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Clinical Implications of a Multiparametric MRI Based Nomogram Applied to Prostate Cancer Active Surveillance

M. Minhaj Siddiqui[a,f], **Hong Truong**[a], **Soroush Rais-Bahrami**[a,g], **Lambros Stamatakis**[a], **Jennifer Logan**[a], **Annerleim Walton-Diaz**[a], **Baris Turkbey**[c], **Peter Choyke**[c], **Bradford J. Wood**[a,d], **Richard Simon**[e], and **Peter A. Pinto**[a,d]

[a]Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

[b]Division of Cancer Prevention, National Cancer Institute, Bethesda, MD

[c]Molecular Imaging Program, National Cancer Institute, National Institutes of Health, Bethesda, MD

[d]Center for Interventional Oncology, Department of Radiology and Imaging Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD

[e]Biometric Research Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Rockville, MD

[f]Currently at Department of Surgery, Division of Urology, University of Maryland, Baltimore MD

[g]Currently at Departments of Urology and Radiology, University of Alabama-Birmingham, Birmingham AL

Abstract

Purpose—Multiparametric-MRI (MP-MRI) may be beneficial in the search for rational ways to decrease prostate cancer interventions in patients on active surveillance (AS). The goal of this study was to apply a previously generated nomogram based on MP-MRI to predict AS eligibility repeat biopsy outcomes.

Materials and Methods—85 patients were reviewed who met AS criteria at entry based on their initial biopsy and then underwent 3.0T MP-MRI with subsequent MRI/Ultrasound (US) fusion guided prostate biopsy between 2007–2012. The accuracy of a previously published nomogram was assessed in patients on AS prior to confirmatory biopsy. For each cut-point value, the number of “biopsies avoided” (i.e. reliance on MRI alone without re-biopsy) was determined over the full range of nomogram cutoffs.

RESULTS—The performance of the MP-MRI AS nomogram was assessed based on a decision to biopsy at various nomogram generated probabilities. Based on cutoff probabilities ranging from

Correspondence to: Peter A. Pinto, Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, 10 Center Drive, MSC 1210, Building 10 CRC Room 2W-5940, Bethesda, MD 20892-1210, Office 3014966353, Fax 3014020922, pintop@mail.nih.gov.

19% to 32% on the nomogram, the number of patients that could be spared a repeat biopsy ranged from 27% to 68% of the AS cohort. The sensitivity of the test in this interval ranged from 97% to 71% and negative predictive value ranged from 91% to 81%.

CONCLUSIONS—MP-MRI based nomograms may reasonably decrease the number of repeat biopsies in patients on AS by as much as 68%. Analysis over the full range of nomogram generated probabilities allows patient and caregiver preference based decision on the risk assumed for the benefit of fewer repeat biopsies.

Keywords

prostate neoplasms; active surveillance; magnetic resonance imaging; early detection of cancer

Introduction

The majority of prostate cancer (PCa) diagnosed in the United States prove to be low-grade, low-volume disease[1]. For these men, American Urologic Association clinical guidelines have recommended active surveillance (AS) as a management option[2]. Practice is somewhat at variance with these guidelines as many patients and their fear that there is unrecognized higher-grade tumor present[3].

Multiparametric prostate MRI (MP-MRI) combined with MRI/Ultrasound (US) fusion-guided biopsy is highly sensitive for high-grade PCa and allows for more reliable characterization of PCa with decreased risk of upgrading[4, 5]. A predictive model was designed and tested to determine AS eligibility for men with PCa that relies solely on MP-MRI to avoid the subjectivity associated with clinical staging, the risk of understaging of prostate biopsy, and the variability in serum PSA often observed in clinical practice[6]. This nomogram uses the 1) number of lesions on MRI, 2) lesion suspicion level based on MP-MRI results (low, moderate, high), and 3) lesion density to predict patients' AS eligibility based on repeat biopsy AS criteria with excellent discriminative ability (AUC = 0.71).

While nomograms provide a user-friendly bedside model to estimate objectively a patient's probability of having indolent cancer, converting a probability into a concrete and practical recommendation can often be challenging. The patient faces a decision which is binary: Do they continue AS or opt for treatment? Yet, a nomogram provides a continuous estimate of the probability that their tumor is safely amenable to AS. In this study, we aimed to optimize the utility of our previously described MRI-based nomogram to predict repeat biopsy to confirm AS eligibility for clinical decision-making and enhanced patient-clinician communication.

Materials and methods

Study population

A retrospective review was performed of an Institutional Review Board-approved study at the National Cancer Institute, National Institutes of Health (ClinicalTrials.gov identifier: NCT00102544). Study cohort enrollment was from August 2007 through August 2012. The initial standard extended-sextant 12-core biopsy pathology was reviewed by a single

pathologist and patients were included if they met the Johns Hopkins AS criteria (PSA density ≤ 0.15, ≤ 2 positive cores, ≤ 50% tumor in any core, Gleason score ≤ 6, and stage T1c).[7] All patients who had not already had PSA progression underwent baseline pre-biopsy MP-MRI. If targetable lesions were identified on MP-MRI, the patients subsequently underwent confirmatory TRUS-guided 12-core extended-sextant prostate biopsy and targeted MRI/US fusion-guided biopsies with electromagnetic tracking, as previously described.[8, 9] Candidacy for continued active surveillance was based on repeat biopsy results. The targeted biopsy results were also incorporated into the assessment of continued candidacy with the criteria of ≤ 50% tumor in any core, Gleason score ≤ 6.

Imaging

MP-MRI was performed using the combination of an endorectal coil (BPX-30, Medrad, Pittsburgh, PA, USA) tuned to 127.8 MHz and a cardiac coil (16-channel) (SENSE, Philips Healthcare, Cleveland, OH) on a 3T magnet (Achieva, Philips Healthcare, Cleveland, OH). The endorectal coil balloon was distended with perfluorocarbon (3 mol/L-Fluorinert, 3M, St. Paul, MN, USA) to a volume of approximately 50 mL to reduce susceptibility artifacts induced by air in the coil's balloon. MRI sequence parameters were detailed in a prior study, and included triplanar T2 weighted (T2W) turbo-spin-echo (TSE), diffusion weighted (DW) MRI, 3 dimensional MR Spectroscopic Imaging, axial pre-contrast T1 weighted (T1W) MRI, and axial 3D fast field echo dynamic contrast-enhanced (DCE) MRI.[10]

For multi-parametric MRI analysis on T2W MR and apparent diffusion coefficient (ADC) maps of DW MRI, the criterion for a "visible" lesion was a well circumscribed, round-ellipsoid low-signal-intensity region within the prostate gland.[10] The 3D-MR spectroscopy analysis evaluated choline/citrate (Cho/Cit) ratios. Voxels were considered abnormal when the Cho/Cit ratio was 3 or more standard deviations (SD) above the mean healthy Cho/Cit ratio value (≥0.373), which was defined as 0.13+/−0.081 based on prior results.[10] DCE MR images were evaluated by direct visual interpretation of raw dynamic enhanced T1W images and the diagnostic criteria for PCa included a focus of asymmetric, early and intense enhancement with rapid wash out compared to the background.[10] The MP-MRI score assigned to each lesion is based on the number of positive sequences (e.g. positive T2W, Diffusion weighted, MR spectroscopy and DCE-MRI is indicative of a high score). In such a way, every lesion was analyzed using a non-weighted scoring system where lesion scores are categorized as low, moderate and high.[11] The PIRADS system was not yet in use at the NCI during the period in which patients were accrued for this study. Although not an exact relationship, the low, and high suspicion on the NIH scale do seem to correlate with PIRADS 1–2 and PIRADS 5 scores. The largest diameter of each lesion was calculated manually on a picture archiving and communication system (PACS) workstation (Carestream, Inc, USA). Again, each visible lesion was manually segmented on a research software platform (iCAD, Nashua, NH, USA) blinded to the clinical and histopathologic data. The tumor volume was determined with the same software after manual segmentation on MRI. For segmenting tumors on MRI, T2W MRI, ADC maps of DW MRI and DCE MRI sequences were used in conjunction although final regions of interest were drawn on T2W MRI for targeting during fusion biopsy. Total MRI prostate volumes were manually obtained for each patient using a semi-automated software.[12]

Data Analysis

A previously described nomogram to predict disqualification from AS based on MP-MRI characteristics was utilized in this study[6]. To further evaluate the nomogram's performance, the nomogram-generated probability was calculated for every patient in that original cohort. Cut-points were then assessed for the nomogram-generated probability of disqualification from AS candidacy based on repeat biopsy. Negative predicted values (NPV) and sensitivity were calculated by comparing the nomogram-generated recommendation against the confirmatory biopsy results. Decision curve analysis was performed utilizing R code made publicly available by Andrew Vickers (http://www.mskcc.org/research/epidemiology-biostatistics/health-outcomes/decision-curve-analysis-0). Leave-one-out cross-validation analyses of the logistic regression model development were performed to evaluate potential data overfitting.

Results

Eighty-five patients were reviewed of whom 25 were no longer eligible for AS on repeat biopsy. Disqualification from AS occurred in 6 men based on target biopsy alone, 6 men on standard biopsy alone, and in 13 men on both biopsy types. The mean age of the population was 60.2 years, mean PSA of 4.8ng/ml, and mean PSA density of 0.09. The mean time from first biopsy to confirmatory targeted MRI/US fusion biopsy was 302 days. A nomogram was derived as previously described to predict the likelihood of disqualification from AS upon repeat biopsy (Figure 1). Within the nomogram, patient MRI traits are input into the nomogram, and the output is the probability that upon repeat biopsy (consistent of a standard 12-core biopsy and targeted biopsy of all MR lesions), the individual will demonstrate pathology which makes him unsuitable for continued AS for his PCa. The cohort from which this predictive model was derived consisted of all men who initially were diagnosed with PCa and amenable to active surveillance. All patients underwent MP-MRI with confirmatory biopsy and findings on MRI were correlated to biopsy outcomes. Using this nomogram, a clinician could theoretically decrease the number or frequency of repeat biopsies that are required to follow a patient with low risk PCa while still closely following the patient. If the nomogram scored above the threshold value, then a repeat biopsy was indicated. If it scored below that value, a repeat biopsy could be avoided. We sought to better characterize the optimal nomogram probability below which a repeat biopsy could safely be avoided or delayed.

Figure 2 demonstrates a waterfall plot of the probabilities of disqualification from AS compared to the actual outcome of AS candidacy based on prostate biopsy. Analysis was performed on the entire cohort to determine how well the nomogram differentiated men who qualified for continued AS versus those who were disqualified on repeat biopsy for AS. We found that this nomogram correlated well with the actual outcome of AS candidacy. For example, 25 patients were within the nomogram probability range of 10–20% predicted rate of disqualification from AS and 3 of these 25 (12%) actually demonstrated progression on repeat biopsy. Similarly, 6 patients were in the nomogram probability range of 60% or higher and 4 out of these 6 (66%) demonstrated repeat progression on repeat biopsy.

Figure 3a shows the nomogram outperforms any solitary characteristic alone by synthesizing inputs of number of lesions, highest suspicion score, and lesion density. This decision curve analysis quantifies the net benefit of using the nomogram by comparing the true positive and false positive counts (while adjusting for the ratio of expected benefit from the repeat prostate biopsy versus the expected benefit of avoiding a repeat prostate biopsy). It demonstrates that selectively deferring a biopsy using the nomogram was provided a net benefit compared to the strategy of simply performing a biopsy on all patients on AS. Figure 3b demonstrates that the net benefit peaks at the probability cutoff of 32% on the nomogram (above 32% repeat biopsy is indicated, and below 32% continued surveillance is suggested).

The analytic performance of this test was defined by characterizing the sensitivity and negative predictive value of all the possible cutoffs on the nomogram which are shown in Figure 4a. Of note, the sensitivity decreases rapidly in the 30–40% cutoff range. Figure 4b shows the number of people who are spared a repeat biopsy as a function of the nomogram cutoff.

Table 1 synthesizes this data for different cut-points on the nomogram below which men would continue AS with no repeat prostate biopsy, and above which they would undergo repeat biopsy to confirm AS candidacy. The cut-point of optimal benefit according to statistical analysis on decision curve analysis was 32%. This correlated with a sensitivity of 71%, a NPV of 81%, and a ratio of 4.3 men spared a biopsy for every one man who incorrectly failed to have a biopsy for disease progression. Theoretically, depending on the individual features of the patient, clinician, and healthcare system, a nomogram threshold could be adjusted such that more men could avoid biopsy for every one man incorrectly biopsied or a higher sensitivity selected. For example, for a ratio of 10, the corresponding nomogram cutoff is 19% and yields 97% sensitivity, 91% NPV, and 27% of patients spared a repeat biopsy. Leave-one-out cross-validation analyses were performed for the various cutoffs to assess the variability within the sensitivities and negative predictive values. There was low variability providing little indication of data overfitting.

Discussion

Nomogram utilization to guide decision-making offer the benefit of synthesizing multiple pieces of information into a unified analysis. In a literature review of PCa nomograms that aid in the identification of low-grade, low stage organ confined disease, 14 publications were identified that provide such information (Table 2). Despite the improved ability of these nomograms to predict outcomes, physician utilization of nomograms remains low as a decision-making instrument[13].

One possible reason for low utilization is that while well designed nomograms may demonstrate good predictive ability, it is often difficult to determine practically how to translate the outcome of the nomogram into a specific patient’s decision process. Patients and their caregivers have to make decision on whether they should proceed with treatment or stay on AS. If a nomogram yields an outcome such as a 30% probability of disease progression, the patient is still left with a difficult decision to make.

We examined the performance of a recently described MRI-based nomogram for PCa AS utilizing easily understood outcome measures. The emphasis was to provide guidance on optimized cutoffs to decide on repeat biopsy of patients on AS based on their MRI findings. We further characterized how the nomogram would influence the number of repeat biopsies avoided. Based on this analysis, a cutoff probability of disqualification from AS in the range of 19–32% on the nomogram resulted in 27–68% of men being monitored only with MRI and without repeat biopsy. Of practical note, the likely range that does not cause too much loss in sensitivity for decreasing the number of biopsies is probably closer to 27–41% as seen in Table 1.

There is great potential benefit in the use of MRI for monitoring AS rather than multiple repeat biopsies. As the process of AS becomes less invasive, greater acceptance amongst patients may follow. Furthermore, with the reliability of MP-MRI to image the entire prostate, it is feasible that patients will feel further reassured that they did not miss any high-grade cancer. The use of MRI for AS monitoring will ultimately be synergistic with better informed repeat prostate biopsies rather than replace them altogether.

One limitation of this study is that the patient population is derived from a population in which many men obtained repeat biopsy for prior negative biopsy in the setting of elevated PSA. Such a cohort may differ from the general population in important ways such as presence of anterior lesions. Another limitation is that application of the nomogram necessitates abnormal findings on the MP-MRI. Men with no lesions on MP-MRI were therefore excluded from this study. Although other studies suggest that lack of any findings on MRI correlate with low-grade PCa if any cancer is present at all, it is unclear if imaging would be effective in following a patient with a baseline normal MP-MRI. One more limitation was that the nomogram was constructed using MRI data only. Future even more powerful nomograms may be possible incorporating all clinical parameters, this was however beyond the scope of this study. Of note, the AS criteria used in this study were amongst the most stringent in practice today. It will be of great interest if MRI performs similarly amongst more lenient criteria. Lastly, a modified AS protocol had to be adapted to incorporate targeted biopsies into the criteria. As the original criteria were based on 12-core biopsies alone, the implications of this change are unclear and will require further studies to better understand. Further development and validation of such clinical decision making aids will be necessary before MRI can be systematically incorporated into AS protocols for patients or applied broadly in consensus recommendations.

Conclusion

In this study, we analyze the performance of an MP-MRI-based nomogram in order to avoid repeat biopsies on an active surveillance cohort. We found that by varying the cut-point of threshold for biopsy, 27%–68% of biopsies could be safely avoided depending on the tolerance for missing disease that would disqualify the patient for AS. Given the slow growth of most PCa, a relatively higher tolerance for missed disease is justifiable as the lesion is likely to increase in the number of risk features on MP-MRI over time. Elucidation of the performance of the nomogram over the full range of the nomogram generated probabilities allows the patient and caregiver to be better informed decision makers,

balancing the risks they are assuming in exchange for the benefit of fewer biopsies. These findings support the further refinement of incorporation of MP-MRI into the AS of patients with low-risk PCa and long-term studies to validate these findings.

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ABBREVIATIONS

AS	Active surveillance
bGS	Biopsy Gleason Score
DRE	Digital Rectal Exam
MRI	Magnetic Resonance Imaging
MR/US	Magnetic Resonance/Ultrasound
MP-MRI	Multiparametric MRI
OR	Odds Ratio
PCa	Prostate Cancer
PSA	Prostate Specific Antigen
TRUS	Transrectal Ultrasound

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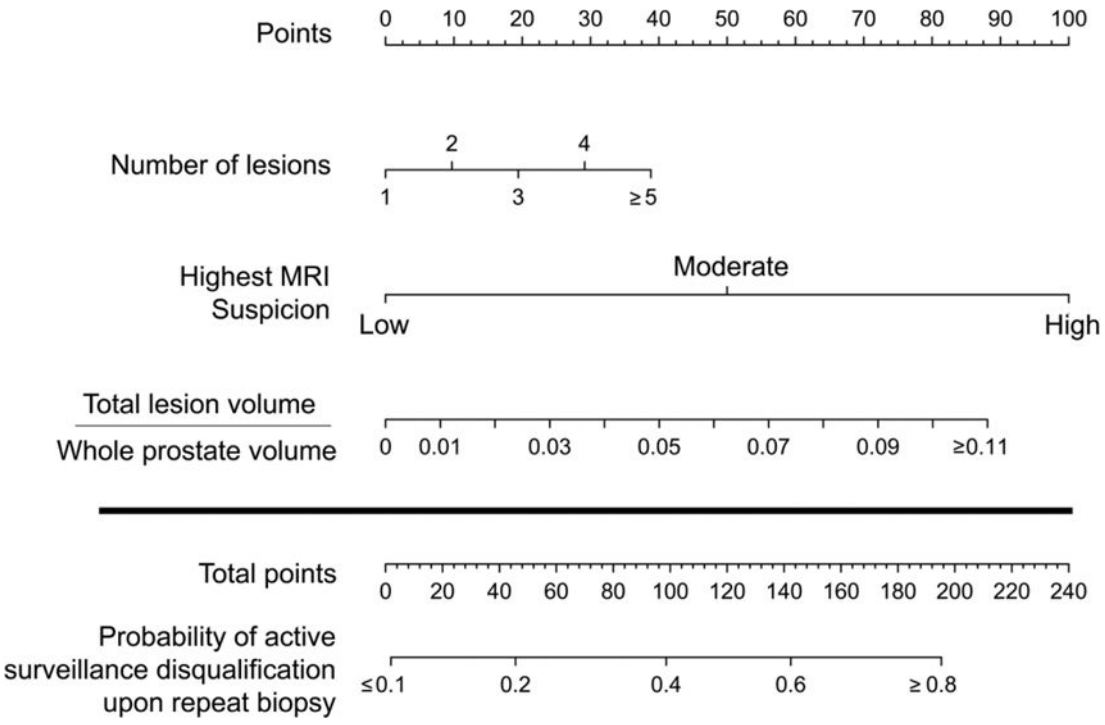


Figure 1.

Nomogram to predict probability of disqualification from active surveillance on repeat biopsy utilizing multiparametric-MRI features of number of lesions seen in the prostate, the highest prostate cancer suspicion score of all of the lesions, and the lesion density defined as the total lesion volume over the total prostate volume

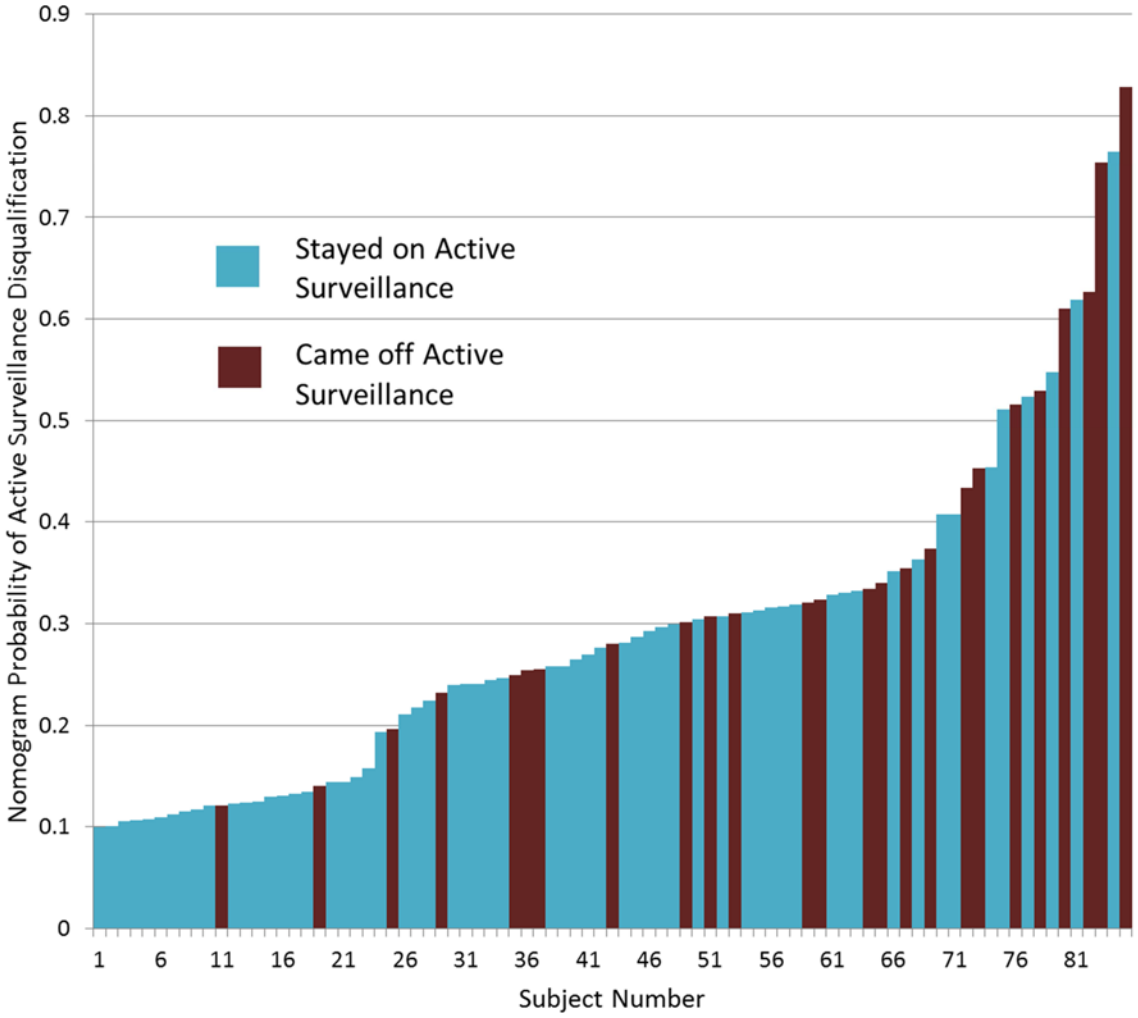
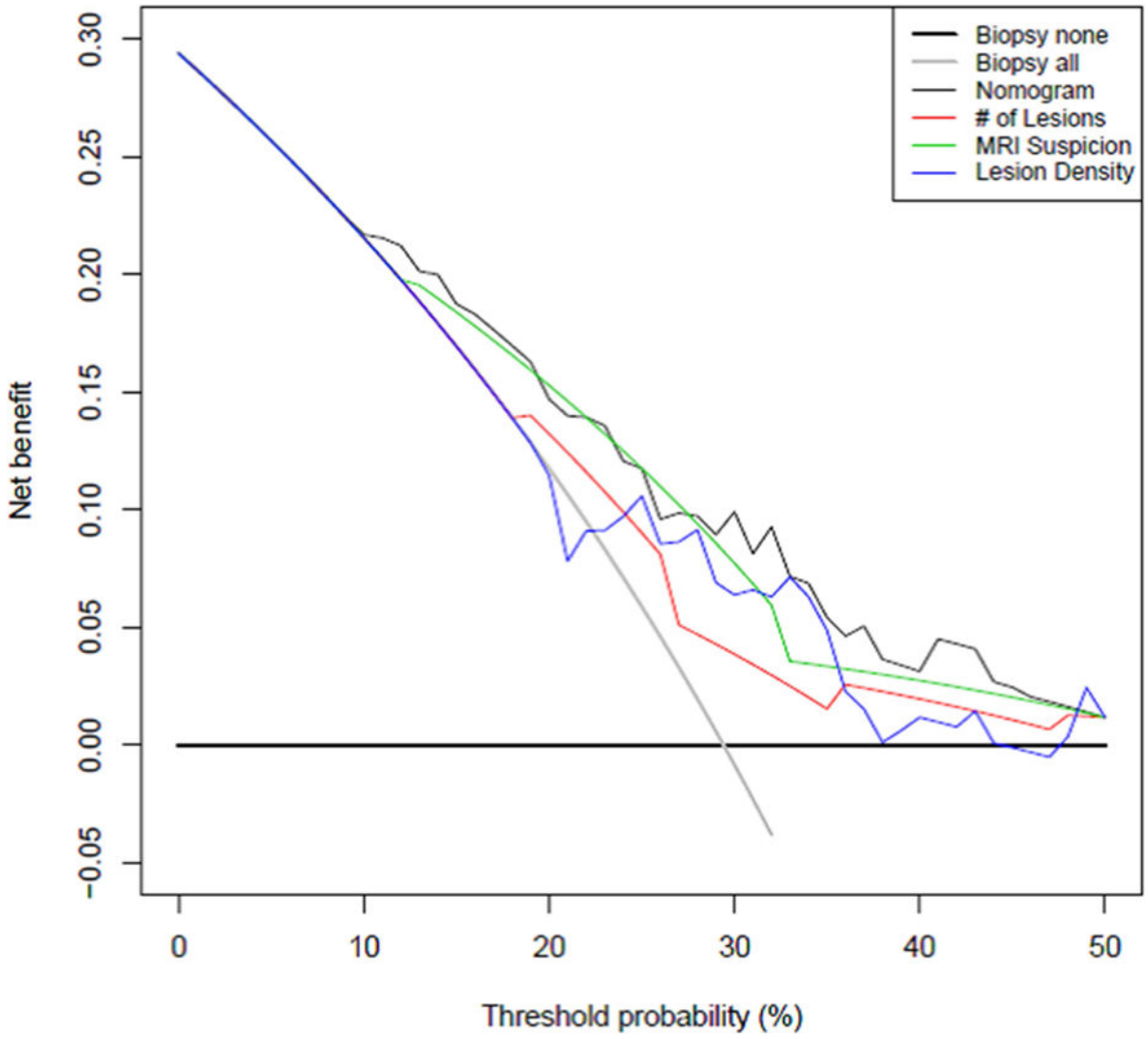


Figure 2.

Waterfall plot of all patients with associated nomogram generated probability of disqualification from active surveillance on repeat biopsy color coded by actual biopsy result.



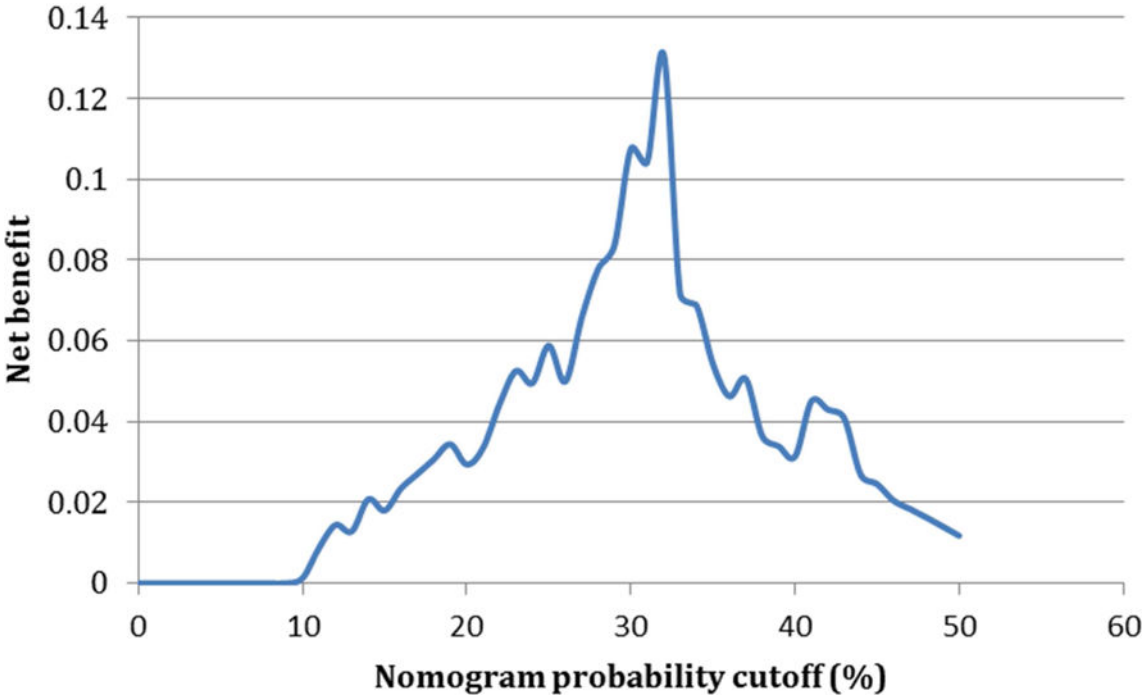


Figure 3.

a: Decision curve analysis demonstrating net benefit of utilizing each nomogram component and the nomogram itself for determination of repeat biopsy on active surveillance patients Net benefit in this analysis was defined as the additional correct identification of an individual who is no longer a good candidate for AS. The curves show that the combination of all the factors leads to the most reliable identification of men who are not good candidates for continued AS. **b:** Additional net benefit at any given nomogram probability cutoff over the strategy of non-selective repeat biopsy on all men utilizing the nomogram to select patient for repeat biopsy. This figure shows that the ability of the nomogram to correctly identify men for AS increases until a certain threshold probability on the nomogram at which point it begins to decrease again.

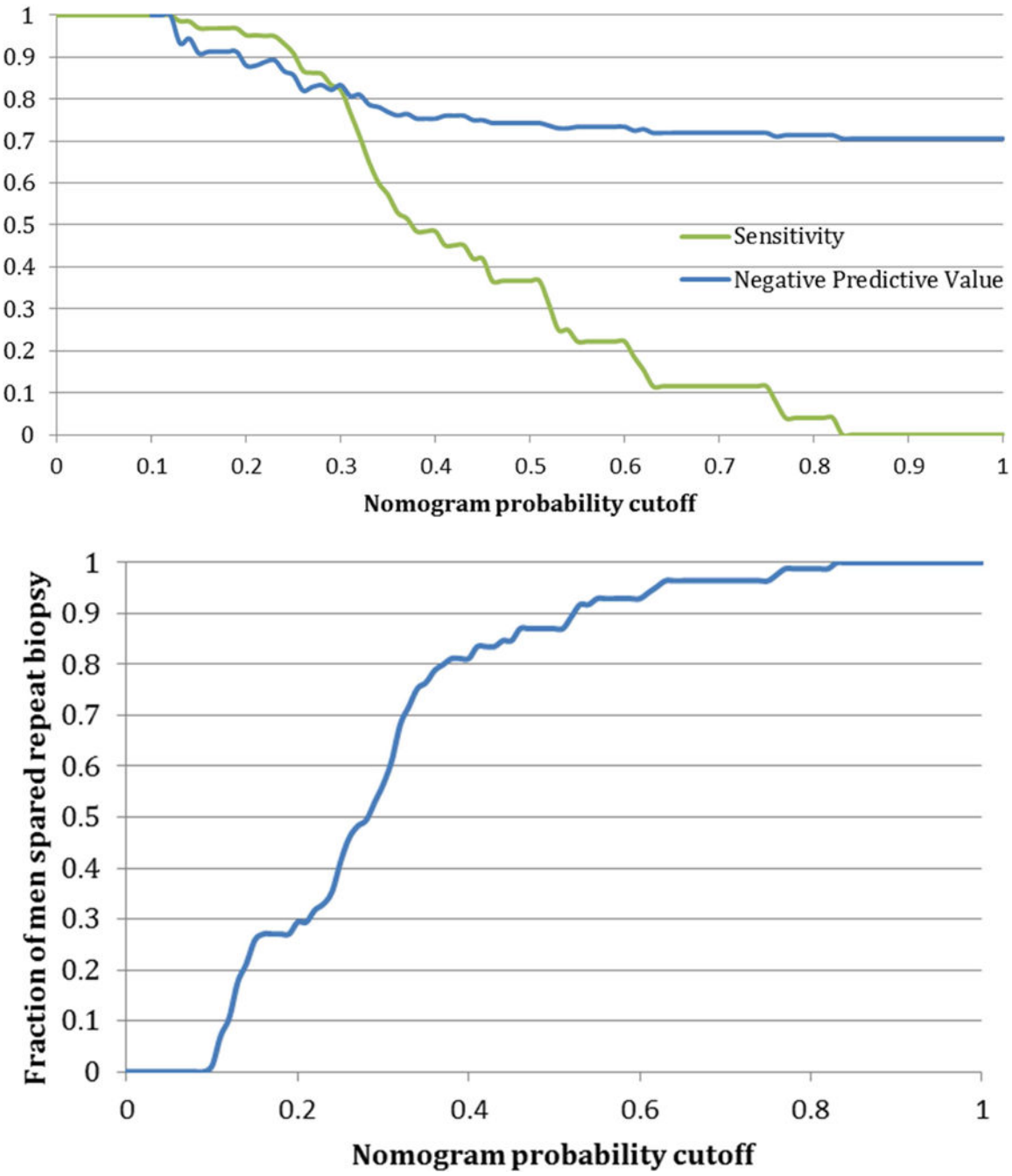


Figure 4.

a: Sensitivity and specificity of the nomogram at all possible probability cutpoints for selecting patients correctly for repeat biopsy on active surveillance **b:** Fraction of patients spared repeat biopsy on active surveillance for each given nomogram cutpoint

Table 1

Comparison of test characteristics at different cutoffs

Nomogram Cutoff	Sensitivity	NPV	% of men spared a repeat biopsy	Net benefit on DCA	Number of men spared biopsy for one false negative
19%	97%	91%	27%	0.03	10.5
22%	95%	89%	32%	0.04	8
25%	91%	86%	41%	0.06	6
28%	86%	83%	49%	0.08	5
32%	71%	81%	68%	0.13	4.3
35%	57%	77%	76%	0.05	3.3

DCA=Decision curve analysis

NPV=Negative predictive value

Table 2

Literature review of published nomograms applicable to active surveillance patients

First Author	Year	Outcome predicted	PSA	PSAD	Clinical stage	bGS	Variables in nomogram						
							Prostate volume	Tumor volume measure	Benign tissue measure	Age	Biopsy method	MRI	other
Partin et al[14]	1997	Organ confinement, Extracapsular extension, Seminal vesical invasion, Lymph node positivity	x		x	x							
Kattan et al[15]	2003	Low volume, low grade organ confined disease	x		x	x	x	x	x				
Nakanishi et al[16]	2007	Low volume, low grade organ confined disease		x				x		x			
Roemeling et al[17]	2007	Low volume, low grade organ confined disease	x			x	x	x	x				
Kulkarni et al[18]	2007	Upgrading from bx Gleason 6 to Gleason 7 or greater at RP	x		x		x	x		x	x		x
Kattan et al[19]	2008	Cancer-specific survival for men with clinically localized PCa managed without curative intent	x		x	x		x		x	x		x
Shukla-Dave et al[20]	2011	Low volume, low grade organ confined disease	x		x		x					x	x
Abdollah et al[21]	2011	10-yr cancer-specific mortality & other-cause mortality rates with PCa treated with RP or AS			x	x				x			x
O'Brien et al[22]	2011	Low volume, low grade organ confined disease		x		x	x	x		x			
Wong et al[23]	2012	High grade or high stage Pca		x	x			x		x			
Sooriakumar an et al[24]	2012	Worsening prognosis (either upgrading or upstaging)	x				x	x					
Iremashvili et al[25]	2013	Progression on repeat biopsy		x		x		x					x
Stamatakis et al[6]	2013	Progression on repeat biopsy						x				x	x
Truong et al[26]	2013	Gleason score upgrading from Gleason 6		x				x					x

bGS=biopsy Gleason score

PSAD=PSA Density

PCa=Prostate cancer

RP=Radical prostatectomy

AS=Active surveillance