, Aronson WJ, Amling CL, et al. Prostate size and risk of high-grade, advanced prostate cancer and biochemical progression after radical prostatectomy: a search database study. J Clin Oncol. 2005; 23(30):7546–7554. [PubMed: 16234520]

17. Briganti A, Chun FK, Suardi N, Gallina A, Walz J, Graefen M, et al. Prostate volume and adverse prostate cancer features: fact not artifact. Eur J Cancer. 2007; 43(18):2669–2677. [PubMed: 17996442]

18. Turley RS, Hamilton RJ, Terris MK, Kane CJ, Aronson WJ, Presti JC Jr, et al. Small transrectal ultrasound volume predicts clinically significant Gleason score upgrading after radical prostatectomy: results from the SEARCH database. J Urol. 2008; 179(2):523–527. discussion 527–528. [PubMed: 18076952]

19. Kassouf W, Nakanishi H, Ochiai A, Babaian KN, Troncoso P, Babaian RJ. Effect of prostate volume on tumor grade in patients undergoing radical prostatectomy in the era of extended prostatic biopsies. J Urol. 2007; 178(1):111–114. [PubMed: 17499289]

20. Kulkarni GS, Lockwood G, Evans A, Toi A, Trachtenberg J, Jewett MA, et al. Clinical predictors of Gleason score upgrading: implications for patients considering watchful waiting, active surveillance, or brachytherapy. Cancer. 2007; 109(12):2432–2438. [PubMed: 17497649]

21. San Francisco IF, DeWolf WC, Rosen S, Upton M, Olumi AF. Extended prostate needle biopsy improves concordance of Gleason grading between prostate needle biopsy and radical prostatectomy. J Urol. 2003; 169(1):136–140. [PubMed: 12478121]

22. Freedland SJ, Kane CJ, Amling CL, Aronson WJ, Terris MK, Presti JC Jr. Upgrading and downgrading of prostate needle biopsy specimens: risk factors and clinical implications. Urology. 2007; 69(3):495–499. [PubMed: 17382152]

23. Turley RS, Terris MK, Kane CJ, Aronson WJ, Presti JC, Amling CL, et al. The association between prostate size and Gleason score upgrading depends on the number of biopsy cores obtained: results from the shared equal access regional cancer hospital database. BJU Int. 2008; 102(9):1074–1079. [PubMed: 18778348]

24. 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; 178(3 Pt 1):833–837. [PubMed: 17631355]

25. Dall'Era MA, Cooperberg MR, Chan JM, Davies BJ, Albertsen PC, Klotz LH, et al. Active surveillance for early-stage prostate cancer: review of the current literature. Cancer. 2008; 112(8): 1650–1659. [PubMed: 18306379]

26. Thong AE, Shikanov S, Katz MH, Gofrit ON, Eggener S, Zagaja GP, et al. A single microfocus (5% or less) of Gleason 6 prostate cancer at biopsy—can we predict adverse pathological outcomes? J Urol. 2008; 180(6):2436–2440. [PubMed: 18930486]

27. Allsbrook WC Jr, Mangold KA, Johnson MH, Lane RB, Lane CG, Amin MB, et al. Interobserver reproducibility of Gleason grading of prostatic carcinoma: urologic pathologists. Hum Pathol. 2001; 32(1):74–80. [PubMed: 11172298]

28. 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(5):1964–1967. [PubMed: 18801515]
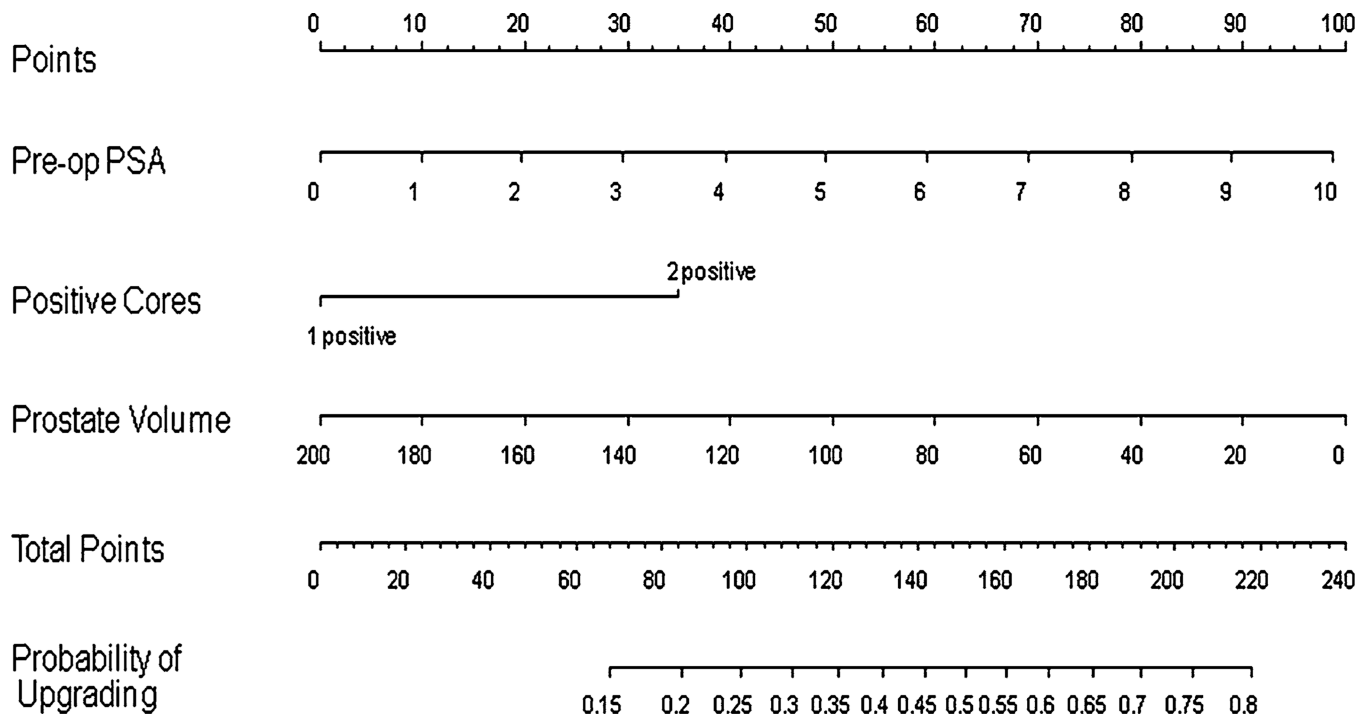
Fig. 1.
Nomogram for the prediction of Gleason upgrading in potential active surveillance patients. Nomogram instructions: To obtain the nomogram-predicted probability of upgrading, locate patient values on each axis. Draw a vertical line to the 'Points' axis to determine how many points are attributed for each variable value. Sum the points for all variables. Locate the sum on the 'Total Points' line to assess the individual probability of upgrading on the 'Probability of Upgrading' line
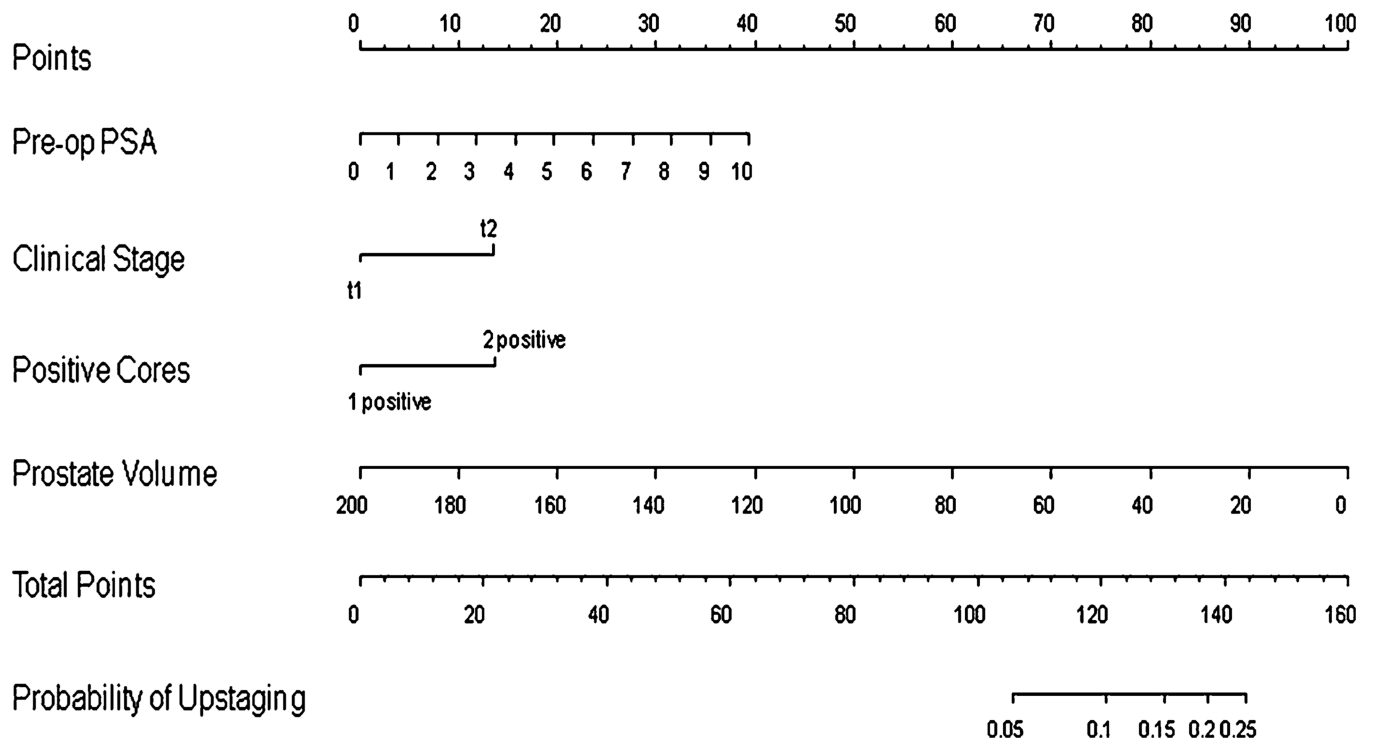
Fig. 2.
Nomogram for the prediction of pathologic upstaging in potential active surveillance patients. Nomogram instructions: To obtain the nomogram-predicted probability of upstaging, locate patient values on each axis. Draw a vertical line to the 'Points' axis to determine how many points are attributed for each variable value. Sum the points for all variables. Locate the sum on the 'Total Points' line to assess the individual probability of upstaging on the 'Probability of Upstaging' line

Points

Pre-op PSA

Positive Cores

Prostate Volume
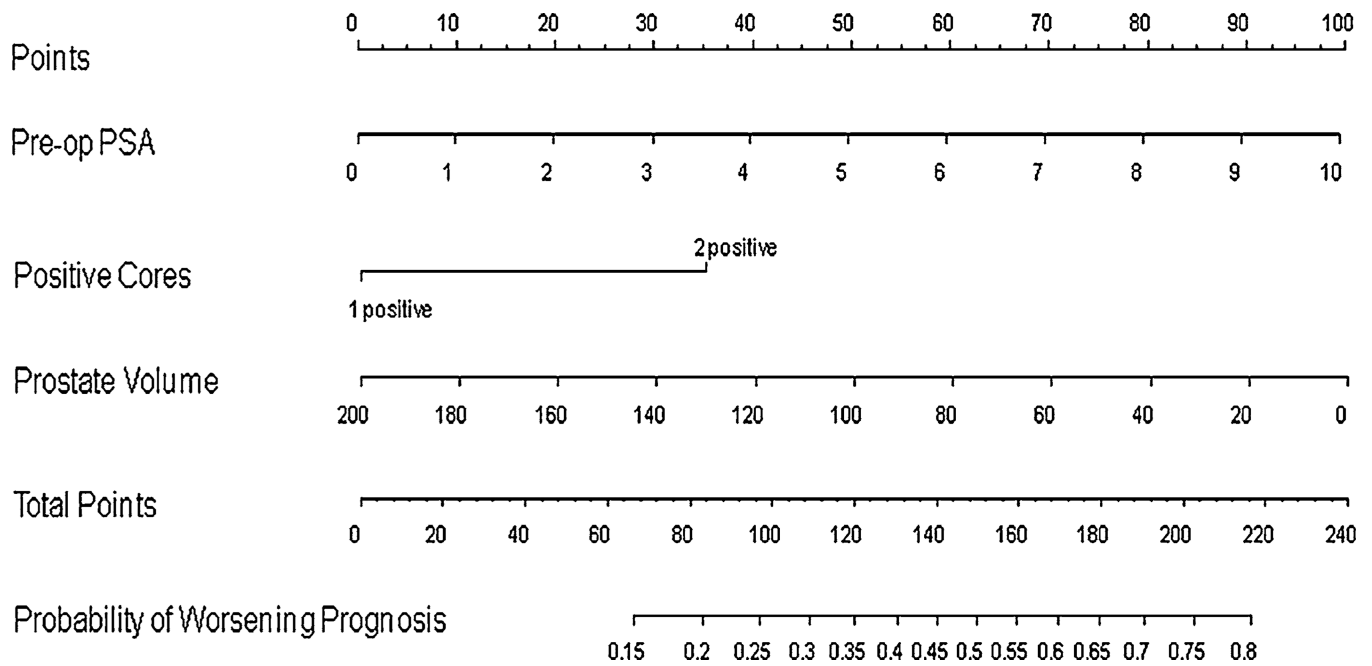
Total Points

Probability of Worsening Prognosis

Fig. 3.
Nomogram for the prediction of worsening prognosis in potential active surveillance patients. Nomogram instructions: To obtain the nomogram-predicted probability of worsening prognosis, locate patient values on each axis. Draw a vertical line to the 'Points' axis to determine how many points are attributed for each variable value. Sum the points for all variables. Locate the sum on the 'Total Points' line to assess the individual probability of worsening prognosis on the 'Probability of Worsening Prognosis' line

Table 1

Comparison of Gleason upgrading in potential active surveillance patients

Variable	Group 1 ($n = 750$) All AS-eligible patients	Group 1A ($n = 453$) No Gleason upgrading	Group 1B ($n = 297$) Positive Gleason upgrading	P value/X^2
Mean age	59 ± 6.9	58.9 ± 7	59.4 ± 6.7	0.279
Mean BMI	27 ± 3.8	26.7 ± 3.8	27.5 ± 3.7	0.004
Mean preop PSA	4.6 ± 1.9	4.4 ± 1.9	5.0 ± 1.8	<0.0001
Total Bx cores				0.89
<18	87.9	87.7	88.1	
18	12.1	12.3	11.9	
Total positive cores				<0.001
1	68.3	74.6	58.6	
2	31.7	25.4	41.4	
Max % of cancer in biopsy				0.02
5	50.9	54.5	45.5	
>5	49.1	45.5	54.5	
Clinical stage				0.5
T1	96.4	96	97	
T2a	3.6	4	3	
HGPIN on Bx				0.37
No	88.1	89.3	87.2	
Yes	11.9	10.7	12.8	
Prostate volume	54 ± 23.2	55.2 ± 24.1	52.1 ± 21.5	0.08
Gleason pathology				<0.0001
6	60.4	100	0	
7	39.2	0	99	
8, 9, 10	0.4	0	1	
pTNM				<0.0001
T1–2	96.1	98.7	92.3	
T3–4	3.9	1.3	7.7	
Positive SM rate	4.7	2.4	8.1	<0.0001

Table 2

Comparison of pathologic upstaging in potential active surveillance patients

Variable	Group 1A ($n = 721$) No upstaging	Group 1B ($n = 29$) Upstaging	P value/X^2
Mean age	59 ± 6.9	60.6 ± 7.0	0.208
Mean BMI	26.9 ± 3.8	28.7 ± 4.7	0.018
Mean preop PSA	4.6 ± 1.9	5.0 ± 1.9	0.261
Total Bx cores			0.582
<18	87.8	84.4	
18	12.2	11.1	
Total positive cores			0.051
1	68.9	51.7	
2	31.1	48.3	
Max % of cancer in biopsy			0.502
5	51.2	44.8	
>5	48.8	55.2	
Clinical stage			0.331
T1	96.5	93.1	
T2a	3.5	6.9	
HGPIN on Bx			0.695
No	88.6	86.2	
Yes	11.4	13.8	
Prostate volume	54.2 ± 23.3	46.7 ± 16.7	0.025
Gleason pathology			<0.0001
6	61.9	20.7	
7	37.8	75.9	
8, 9, 10	0.3	3.4	
pTNM			<0.0001
T1–2	100	0	
T3–4	0	100	
Positive SM rate	3.7	27.6	<0.0001

Table 3

Comparison of either upgrading or upstaging in potential active surveillance patients

Variable	Group 1A ($n = 447$) No Gleason upgrading/upstaging	Group 1B ($n = 303$) Positive Gleason upgrading/upstaging	P value/X^2
Mean age	58.8 ± 6.9	59.4 ± 6.7	0.241
Mean BMI	26.7 ± 3.8	27.5 ± 3.8	0.003
Mean preop PSA	4.4 ± 1.9	4.9 ± 1.8	<0.001
Total Bx cores			0.937
<18	87.8	88	
18	12.2	12	
Total positive cores			<0.0001
1	74.7	58.7	
2	25.3	41.3	
Max % of cancer in biopsy			0.015
5	54.6	45.5	
>5	45.4	54.5	
Clinical stage			0.717
T1	96.2	96.7	
T2a	3.8	3.3	
HGPIN on Bx			0.467
No	89.2	87.5	
Yes	10.8	12.5	
Prostate volume	55.1 ± 24.2	52.1 ± 21.4	0.078
Gleason pathology			<0.0001
6	100	2	
7	0	97	
8, 9, 10	0	1	
pTNM			<0.0001
T1–2	100	90.4	
T3–4	0	9.6	
Positive SM rate	2.2	8.3	<0.0001

Table 4

Univariable analysis for the prediction of Gleason upgrading in potential active surveillance patients

Predictors of upgrading	Univariable analyses			
	OR	95% CI on OR	*P* value	PA; %
Preop PSA (continuous)	1.17	1.08, 1.27	<0.0001	59.0
Clinical stage (t2 vs. t1)	0.76	0.34, 1.70	0.4990	50.5
Biopsy cores (18 vs. <18)	0.97	0.60, 1.55	0.8853	50.2
Positive cores (2 vs. 1)	2.08	1.52, 2.84	<0.0001	58.0
Max % Bx (>5% vs. 5%)	1.44	1.07, 1.93	0.0152	54.5
HGPIN Bx (yes vs. no)	1.23	0.78, 1.93	0.3731	51.1
Prostate volume (continuous)	0.99	0.99, 1.00	0.0796	54.3

PA predictive accuracy (AUC from c-statistic)

Table 5

Multivariable analysis for the prediction of Gleason upgrading in potential active surveillance patients

Predictors of upgrading	*P* value	Adjusted OR	95% CI for OR	
			Lower	Upper
Preop PSA	<0.0001	1.237	1.129	1.354
Clinical stage	0.374	0.675	0.284	1.606
Biopsy cores	0.864	1.044	0.639	1.704
Positive cores	<0.0001	1.942	1.384	2.724
Max % Bx	0.344	1.168	0.847	1.611
HGPIN Bx	0.228	1.348	0.830	2.191
Prostate volume	0.011	0.990	0.982	0.998

PA = 64.5%; Preop PSA: Continuous in model; Clinical stage: t2 versus t1 (referent); Biopsy cores: 18 cores versus <18 cores (referent); Positive cores: 2 positive cores versus 1 positive core (referent); Max % Bx: >5% (median) versus 5% (referent); HGPIN Bx: yes versus no (referent); Prostate volume: Continuous in model

Table 6

Univariable analysis for the prediction of pathologic upstaging in potential active surveillance patients

Predictors of upstaging	Univariable analyses			
	OR	95% CI on OR	*P* value	PA; %
Preop PSA (continuous)	1.12	0.92, 1.35	0.2611	55.6
Clinical stage (t2 vs. t1)	2.06	0.47, 9.16	0.3410	51.7
Biopsy cores (18 vs. <18)	0.90	0.27, 3.07	0.8698	50.5
Positive cores (2 vs. 1)	2.07	0.98, 4.36	0.0556	58.6
Max % Bx (>5% vs. 5%)	1.29	0.61, 2.72	0.5034	53.2
HGPIN Bx (yes vs. no)	1.24	0.42, 3.66	0.6951	51.2
Prostate volume (continuous)	0.98	0.96, 1.00	0.0799	59.5

PA predictive accuracy (AUC from c-statistic)

Table 7

Restricted multivariable analysis for the prediction of pathologic upstaging in potential active surveillance patients

Predictors of upstaging	*P* value	Adjusted OR	95% C.I. for OR	
			Lower	Upper
Preop PSA	0.060	1.212	0.992	1.481
Clinical stage	0.394	1.937	0.423	8.865
Positive cores	0.083	1.946	0.917	4.129
Prostate volume	0.046	0.976	0.953	1.000

PA = 65.2%; Preop PSA: Continuous in model; Clinical stage: t2 versus t1 (referent); Positive cores: 2 positive cores versus 1 positive core (referent); Prostate volume: Continuous in model

Table 8

Univariable analysis for the prediction of worsening prognosis in potential active surveillance patients

Predictors of worsening prognosis	Univariable analyses			
	OR	95% CI on OR	*P* value	PA; %
Preop PSA (continuous)	1.17	1.08, 1.27	<0.0001	58.9
Clinical stage (t2 vs. t1)	0.86	0.39, 1.91	0.7170	50.3
Biopsy cores (18 vs. <18)	0.98	0.62, 1.57	0.9369	50.1
Positive cores (2 vs. 1)	2.08	1.52, 2.84	<0.0001	58.0
Max % bx (>5% vs. 5%)	1.44	1.07, 1.93	0.0152	54.5
HGPIN Bx (yes vs. no)	1.18	0.75, 1.86	0.4672	50.9
Prostate volume (continuous)	0.99	0.99, 1.00	0.0797	54.2

PA predictive accuracy (AUC from c-statistic)

Table 9

Multivariable analysis for the prediction of worsening prognosis in potential active surveillance patients

Predictors of worsening prognosis	*P* value	Adjusted OR	95% C.I. for OR	
			Lower	Upper
Preop PSA	<0.0001	1.239	1.132	1.357
Clinical stage	0.575	0.785	0.338	1.825
Biopsy cores	0.800	1.065	0.654	1.735
Positive cores	<0.0001	1.934	1.379	2.710
Max % Bx	0.343	1.168	0.848	1.609
HGPIN Bx	0.304	1.289	0.794	2.094
Prostate volume	0.010	0.990	0.982	0.998

PA = 64.4%; Preop PSA: Continuous in model; Clinical stage: t2 versus t1 (referent); Biopsy cores: 18 cores versus <18 cores (referent); Positive cores: 2 positive cores versus 1 positive core (referent); Max % Bx: >5% (median) versus 5% (referent); HGPIN Bx: yes versus no (referent); Prostate volume: Continuous in model