

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

In-parallel comparative evaluation between multiparametric magnetic resonance imaging, prostate cancer antigen 3 and the prostate health index in predicting pathologically confirmed significant prostate cancer in men eligible for active surveillance

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1599971> since 2016-10-25T14:46:41Z

Published version:

DOI:10.1111/bju.13318

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



**IN PARALLEL COMPARATIVE EVALUATION BETWEEN
MULTIPARAMETRIC MRI, PCA3 AND PHI IN PREDICTING
PATHOLOGICALLY CONFIRMED SIGNIFICANT PROSTATE
CANCER IN MEN ELIGIBLE FOR ACTIVE SURVEILLANCE**

Journal:	<i>BJU International</i>
Manuscript ID:	Draft
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	<p>Porpiglia, Francesco; San Luigi Hospital, Dpt of Clinical and Biological Sciences, Division of Urology, University of Turin Cantiello, Francesco; Magna Graecia University, Urology Unit De Luca, Stefano; San Luigi Gonzaga Hospital and University of Torino, Division of Urology Manfredi, Matteo; San Luigi Gonzaga Hospital and University of Torino, Division of Urology Veltri, Andrea; University of Turin, Dept of Radiology Russo, Filippo; Candiolo Cancer Institute, Dept of Radiology Sottile, Antonino; Candiolo Cancer Institute, Dept of Laboratory Medicine Damiano, Rocco; CHAIR OF UROLOGY, DEPARTMENT OF CLINICAL AND EXPERIMENTAL MEDICINE</p>
Keywords:	multiparametric MRI, PHI, PCA3, Prostate Cancer, Prognostic Accuracy, Active Surveillance
Abstract:	<p>Objective: To assess the performance capabilities of multiparametric Magnetic Resonance Imaging (mpMRI), Prostate Health Index (PHI) and Prostate Cancer Antigen 3 gene (PCA3) in predicting the presence of pathologically confirmed significant Prostate Cancer (PCSPCa), according to the European Randomized Study of Screening Prostate Cancer (ERSPC) definition, in a same cohort of patients who underwent Radical Prostatectomy (RP) but eligible for Active Surveillance (AS).</p> <p>Materials and Methods: An observational retrospective study was performed in 120 prostate cancer (PCa) patients treated with robot-assisted RP but eligible for AS according to Prostate Cancer Research International: Active Surveillance (PRIAS) criteria. Blood and urinary specimens were collected before initial prostate biopsy for PHI and PCA3 measurements, respectively. In addition, all patients underwent preoperatively and after 6-8 weeks from biopsy to mpMRI with a 1.5T scanner using a 4-5 channel phase array coil combined with an endorectal coil. mpMRI images were assessed and diagrams depicting prostate sextants were used to designate regions of abnormalities within the prostate. Findings in the prostate were assigned to one of five categories according Prostate Imaging-Reporting and Data System guidelines (PI-</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	<p>RADS) and considered positive for PCa if final PI-RADS was >3 and negative if ≤ 3.</p> <p>Results: A pathologically confirmed reclassification was observed in 55 patients (45.8%). mpMRI demonstrated a good specificity and negative predictive value (0.61 and 0.73, respectively) for ruling out a PCSPCa compared with PHI and PCA3. On multivariate analyses and after one thousand bootstrapping resampling, the inclusion of both PHI and mpMRI significantly increased the accuracy of the base model in predicting PCSPCa. Particularly, to predict PCSPCa, the base model had an AUC of 0.71 which significantly increased by 4% with the addition of PHI (AUC=0.75; $p<0.01$) and by 7% with the addition of mpMRI (AUC=0.78; $p<0.01$). Decision curve analysis revealed that the multivariable model with mpMRI had the highest net benefit.</p> <p>Conclusion: In a same cohort of patients underwent to RP but eligible to AS, mpMRI and, to a lesser extent, PHI showed an important role in discriminating the presence of a PCSPCa. Consequently, they could be useful in both the selection and monitoring of patients undergoing AS.</p>

SCHOLARONE™
Manuscripts

Peer Review

1
2
3 **IN PARALLEL COMPARATIVE EVALUATION BETWEEN MULTIPARAMETRIC MRI,**
4 **PCA3 AND PHI IN PREDICTING PATHOLOGICALLY CONFIRMED SIGNIFICANT**
5 **PROSTATE CANCER IN MEN ELIGIBLE FOR ACTIVE SURVEILLANCE**
6
7
8
9

10 Porpiglia F¹, Cantiello F², De Luca S¹, Manfredi M¹, Veltri A³, Russo F⁴, Sottile A⁵, Damiano R⁶

11
12
13
14 Divisions of ¹Urology and ³Radiology, San Luigi Gonzaga Hospital and University of Turin,
15 Orbassano, Turin, Italy

16
17
18
19 ²Urology Unit, Magna Graecia University of Catanzaro and Master in Laparoscopic and Robotic
20 Surgery, San Luigi Gonzaga Hospital and University of Turin, Orbassano, Turin, Italy

21
22
23
24 Division of ⁴Radiology and ⁵Laboratory Medicine, Candiolo Cancer Institute, Turin, Italy

25
26
27
28 ⁶Urology Unit, Magna Graecia University of Catanzaro, Italy

29
30
31
32
33 **Running Title:** multiparametric MRI, PHI, PCA3 and final pathological features

34
35 **Keywords:** multiparametric MRI, PHI; PCA3; radical prostatectomy; prostate cancer; prognostic
36 accuracy; active surveillance.

37
38
39 **Tables:** 2

40
41 **Figures:** 1

42
43 **Abstract Words Count:** 351

44
45 **Manuscript Words Count:** 3667

46
47
48 ***Corresponding author:**

49
50 Francesco Cantiello, MD, PhD
51 Urology Unit, Magna Graecia University of Catanzaro
52 Viale Europa, Germaneto, Catanzaro 88100, ITALY
53 E-mail: cantiello@unicz.it
54 Telephone number: +39 338 7914352
55
56
57
58
59
60

ABSTRACT

Objective: To assess the performance capabilities of multiparametric Magnetic Resonance Imaging (mpMRI), Prostate Health Index (PHI) and Prostate Cancer Antigen 3 gene (PCA3) in predicting the presence of pathologically confirmed significant Prostate Cancer (PCSPCa), according to the European Randomized Study of Screening Prostate Cancer (ERSPC) definition, in a same cohort of patients who underwent Radical Prostatectomy (RP) but eligible for Active Surveillance (AS).

Materials and Methods: An observational retrospective study was performed in 120 prostate cancer (PCa) patients treated with robot-assisted RP but eligible for AS according to Prostate Cancer Research International: Active Surveillance (PRIAS) criteria. Blood and urinary specimens were collected before initial prostate biopsy for PHI and PCA3 measurements, respectively. In addition, all patients underwent preoperatively and after 6-8 weeks from biopsy to mpMRI with a 1.5T scanner using a 4-5 channel phase array coil combined with an endorectal coil. mpMRI images were assessed and diagrams depicting prostate sextants were used to designate regions of abnormalities within the prostate. Findings in the prostate were assigned to one of five categories according Prostate Imaging-Reporting and Data System guidelines (PI-RADS) and considered positive for PCa if final PI-RADS was >3 and negative if ≤ 3 .

Results: A pathologically confirmed reclassification was observed in 55 patients (45.8%). mpMRI demonstrated a good specificity and negative predictive value (0.61 and 0.73, respectively) for ruling out a PCSPCa compared with PHI and PCA3. On multivariate analyses and after one thousand bootstrapping resampling, the inclusion of both PHI and mpMRI significantly increased the accuracy of the base model in predicting PCSPCa. Particularly, to predict PCSPCa, the base model had an AUC of 0.71 which significantly increased by 4% with the addition of PHI (AUC=0.75; $p<0.01$) and by 7%

1
2
3 with the addition of mpMRI (AUC=0.78; $p<0.01$). Decision curve analysis revealed that the
4
5 multivariable model with mpMRI had the highest net benefit.
6
7

8 **Conclusion:** In a same cohort of patients underwent to RP but eligible to AS, mpMRI and, to a lesser
9
10 extent, PHI showed an important role in discriminating the presence of a PCSPCa. Consequently, they
11
12 could be useful in both the selection and monitoring of patients undergoing AS.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

INTRODUCTION

In the era of opportunistic screening, the increasingly widespread use of Prostate Specific Antigen (PSA) test has led an increased incidence of low risk Prostate Cancers (PCa) that present a low likelihood of future progression during lifetime and could benefit of Active Surveillance (AS). AS aims to mitigate the overtreatment of indolent disease and potentially harmful side effects of active treatments, retaining the option of definitive therapy for patients who are reclassified over time as high risk [1]. The short and medium term safety for AS has been well demonstrated in multiple study cohort with only rare occurrence of PCa related death or metastasis reported. [2-5]. More recently, Klots et al confirmed the feasibility of AS in a large cohort study with a long-term follow-up, reporting a 10- and 15- year actuarial cancer-specific survival rates of 98.1 and 94.3%, respectively, with an active treatment free survival of 75.7, 63.5 and 55.0% at 5, 10 and 15 years, respectively [6].

However, the long term safety and effectiveness of AS depends on ability to select appropriate patients. At today, current stratification risk schemes are not perfect and the clinical and pathological parameters (total PSA, density PSA, biopsy Gleason Scores, number of positive cores, percentage of core involvement, clinical Stage) traditionally used to identify the presence of indolent PCa misclassify some patients, which are selected with apparent low risk disease and then harbor unfavorable disease. This is likely attributable to an initial misclassification instead of a true progression of indolent cancer, given the multifocality of the disease and the well-known clonal heterogeneity of PCa. In fact, in the updated results from the Prostate Cancer Research International: Active Surveillance (PRIAS study), 28% of the cohort experienced disease reclassification (defined as Gleason score >6 and/or more than two positive cores) at the first repeated biopsy during follow-up [7]. Furthermore, 20-30% of men

1
2
3 eligible for AS but elect to primary radical prostatectomy (RP) are found to have unfavorable
4
5 (Gleason \geq 7 or pT3) disease at RP [8]. On the other hand, we must not forget that current AS criteria
6
7 may be too strict, thereby excluding some patients in whom expectant management would be
8
9 appropriate and safe. In this context, GS 3+4 patients, with a very small volume of a secondary
10
11 Gleason 4 and a PSA<10 ng/ml, have been shown to have a disease comparable to GS 3+3 patients
12
13 [9,10].
14
15

16
17
18 For these reasons, there is an urgent need to better tools, including biomarkers and new imaging
19
20 technique, that could be used to better select patients for AS and to monitor them during their
21
22 subsequent course. Van der Bergh et al [11] recently published a systematic review of 30 studies on all
23
24 clinical tools for AS patients selection and monitoring, including studies on magnetic resonance
25
26 imaging (MRI), on serum biomarkers (-2proPSA, an isoform of PSA, and the Prostate Health Index,
27
28 PHI) and on urinary markers (Prostate Cancer Antigen 3 gene, PCA3). The authors concluded that the
29
30 use of high quality multiparametric MRI (mpMRI) showed particular promise because of the very high
31
32 negative predictive value respect to significant PCa and a favorable mpMRI might obviate the need for
33
34 repeat biopsy during AS. In addition, the use of PSA isoform data to current AS criteria might provide
35
36 further added benefit.
37
38
39

40
41
42 Keeping this in mind, we evaluate the performance capabilities of PHI, PCA3 and mpMRI in
43
44 predicting the presence of pathologically confirmed significant PCa (PCSPCa, updated ERSPC
45
46 definition) in a same cohort of patients who underwent RP but eligible for AS.
47
48
49

50 51 52 53 **MATERIAL AND METHODS** 54

55
56 We retrospectively reviewed our RP database from January 2012- December 2014, consisting of
57
58 patients with biopsy-proven, clinically localized PCa who underwent to robot-assisted RP at a surgical
59
60

1
2
3 high volume center (San Luigi Hospital, Orbassano, University of Turin) and to mpMRI at two
4
5 important and proved expertise centers in mpMRI (San Luigi Hospital, Orbassano, University of Turin
6
7 and Cancer Institute of Candiolo, Turin). From this database, we identified patients eligible for AS
8
9 based on PRIAS criteria (clinical stage T1c or T2 disease, PSA level of ≤ 10 ng/ml, Gleason score ≤ 6 ,
10
11 PSA-D of <0.2 ng/ml and one or two positive biopsy cores) [7]. These patients had been proposed AS
12
13 but they had refused opting for surgery. We excluded patients who received neo-adjuvant hormonal
14
15 therapy (anti-androgens or luteinizing hormone-releasing hormone analogues or antagonists) or/and
16
17 other hormonal preparations (ie, 5-alpha reductase inhibitors), patients with bacterial acute prostatitis or
18
19 previous prostate surgery in the 3 months prior to biopsy, subjects with chronic renal disease, marked
20
21 blood protein alterations (plasma normal range: 6-8 g/100 ml), hemophilia, or those previously
22
23 multiply transfused in order to not alter fPSA concentrations and consequently of -2proPSA[12]. A
24
25 final cohort of 120 patients was identified.
26
27
28
29
30
31

32 All patients underwent serum measurements of tPSA, %fPSA and PHI before biopsy. The PHI analyses
33
34 were performed using Hybritech Calibrated Access assays (Beckman Coulter, Brea, California) after
35
36 processing with a Unicel DxI 800 Immunoassay System analyzer (Beckman Coulter). In addition, all
37
38 patients underwent PCA3 testing before prostate biopsy via a Progenesa PCA3 assay (Gen-Probe Inc,
39
40 San Diego, California) according to the manufacturer's specific instructions. All examinations were
41
42 carried out at Laboratory Medicine of San Luigi Hospital, Orbassano, Turin for PCA3 and at Cancer
43
44 Institute of Candiolo, Turin for PHI.
45
46
47

48 Finally, all patients underwent preoperatively and after 6-8 weeks from biopsy (to minimize post-
49
50 biopsy artifact) to mpMRI with a 1.5T scanner (SIGNA Excite HD, GE Healthcare,) using a 4-channel
51
52 phase array coil combined with an endorectal coil (Medrad, Warrendale) or with a 1.5T scanner
53
54 (Achieva HD, Philips Healthcare) using a 5-channel phase array coil combined with an endorectal coil
55
56 (Medrad, Warrendale). The prostate and seminal vesicle anatomy was assessed on T2-weighted images
57
58
59
60

1
2
3 in the axial, coronal and sagittal planes. T1 fast spin echo axial images were generated to identify areas
4 of intraprostatic hemorrhage and to evaluate the pelvic lymph nodes and bones. Functional information
5 was obtained by Diffusion Weight Imaging (DWI) and Dynamic Contrast Enhanced (DCE) MRI. DWI
6 was performed using axial echo planar imaging sequences at different b-values. The sequences
7 parameters satisfied the recommendations from an European consensus meeting on MRI imaging for
8 the detection, localization and characterization of PCa [13].
9

10 All images were sent to two workstations and post processed (Functool v. 9.4.05a, GE Healthcare and
11 Intellispace Portal v. 6.0.3.12200, Philips Healthcare). Two single experienced uro-radiologists
12 analyzed the mpMRI findings. The uro-radiologists were blinded to the biomarkers results and to the
13 pathologist biopsy reports. Diagnostic features for malignancy were a low T2 signal in the peripheral
14 zone, a relatively low Apparent Diffusion Coefficient (ADC) calculated from DWI, early enhancement
15 and washout on DCE MRI. For the transitional zone a poorly defined nodule that distorted the normal
16 architecture and had concordant abnormalities on DWI and DCE was considered suspicious for
17 malignancy. mpMRI images were assessed and diagrams depicting prostate sextants were used to
18 designate regions of abnormalities within the prostate. Findings in the prostate were assigned to one of
19 five categories according Prostate Imaging-Reporting and Data System guidelines, developed by the
20 European Society of Urogenital Radiology (ESUR) in order to standardize the evaluation and reporting
21 of prostate mpMRI [14]. A recent meta-analysis on the use of PI-RADS for PCA detection with
22 mpMRI showed a good diagnostic accuracy with a sensitivity of 0.78 and a specificity of 0.79 [15].
23 Particularly, we assigned a 0-5 score to each of the three MRI sequences (T2-weighted, DWI and
24 dynamic contrast enhanced MRI) and a final PI-RADS score was obtained by adding the single scores
25 and dividing by three (rounding down or up depending on the case). Overall, the mpMRI finding was
26 considered positive if final PI-RADS was > 3 and negative if ≤ 3 .
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 RP specimens were evaluated using serially 3 mm sectioned whole-mount specimens according to the
4
5 Stanford protocol [16] and primary and secondary Gleason Score (GS) were assigned by an
6
7 experienced uropathologist, blinded to the biomarkers value and mpMRI results, according to the 2005
8
9 consensus conference of the International Society of Urological Pathology definitions [17]
10
11

12
13 For study purposes, all tumor foci were identified. Specifically, we evaluated the largest tumor focus of
14
15 the prostate - index tumor lesion (approximately a lesion of 1 cm corresponds to a spherical volume of
16
17 0.5 ml) and cumulative tumor volume was assessed using computerized planimetry accounting for all
18
19 tumor foci [18].
20
21

22
23 The primary end points of the study were to determine the performance capabilities of PHI, PCA3 and
24
25 mpMRI in parallel in predicting the presence of PCSPCa using the ERSPC definition (insignificant
26
27 PCa at RP: organ-confined Gleason 3+3 tumours, with no Gleason grade 4 or 5, index tumour volume
28
29 $\leq 1.3 \text{ cm}^3$ and a total tumour volume of $\leq 2.5 \text{ cm}^3$) [19]. In according with other authors [20] we used
30
31 these criteria because we consider the well-established 0.5 cm^3 PCa volume threshold for the index
32
33 tumor in the classic histopathologic Epstein definition of insignificant PCa (absence of GS pattern 4 or
34
35 5, extra capsular disease and a lesion $>0.5 \text{ cm}^3$) too much restrictive. Indeed, against the small
36
37 (approximately 5%) increased risk of underestimation of significant PCa, a much larger proportion of
38
39 men would have the chance to enter and participate in AS programs and forgo definitive treatments.
40
41 This situation would be beneficial of both quality of life and costs.
42
43
44
45
46
47

48 The study was designed according to the Standards for the Reporting of Diagnostic Accuracy Studies
49
50 (STARD) methodology to test the sensitivity, specificity, and accuracy of -2proPSA, its derivates,
51
52 PCA3 and mpMRI (<http://www.stard-statement.org>).
53
54

55
56 *Statistical analysis*
57
58
59
60

1
2
3 The qualitative data were tested using the chi-square test or Fisher's exact test as appropriate and the
4
5 continuous variables were tested by Mann-Whitney U-Test or T-Student Test according to their
6
7 distribution (according to Kolmogorov-Smirnov test) and presented as median (IQR) or mean (\pm
8
9 standard deviation), as appropriate. Univariate and multivariate logistic regression analyses were
10
11 carried out to identify variables potentially predictive of PCSPCa.
12
13

14
15 We preferred to exclusively consider PHI and exclude from the univariate and multivariate analysis
16
17 both the -2proPSA and its derivative -2proPSA over fPSA (%-2proPSA) because the variable PHI
18
19 could be more easy to interpret and understand by the reader since it is generally evaluated in a clinical
20
21 setting and because statistically speaking, PHI could capture much of the effects and obscure results
22
23 when it is evaluated in same multivariate analysis together with its components (-2proPSA), as
24
25 previously described [21].
26
27
28
29

30
31 Predictive accuracy of the model was assessed in term of the area under the receiver operating
32
33 characteristics curve (AUC) value. One thousand bootstrap resamples were used for all accuracy
34
35 estimates and to reduce overfit bias. The areas under the curve were compared via the Mantel-Haenszel
36
37 test.
38
39

40
41 We performed decision curve analysis (DCA) to evaluate the potential clinical usefulness of making
42
43 decisions based on the models including the markers [22].
44

45
46 We estimated net benefit (NB) for prediction models by summing the benefits (true-positive PCSPCa)
47
48 and subtracting the harms,(false-positive PCSPCa). The threshold probability of each model were
49
50 estimated. The interpretation of DCA is straightforward; a model with the highest NB at a particular
51
52 threshold should be chosen over alternative models. For all statistical comparisons significance was
53
54 considered as $p < 0.05$. Standard statistical software was used (SPSS v.18.0,IBMCorp,Armonk, NY,
55
56 USA; R version 2.15.2, R Foundation for Statistical Computing, Vienna, Austria).
57
58
59
60

RESULTS

After pathological specimens examination of all included subjects, we observed pathologically confirmed reclassification in 55 patients (45.8%). Table 1 summarizes the characteristics of patients according to the presence or not of PCSPCa. A positive mpMRI (PI-RADS ≥ 4) was found in 72.7% of PCSPCa and a negative mpMRI (PI-RADS ≤ 3) in 61% of PCIPCa. The sensitivity of mpMRI (PI-RADS ≥ 4) was 73%, the specificity (PI-RADS ≤ 3) was 61%, the negative predictive value (NPV) was 73% and the positive predictive value (PPV) was 61.5%. At the best balance value between sensibility and specificity (PHI ≥ 32.47), the sensitivity of PHI was 75%, the specificity was 54%, the NPV was 66% and the PPV was 67%. At the best balance value between sensibility and specificity (PCA3 ≥ 52.50), the sensitivity of PCA3 was 73%, the specificity was 64%, the NPV was 37% and the PPV was 76%.

On multivariate analyses and after one thousand bootstrapping resampling, the inclusion of both PHI and mpMRI significantly increased the accuracy of the base model in predicting PCSPCa, that included patient age, total PSA, free/total PSA ratio, PSA density, clinical stage, biopsy GS, number of positive cores (2 vs. 1). To predict PCSPCa, the base model had an AUC of 0.71 which significantly increased by 4% with the addition of PHI (AUC=0.75; $p < 0.01$) and by 7% with the addition of mpMRI (AUC=0.78; $p < 0.01$) (Table 2).

At the threshold $> 20\%$ the prediction models including mpMRI added value over base model. At the threshold $> 60\%$ the prediction models including PHI added Net Benefit over base model. The model including PCA3 did not added value (Figure 1).

DISCUSSION

A lot of published studies evaluated the utility of PCA3 and PSA isoforms, in addition to clinical and pathological parameters, to determine initial eligibility for AS and to monitor disease progression [11]. Recently, it has been published a direct comparison between PHI and PCA3 in a same cohort of patients underwent RP in predicting final pathologic features, demonstrating that PHI was significantly better than PCA3 in discriminating the presence of PCSPCa according to Epstein criteria [21]. Based on these results, the same authors also demonstrated that Epstein and PRIAS protocols could be improved by the addition of PCA3 or PHI resulting in greater NB in predicting insignificant prostate cancer in men eligible for AS. Particularly, PHI outperformed PCA3 demonstrating a better discriminative performance [21].

However, recent evidences also suggest a particular and prominent role played by mpMRI in this clinical scenario [23,24,25] For these reasons, in the current study, using histology at RP time as the reference standard, we evaluated the performance of mpMRI and urinary and serum biomarkers in parallel, demonstrating a higher capability of mpMRI than biomarkers in detecting pathologically confirmed significant disease according to the ERSPC definition. At our acknowledge, this is the first study the evaluates the prognostic performance of these three new tools in the same dataset of patients. In our cohort, mpMRI showed the highest gain in predictive accuracy of PCSPCa than both PCA3 and PHI (AUC=0.78; $p<0.01$). A negative prostate mpMRI has been shown to have a NPV for ruling out PCSPCa of 73%. Consequently, we can hypothesize that patients with a negative mpMRI and low-risk disease should be encouraged to pursue AS and a favourable mpMRI might obviate the need for repeat biopsy during AS follow up in two third of cases. On the other hand, we observed a lower PPV of 61% for a high risk disease. This suggests that lesions seen on mpMRI (or modification in mpMRI findings during AS program) not necessary correspond to not favorable PCa and it should ideally be confirmed

1
2
3 on prostate biopsy rather than being an indicator for RP. Herein, after performing DCA we
4
5 demonstrated that adding mpMRI and PHI added net benefit over base model when the threshold
6
7 probabilities was greater than 20% for mpMRI and greater than 60% for PHI. To reduce the ever-
8
9 increasing number of patients suitable for AS, we applied this new statistical evaluation to help us to
10
11 better understand the clinical benefit of adding mpMRI, PCA3 or PHI to a base model in order to
12
13 improve the clinical decision-making and better choose patients candidate to AS.
14
15

16
17
18 However, with regard to this clinical scenario there are two important problem. No accepted definition
19
20 of “radiological” progression in MRI in patients underwent AS has been formulated. This definition
21
22 can be based both on morphological parameters (volume measured on T2W or contrast-enhanced
23
24 images) and functional parameters (changes during time in qualitative and quantitative findings derived
25
26 most of all from DWI sequences, using a specific standardized reporting system). For this reason, at
27
28 today, a mpMRI alone is not able to really identify the disease progression and a combination of
29
30 radiological and biopsy findings is still necessary. Second, whether MRI-target biopsies, or MRI/TRUS
31
32 fusion biopsies, should be always completed by systematic TRUS-guided biopsies during first or repeat
33
34 prostate biopsy in AS program remains unknown [26]. In addition, when transperineal saturation
35
36 biopsy is set as the reference standard, approximately 10% of men with negative MRI and, for this
37
38 reason, not underwent to transrectal ultrasound guided transperineal fusion biopsy still harbor
39
40 intermediate risk disease [27]. It is plausible that with increasing precision in MRI target biopsy
41
42 technologies, systematic biopsy will lose value. Moreover, histology parameters available at MRI
43
44 target biopsy may not necessarily have the same value of those available at systematic TRUS guided
45
46 biopsy. Typically, there is an upgrade in GS and higher percentage of cancer per core with MRI target
47
48 biopsy. Consequently, a new definition of pathological significant PCa with MRI target biopsy should
49
50 be necessary, most of all whether we perform MRI target biopsy alone.[26]
51
52
53
54
55
56
57
58
59
60

1
2
3 There are several studies evaluating the performance of mpMRI in AS cohorts, using both RP histology
4 and repeat biopsy data, and a systematic review has been also recently published [28]. However, it is
5 necessary to emphasize that the evidence and the strength of this review are limited by the small
6 number of studies and by the lack of standardization within these studies in terms of population study (
7 age, prostate volume), selection criteria (Epstein, PRIAS), standardization in reporting MRI findings,
8 detection and definition of clinically significant disease and type of follow up. In this review, data
9 synthesis from RP histology (patients eligible for AS but undergone to RP with preoperatively MRI)
10 showed that the likelihood of a positive MRI preoperatively was 73% and upgrading occurred in 43%
11 of patients with positive MRI than 27% of patients with negative MRI, whereas no difference occurred
12 in terms of upstaging between two groups. Data synthesis from men undergoing MRI and repeat
13 standard biopsy on AS, confirmed that MRI is positive in roughly two-thirds of men: following positive
14 MRI, reclassification occurred in 39% than 17% in patients with negative MRI. Focusing on positive
15 MRI and MRI-target biopsy only, reclassification as significant PCa occurred in 47% of cases,
16 confirming a strong correlation between a positive MRI and upgrading during AS follow up and the
17 potential possibility to avoid biopsy in men with stable PSA and negative MRI.
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 There are also other studies, available in literature, that have not been included in this review
40 [29,30,31]. However, these studies confirmed a very high NPV and specificity for disease upgrading
41 (significant disease) in case of low suspicious scores, confirming that a favorable MRI may be used for
42 selection and follow up of patients during AS and might obviate the need for repeat biopsies.
43 Contextually, the PPV of MRI for higher risk disease seems to be lower in the selected population of
44 patients with low-risk cancers, suggesting that lesion seen on MRI in patients on AS should be
45 necessarily confirmed on guided biopsy. Stamakis et al [30] showed, in their multivariate analysis, that
46 a model incorporating three MRI variables, number of lesion, rate of suspicious and density of lesion
47 (lesion volume divided by prostate volume) presented a reasonable AUC of 0.72 for predicting
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 suitability for continued AS at repeat biopsy. Most recently Diaz et al [32] confirmed that mpMRI
4 associated a MRI/TRUS fusion biopsy substantially increased the number of pathological progression
5 that would not have been detected by standard biopsy alone. In addition, stable findings on mpMRI
6 were strongly associated with GS stability in patients with GS 6 PCa on AS and could potentially
7 reduce the number of unnecessary biopsies in men undergoing AS (NPV and specificity of 80%).
8
9

10 MRI characteristics have been also incorporated into established predictive preoperative nomograms of
11 pathologically significant PCa. Shukla-Dave et al [33] demonstrated that MRI increased the accuracy
12 of base models (including clinical an pathologic factor) in predicting insignificant disease.
13
14

15 Regarding the sequences of mpMRI, several studies showed the primary importance of DWI during
16 MRI in holding additional information in selection of patients on AS and during follow up. The
17 Apparent Diffusion Coefficient (ADC) of DWI provide information on tumor characteristics such as on
18 tumor aggressiveness. Recently, it has been documented that ADC values are inversely correlated
19 with GS in PCa and may be help in differentiation of low, intermediate and high risk cancer [34].
20 Furthermore, ADC of DWI may be a useful marker for predicting insignificant PCa in candidates for
21 AS as well as for predicting PCa progression during the monitoring of these patients [35]
22
23

24 Our study is not devoid of limitations. First, the study was limited by the relatively small number of
25 cases examined and further studies with a larger number should be performed to confirm our findings.
26 Second, the inclusion of only two expert uro-radiologists who interpreted all of the mpMR images may
27 affect the reproducibility of our results in clinical practice. In this context, mpMRI should be
28 standardized not only with regard to image reporting systems, but also with regard to technical
29 equipment and examination protocols, image acquisition, processing and post-processing. Third, the
30 study does not include any discussion of costs and logistics. Given the current health care crisis, these
31 issues are of key importance and further studies should be advised.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Notwithstanding these limitations, we believe that our results are noteworthy and could be transferable
4 to the urological community. mpMRI should be considered a promising tool in order to obtain
5 important information for the best selection of patients to AS program and also during follow up to
6 reduce the number of repeat prostate biopsy. Among biomarkers, PHI appears to add further
7 information in this clinical setting, suggesting a possible combination of these tools.
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

25 **CONCLUSION**

26
27
28 Diverse novel tools are available that may further improve current AS protocols. We showed an
29 important role of PHI and, most of all, of mpMRI in discriminating the presence of a PCSPCa in a
30 cohort of patients underwent to RP but eligible to AS. Consequently, their use could improve the risk
31 assessment in patients candidate to AS and also reduce the burden of monitoring during AS. However,
32 the added value of mpMRI and PSA isoforms should be further assessed in prospective studies.
33
34
35
36
37
38
39
40
41
42

43 **AKNOWLEDGEMENT**

44
45
46 Nothing to declare
47
48
49
50
51

52 **CONFLICT OF INTEREST STATEMENT**

53
54
55 Each author declares no conflict of interest.
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

1. Loeb S, Bruinsma SM, Nicholson J et al. Active surveillance for prostate cancer: a systematic review of clinicopathologic variables and biomarkers for risk stratification. *EurUrol* 2015; 67: 619-626
2. Dall'Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate cancer: a systematic review of the literature. *Eur Urol*. 2012 Dec; 62:976-83
3. 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010; 28:126-31
4. Selvadurai ED, Singhera M, Thomas K, et al. Medium-term outcomes of active surveillance for localized prostate cancer. *European urology*. 2013; 64:981-7
5. Welty CJ, Cowan JE, Nguyen H, et al. Extended Follow-Up and Risk Factors for Disease Reclassification from a Large Active Surveillance Cohort for Localized Prostate Cancer. *J Urol* 2014 Sep 28; doi: 10.1016/j.juro.2014.09.094

- 1
2
3 6. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance
4 cohort of patients with prostate cancer. *Journal of Clinical Oncology* 2015 Jan 20; 33:272-7
5
6
7
- 8 7. Bul M, Zhu X, Valdagni R, et al. Active surveillance for low-risk prostate cancer worldwide:
9 the PRIAS study. *European urology*. 2013; 63:597-603
10
11
- 12 8. Iremashvili V, Pelaez L, Manoharan M et al. Pathologic cancer characteristics in patients
13 eligible for AS: a head to head comparison of contemporary protocols. *EurUrol* 2012; 62:462-468
14
15
- 16 9. Cooperberg MR, Cowan JE, Hilton JF et al. Outcomes of active surveillance for men with
17 intermediate-risk prostate cancer. *Journal of Clinical Oncology* 2011;29:228-234
18
19
- 20 10. Bul M, Van der Bergh NC, Zhu X et al Outcomes of initially expectantly managed patients with
21 low or intermediate risk screen-detected localized prostate cancer. *BJU Int* 2012; 110:1672-1677
22
23
- 24 11. Van der Bergh NC, Ahmed HU, Bangma CH et al. New tools to improve patient selection and
25 monitoring on active surveillance for low-risk prostate cancer: a systematic review. *Eur Urol* 2014; 65:
26 1023-1031
27
28
- 29 12. Porpiglia F, Russo F, Manfredi M et al. The roles of multiparametric magnetic resonance
30 imaging, PCA3 and prostate health index-which is the best predictor of prostate cancer after a negative
31 biopsy? *J Urol* 2014; 192:60-66
32
33
- 34 13. Dickinson L, Ahmed HU, Allen C et al. Magnetic resonance imaging for the detection,
35 localization, and characterization of prostate cancer: recommendations from a European consensus
36 meeting. *Eur Urol* 2011; 59:477-494
37
38
- 39 14. Berentsz JO, Richenberg J, Clements R et al. ESUR prostate MR guidelines 2012. *Eur Rad*
40 2012; 22:746-757
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 15. Hamoen E, de Rooij M, Witjes JA, Barentsz JO, Rovers MM. Use of the Prostate Imaging
4 Reporting and Data System (PI-RADS) for Prostate Cancer Detection with Multiparametric Magnetic
5 Resonance Imaging: A Diagnostic Meta-analysis. *Eur Urol* 2015; 67: 1112-1121
6
7
- 8
9
10
11 16. Van der Kwast TH, Amin MB, Billis A, et al. International Society of Urological Pathology
12 (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working
13 group 2: T2 substaging and prostate cancer volume. *Mod Pathol* 211; 24:16-25
14
15
- 16
17
18 17. Epstein JI, Allsbrook WC, Jr., Amin MB, Egevad LL. The 2005 International Society of
19 Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J*
20 *SurgPathol* 2005; 29:1228-1242
21
22
- 23
24
25 18. Chen ME, Johnston D, Reyes AO, Soto CP, Babaian RJ, Troncoso P. A streamlined three-
26 dimensional volume estimation method accurately classifies prostate tumors by volume. *The Am J*
27 *SurgPathol* 2003; 27:1291-1301
28
29
- 30
31
32 19. Wolters T, Roobol MJ, van Leeuwen PJ, et al. A critical analysis of the tumor volume threshold
33 for clinically insignificant prostate cancer using a data set of a randomized screening trial. *J Urol* 2011;
34 185:121-125
35
36
- 37
38
39 20. Van der Kwast TH. The trade-off between sensitivity and specificity of clinical protocols for
40 identification of insignificant prostate cancer. *Eur Urol* 2012; 62:469-471
41
42
- 43
44
45 21. Cantiello F, Russo GI, Ferro M, et al. Prognostic accuracy of Prostate Health Index and urinary
46 Prostate Cancer Antigen 3 in predicting pathologic features after radical prostatectomy. *Urol Oncol*
47 2015; ;33:163.e15-23.
48
49
- 50
51
52 22. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction
53 models. *Med Decis Making* 2006; 26:565-574
54
55
- 56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
23. Lee DJ, Ahmed HU, Moore CM, Emberton M, Ehdaie B. Multiparametric magnetic resonance imaging in the management and diagnosis of prostate cancer: current applications and strategies. *Curr Urol Rep* 2014; 15: 390
 24. Johnson LM, Choyke PL, Figg WD, Turkbey B. The role of MRI in prostate cancer active surveillance. *BioMed Research International* 2014: 203906. doi: 10.1155/2014/203906.
 25. Van den Bergh RC, Ahmed HU, Bangma CH, Cooperberg MR, Villers A, Parker CC. Novel tools to improve patient selection and monitoring on active surveillance for low-risk prostate cancer: a systematic review. *EurUrol* 2014; 65:1023-1031.
 26. Giannarini G, Zazzara M, Rossanese M et al. Will Multi-Parametric Magnetic Resonance Imaging be the Future Tool to Detect Clinically Significant Prostate Cancer? *Front Oncol* 2014; 4:294.
 27. Kuru TH, Roethke MC, Seidenader J et al. Critical evaluation of magnetic resonance imaging targeted, transrectal ultrasound guided transperineal fusion biopsy for detection of prostate cancer. *J Urol* 2013; 190: 1380-1386
 28. Schoots IG, Petrides N, Giganti F, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. *Eur Urol* 2015; 67: 627-636
 29. Vargas HA, Akin O, Afaq A, et al. Magnetic resonance imaging for predicting prostate biopsy findings in patients considered for active surveillance of clinically low risk prostate cancer. *J Urol* 2012; 188:1732-1738.
 30. Stamatakis L, Siddiqui MM, Nix JW, et al. Accuracy of multiparametric magnetic resonance imaging in confirming eligibility for active surveillance for men with prostate cancer. *Cancer* 2013; 119:3359-66.

- 1
2
3 31. Mullins JK, Bonekamp D, Landis P, et al. Multiparametric magnetic resonance imaging
4 findings in men with low-risk prostate cancer followed using active surveillance. BJU Int 2013; 111:
5 1037-1045
6
7
8
9
10
11 32. Walton Diaz A, Shakir NA, George AK, et al. Use of serial multiparametric magnetic
12 resonance imaging in the management of patients with prostate cancer on active surveillance. Urol
13 Oncol 2015; 33:202.e1-7
14
15
16
17
18 33. Shukla-Dave A, Hricak H, Akin O, et al. Preoperative nomograms incorporating magnetic
19 resonance imaging and spectroscopy for prediction of insignificant prostate cancer. BJU Int 2012;
20 109:1315-1322
21
22
23
24
25
26 34. Somford DM, Hoeks CM, Hulsbergen-van de Kaa CA, et al. Evaluation of diffusion-weighted
27 MR imaging at inclusion in an active surveillance protocol for low-risk prostate cancer. Invest Radiol
28 2013; 48: 152-157
29
30
31
32
33
34 35. Kim TH, Jeong JY, Lee SW, et al. Diffusion-weighted magnetic resonance imaging for
35 prediction of insignificant prostate cancer in potential candidates for active surveillance. Eur Radiol
36 2015; 25:1786-1792
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1. Baseline characteristics of patients (n= 120)

	Pathologically Confirmed Significant PCa	Pathologically Confirmed Insignificant PCa	p-value
Patients, n (%)	55	65	
Median (IQR) age, years	65.0 (57.0-70.0)	66.0 (64.00-69.00)	0.55
Median (IQR) PSA, ng/ml	7.0 (6.39-10.10)	5.75 (4.88-9.22)	<0.01
Median (IQR) %fPSA	16.21 (13.00-10.00)	17.66 (15.00-19.00)	0.35
Median (IQR) PSA-D, ng/ml ²	0.16 (0.15-0.24)	0.13 (0.11-0.21)	0.08
Median (IQR) Prostate Volume, ml	42.76 (42.16-43.77)	43.39 (42.75-44.15)	0.09
Median (IQR) PHI	50.89 (28.44-61.33)	32.83 (29.08-45.29)	0.02
Median (IQR) PCA3	47.0 (13.0-58.00)	49.0 (28.0-65.0)	0.08
Clinical stage, n (%)			<0.01
T1c	40 (72.7)	60 (92.3)	
T2	15 (27.3)	5 (7.7)	
Median (IQR) number of positive cores	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.44
Pathological Index Tumoral Lesion Volume, n.(%)			<0.01
<1.3ml	7(12.7)	65 (100)	
>1.3ml	48 (87.3)		
Pathological T stage, n.(%)			<0.01
pT2	50 (90.9)	65 (100)	
≥pT3	5 (9.1)		
Extracapsular invasion, n.(%)			<0.01
Yes	5 (9.1)		
Not	50 (90.9)	65(100)	
Seminal Vesicles invasion, n.(%)			--
Yes			
Not	55(100)	65(100)	
Pathological Gleason score,n(%)			<0.01
≤6	20 (36.4)	60 (92.3)	
7	30 (54.5)	5(7.7)	
≥8	5 (9.1)		
mpMRI, n.(%)			<0.01
Pos	40 (72.7)	25 (38.5)	
Neg	15 (27.3)	40 (61.5)	

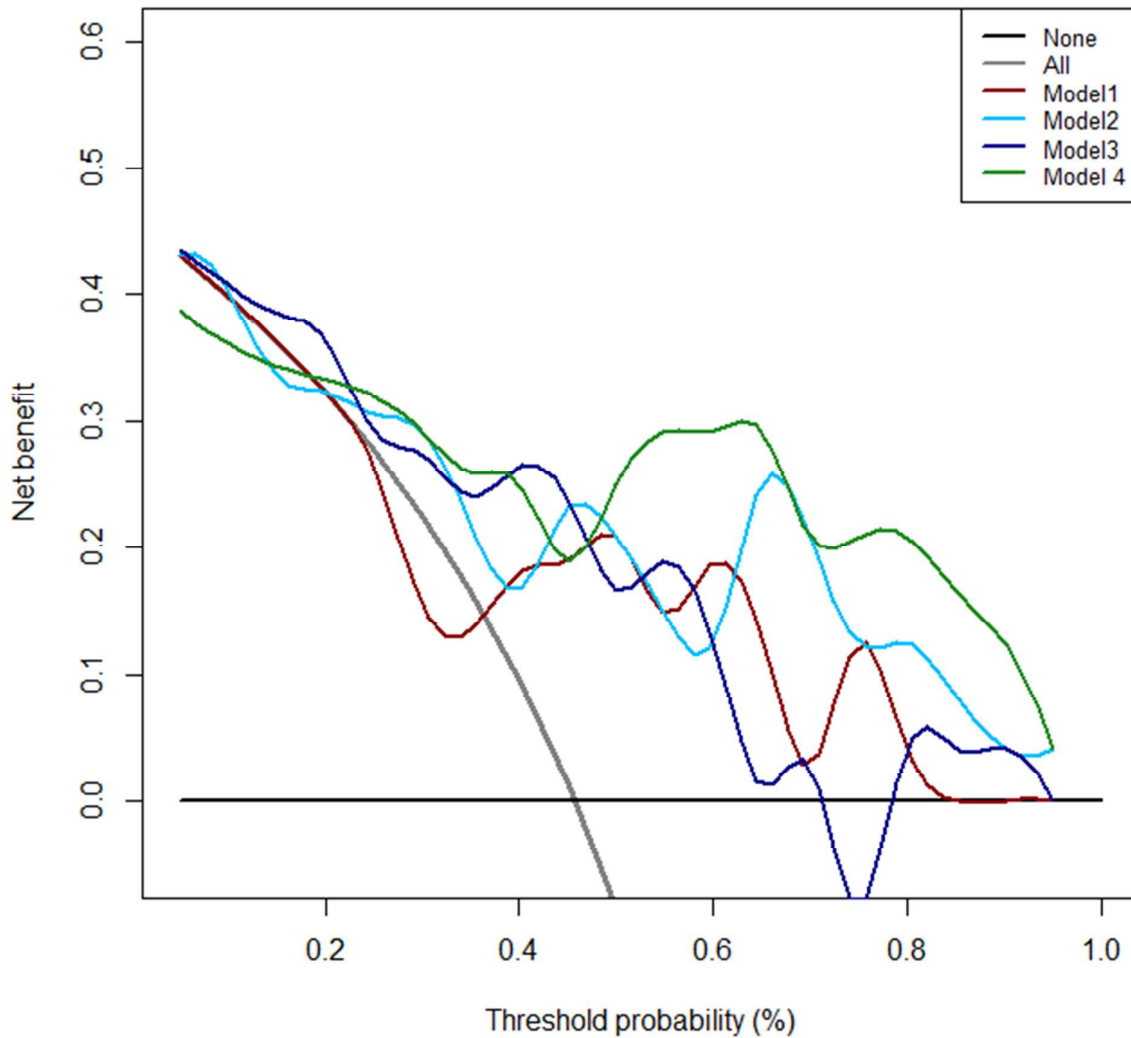
Table 2: Multivariate analysis predicting the probability of Pathologically Confirmed Significant Prostate Cancer

Predictors	Base Model† OR (95% CI)	p-value	Base Model with PHI† OR (95% CI)	p-value	Base Model with PCA3† OR (95% CI)	p-value	Base Model with mpMRI† OR (95% CI)	p-value
tPSA	1.082 (0.945-1.239)	0.25	1.110 (0.965-1.275)	0.14	1.072 (0.934-1.222)	0.32	1.199 (1.020-1.409)	0.02
f/tPSA	1.061 (0.982-1.147)	0.13	1.097 (1.008-1.195)	0.03	1.063 (0.978-1.149)	0.11	1.135 (1.134-1.241)	<0.01
Clinical stage, T2 vs. T1	4.211 (1.365-12.993)	0.12	1.926 (0.562-6.592)	0.29	9.317 (2.441-35.562)	0.01	2.348 (0.706-7.805)	0.16
N Pos Cores	1.232 (0.558-2.772)	0.02	1.060 (0.451-2.473)	0.08	3.078 (1.080-8.766)	0.03	1.449 (0.615-3.413)	0.39
PHI	-	-	1.044 (1.014-1.076)	<0.01	-	-	-	-
PCA3	-	-	-	-	1.02 (0.942-1.064)	<0.01	-	-
mpMRI	-	-	-	-	-	-	7.532 (2.812-20.173)	<0.01
AUC of Multivariate models %	0.71	-	0.75	-	0.72	-	0.78	-
Gain in predictive accuracy %	-	-	0.04	<0.01	0.01	<0.01	0.07	<0.01

OR= odds ratio; CI= confidence interval; tPSA =total PSA; f/tPSA=free/total PSA; N.Pos.Cores= number of positive cores; DRE= digital rectal exploration; PHI=prostate health index;PCA3=prostate cancer antigen 3; mpMRI=multiparametric magnetic resonance imaging; AUC= area under the curve
 *p<0.05 vs. Base model at Mantel-Haenszel test
 † adjusted for age, prostate volume and biopsy gleason score

Peer Review

Figure 1. Decision curve analysis of the effect of prediction models on the detection of significant PCa. The net benefit is plotted against various threshold probabilities. Model 1 includes PSA, PSA f/t, DRE, age, positive cores and biopsy gleason. Model 2 includes all the factors in Model 1 plus PHI. Model 3 includes all the factors in Model 1 plus PCA3. Model 4 includes all the factors in Model 1 plus mpMRI.



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60