

Platinum Priority – Collaborative Review – Prostate Cancer

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Novel Tools to Improve Patient Selection and Monitoring on Active Surveillance for Low-risk Prostate Cancer: A Systematic Review

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Abstract

Context: Active surveillance (AS) is an alternative to initial radical treatment of low-risk prostate cancer (PCa). Current criteria for selection and follow-up incorrectly exclude some patients eligible for AS and misclassify some who actually harbour significant disease. Better prediction of cancer behaviour at diagnosis would allow less strict monitoring and may improve acceptance of AS.

Objective: To review and critically analyse the literature on the value of novel clinical tools for patient selection and monitoring on AS.

Evidence acquisition: A comprehensive search of the PubMed database until July 10, 2013, was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis statement guidelines. Studies assessing novel markers and diagnostics for patient selection for AS and follow-up during AS were included. Studies analysing only classic clinical parameters used in current protocols (prostate-specific antigen, prostate volume, number of (positive) prostate biopsies, percentage malignant tissue, Gleason score) were excluded. This review focuses only on the AS setting and not on predicting insignificant disease in general.

Evidence synthesis: Of 787 studies on AS, 30 were included in this review: 14 on magnetic resonance imaging (MRI), 5 on serum markers, 5 on urinary markers, 4 on histopathology markers, and 2 on germline genetic markers. Several of these markers improve the prediction of tumour volume, tumour grade, or time to active treatment. MRI has a high specificity for low-risk PCa; new serum markers are associated with unfavourable disease. In none of the studies was the new marker used as the primary decision tool. Long-term outcome measures such as mortality were not assessed. The definition of indolent PCa is disputable.

Conclusions: Imaging and serum markers may improve future patient selection for AS and follow-up during AS. Prospective studies should aim to further evaluate the clinical utility of these new markers with respect to longer term outcomes of AS.

Patient summary: We searched the literature for articles reporting new ways to safely monitor low-risk prostate cancer for patients who have not had radical treatment. We found 30 articles. The most promising tools appear to be magnetic resonance imaging scans and various new blood markers. These may be used in the future within active surveillance regimens.

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1. Introduction

Active surveillance (AS) is an alternative to initial radical treatment of low-risk prostate cancer (PCa) [1,2]. The current protocols combine clinical T stage, prostate-specific antigen (PSA), PSA density, Gleason score, number of positive prostate biopsies, and/or amount of malignant tissue per core to select patients with assumed low-risk tumours for AS [3]. Patients are monitored with repeat prostate biopsies and PSA kinetics to detect initial undersampling or disease progression. If there is evidence of higher risk disease, patients are offered treatment with curative intent. AS aims to delay or avoid radical treatment and its related morbidity without compromising survival.

Even with the most stringent selection criteria, some patients with apparently low-risk disease actually harbour unfavourable disease due to inaccuracies in currently used (repeat) biopsy protocols [4,5]. In contrast, current AS criteria may be too strict, thereby excluding some patients in whom expectant management would be appropriate and safe [6]. There is therefore an unmet need for better tools (including biomarkers, imaging, and targeted biopsies) that could be used to select patients for AS and to monitor them during their subsequent course.

A range of novel markers might improve the prediction of tumour volume, tumour grade, and the natural history of PCa. This review summarises the evidence regarding these markers in the context of AS.

2. Evidence acquisition

2.1. Study selection

We conducted a systematic review of the PubMed database according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement guidelines [7]. Predefined search terms were used to identify articles published before July 10, 2013, describing novel markers used in AS for PCa. The search terms used were *prostate cancer* and (*active surveillance* or *expectant management*) (title/abstract).

2.2. Inclusion criteria

Studies with the following attributes were included for review:

- Those assessing the value of novel markers for outcomes in an AS setting
- Those studying markers not used in current AS protocols [3] (ie, not clinical T stage, PSA, PSA density, Gleason score, total and positive number of prostate biopsies and biopsy series, and percentage malignant tissue per core, nomograms including only these variables)

- Those studying markers currently available for use in clinical practice
- Original articles written in the English language,

3. Evidence synthesis

3.1. Search results

The literature search identified 30 original articles that were included for review: 14 on magnetic resonance imaging (MRI) [8–21], 5 on serum markers [22–26], 5 on urinary markers [27–31], 4 on histopathology markers [32–35], and 2 on germline genetic markers [36,37]. Figure 1 presents the search strategy and study selection flowchart. Table 1 presents the main pros and cons of the novel tools studied in the specific AS situation.

3.2. Novel markers for active surveillance

3.2.1. Magnetic resonance imaging

Four studies compared prostate MRI findings with radical prostatectomy (RP) results in patients who would have been eligible for AS.

Lee et al. retrospectively compared the maximal lesion diameter on 3-T diffusion-weighted (DW) MRI with RP outcomes ($n = 188$) [8]. Median number of biopsy cores at diagnosis was 12. In 72 patients, no tumour was identified on MRI, 43 had a lesion <1 cm, and 73 had a lesion >1 cm. A diameter >1 cm versus no tumour <1 cm was associated with Gleason score >6 (39% vs 20%; $p = 0.007$) and tumour volume (mean 1.09 vs 0.73 ml; $p = 0.018$). Lee et al. also found that patients with PSA ≤ 10 ng/ml and Gleason 6 disease and without visible tumour on DW 3-T MRI showed similar postoperative rates of organ-confined Gleason 6 disease whether or not they were considered suitable for AS according to the Prostate Cancer Research International Active Surveillance (PRIAS) criteria (stage T1–2, PSA ≤ 10.0 , PSA density <0.2 , 1–2 positive cores) (152 of 238 [63.9%] vs 35 of 59 [59.3%], respectively ($p = 0.549$) ($n = 464$) [9].

In their retrospective study, Guzzo et al. did not find any association between visualisation of tumour on T2-weighted MRI and Gleason upgrading, extracapsular extension (ECE), or positive surgical margins (PSMs) in patients suitable for AS who received surgery ($n = 172$) [10]. However, the study used cases dating back to 1991, and since then MRI techniques have improved significantly.

Turkbey et al. analysed preoperative 3-T multiparametric (MP)-MRI ($n = 133$) [11]. Lesions were identified on MRI in 126 cases (95%). MRI showed sensitivity of 93%, positive predictive value (PPV) of 57%, and overall accuracy of 92% (11 cases misclassified) in predicting insignificant pathologic disease (defined as tumour volume <0.5 ml, no Gleason pattern 4, no ECE, and no seminal vesicle invasion), outperforming Epstein, d'Amico, and Cancer of the Prostate Risk Assessment criteria. Epstein biopsy criteria misclassified 16 patients (5 AS candidates, 11 non-AS); adding MRI corrected for 12 of these (4 AS, 8 non-AS).

Ploussard evaluated the role of 1.5-T MRI disease staging (T1–2 vs T3–4) with endorectal coil done >6 wk after biopsy

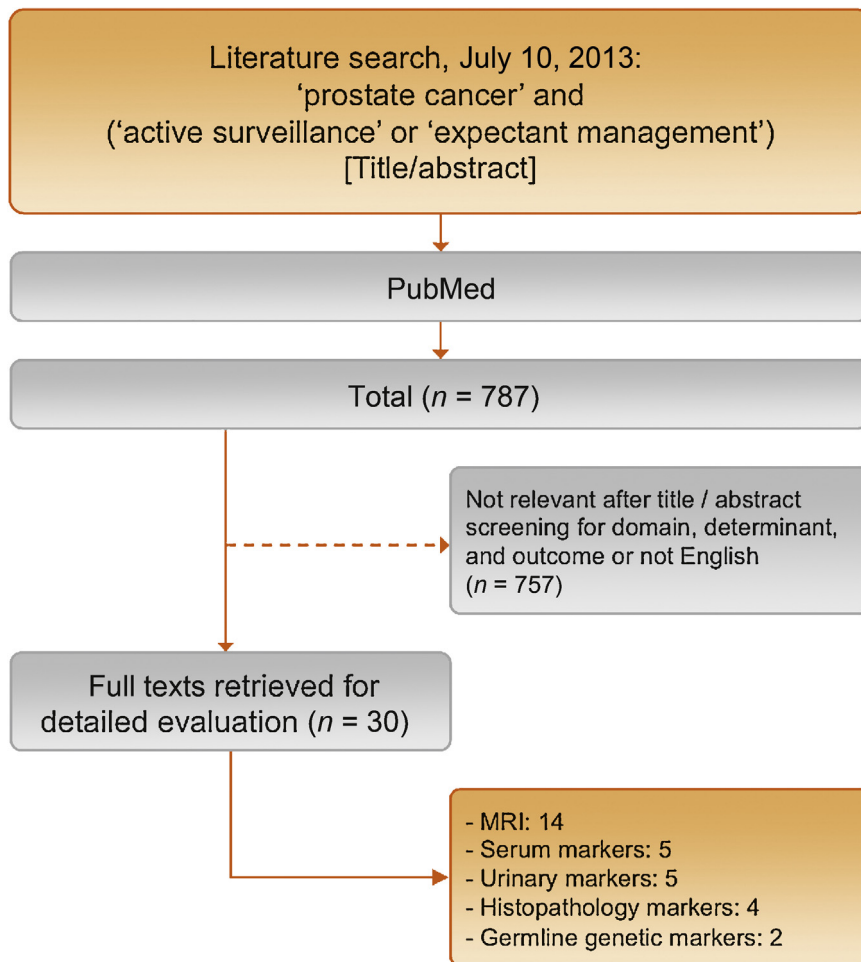


Fig. 1 – Literature search and selection of studies flowchart.
MRI = magnetic resonance imaging.

in patients suitable for AS according to stringent criteria (PSA ≤ 10 , $\leq T2a$, fewer than three positive biopsies, < 3 mm tumour per core) in patients who were diagnosed using an extensive 21-core biopsy protocol ($n = 96$) [12]. No association of MRI stage with RP Gleason upgrading, ECE, PSM, or any unfavourable disease was found. The indication for MRI was not stated (64 comparable patients did not undergo MRI), and DW imaging was not carried out.

Six studies assessed the relation between MRI findings and AS outcome data, such as repeat biopsy findings.

Vargas et al. performed 1.5- or 3-T MRI in patients on AS before confirmatory 12-core biopsy ($n = 388$) [13]. Three radiologists scored images for the presence of a tumour on a 5-point scale. Low suspicion scores (scores 1–2) showed high negative predictive value (NPV) for upgrading on biopsy (96–100%) and high specificity (95–100%), indicating that biopsy might have been safely avoided in these patients. The PPV (21–26%) and sensitivity (6–32%) for biopsy upgrading were low. At the other side of the spectrum, high suspicion score (score 5) on MRI showed high sensitivity (87–98%) for biopsy upgrading but relatively low specificity (22–37%). Area under the receiving

operator curve (ROC) curves for the prediction of low-risk PCa for the three reviewers were 0.69, 0.76, and 0.79. Even for the experienced readers, interobserver agreement was only moderate (κ score: 0.41–0.61).

Fradet et al. had 1.5-T MRI and MRI spectroscopy radiology reports reviewed by two urologists, stratifying findings into normal or abnormal ($n = 114$) [14]. The indication for performing an MRI was not mentioned. An abnormal result was associated with Gleason upgrading at repeat biopsy in AS patients (hazard ratio [HR]: 4.0; 95% confidence interval [CI], 1.1–14.9). In 69% of 114 patients, a lesion was identified. Of 18 patients with normal MRI who underwent repeat biopsy, 2 (11%) had upgrading.

Stamatakis et al. reported the findings of 3-T MP-MRI in AS patients according to the Johns Hopkins criteria ($n = 85$) [15]. The number of lesions on MRI, rate of suspicion of lesions (number of positive sequences), and lesion density (lesion volume divided by prostate volume) were associated with findings at confirmatory biopsy, including MRI-transrectal ultrasound (TRUS) fusion-guided biopsies. The ROC curve of the model incorporating these three MRI variables showed a reasonable area under the curve (AUC)

Table 1 – Main pros and cons of novel tools studied in the specific active surveillance situation

Modality	Pro	Con
Magnetic resonance imaging	<ul style="list-style-type: none"> - Potential association with disease stage and grade over clinical criteria - Additional value of multiparametric analysis and ADC - High specificity for low-risk disease 	<ul style="list-style-type: none"> - Relatively low sensitivity for higher risk disease - Unsolved issues on interobserver variability, reproducibility, selection bias, costs - Prospective blinded analysis needed
Serum markers	<ul style="list-style-type: none"> - Association with unfavourable repeat biopsy findings and switch to active therapy 	<ul style="list-style-type: none"> - Overlap between favourable and unfavourable findings limit use as single threshold
Urinary markers	<ul style="list-style-type: none"> - Association with unfavourable repeat biopsy and RP findings - Association mainly with tumor volume - Easily obtainable 	<ul style="list-style-type: none"> - Small percentage with low PCA3 scores with high predictive accuracy - Limited association with disease stage and Gleason score
Histopathology markers	<ul style="list-style-type: none"> - Association with unfavourable repeat biopsy findings - Additional information from already available material 	<ul style="list-style-type: none"> - Potential biopsy sampling error - Small retrospective studies, intermediate end points
Germline genetic markers	<ul style="list-style-type: none"> - Potential association with unfavourable RP findings - Potential of prediagnostic risk assessment 	<ul style="list-style-type: none"> - Scarce data - Prospective analysis lacking

ADC = apparent diffusion coefficient; PCA3 = prostate cancer antigen 3; RP = radical prostatectomy.

of 0.72 for predicting suitability for continued AS at repeat biopsy. AS candidates had low, medium, and high MRI suspicion rates of 40%, 53%, and 7%; non-AS had 12%, 68%, and 20%, respectively.

Vasarainen et al. performed 3-T DW-MRI in addition to repeat biopsies after 1 yr within the Finnish arm of the PRIAS trial ($n = 80$) [16]. A suspicious lesion (review by two genitourinary radiologists) was found in 50% of patients, with 75% of these also appearing malignant on apparent diffusion coefficient (ADC) image maps. Tumour appearance did not correlate with any clinical parameter, repeat biopsy findings, or stopping AS.

Margel et al. studied 1.5-T MRI findings for malignancy of a single observer in AS patients before 12-core, guided if possible, confirmatory biopsy ($n = 56$) [17]. The end point was reclassification to disease considered no longer suitable for AS (Gleason >6 , more than two positive biopsies, or $>50\%$ tumour in a single core). The rate of confirmatory biopsy reclassification was only 3.5% in the 38% of patients where no cancer was found on MRI, 10.7% in the 40% of patients in whom MRI and initial biopsy were concordant, and 17.9% in the 22% of patients who showed a significant lesion >1 cm on MRI.

Mullins et al. studied the association of the pathologic index lesion (two positive biopsies in the same prostate sextant) with the MRI index lesion (suspicious lesion ≥ 10 mm or more than two suspicious lesions in prostate sextant) in patients on AS at Johns Hopkins ($n = 50$) [18]. The 3-T MP-MRI showed high specificity (97%) and high NPV (90%), but low sensitivity (19%) and PPV (46%) for the detection of a pathologic index lesion. Biopsy reclassification rates (Gleason pattern >3 , more than two cores, or $>50\%$ core involvement) of patients with abnormal versus normal MRI were 40% versus 12.5%, respectively.

Three studies specifically assessed the value of ADC on MRI.

Van As et al. studied the ADCs of 1.5-T MRI lesions corresponding with positive biopsy in the same prostate region ($n = 86$) [19]. ADC was significantly related to adverse pathology on repeat biopsy, with area under the ROC of 0.83. By way of comparison, PSA had an AUC of 0.77.

Interestingly, among those patients with a favourable ADC, none had adverse pathology at repeat biopsy, suggesting that repeat biopsy might be unnecessary in men with a favourable MRI.

Somford et al. performed 3-T MP-MRI with endorectal coil (including T2-weighted and DW images) in patients included in an AS protocol ($n = 54$) [20]. At least one suspicious region (two in most patients) was identified in 98% of patients and biopsied. These MRI-guided biopsies to suspicious areas identified PCa in just over half the lesions (29 of 53 [55%]) of which 21% (6 of 29) were upgraded. Mean ADC of lesions was different between MRI-guided biopsies that showed no cancer (1.26 [standard deviation (SD): 0.25]), low-grade PCa (1.09 [SD: 0.25]), and high-grade PCa (0.84 [SD: 0.35]). The area under ROC curve of this predictor was 0.73 for predicting any cancer (the AUC for predicting significant PCa was not presented).

Morgan et al. analysed AS patients who all underwent 1.5-T DW-MRI both at inclusion and follow-up ($n = 50$) [21]. ADC of both tumour area and whole prostate decreased during follow-up of patients who showed disease progression. A 10% ADC reduction showed high sensitivity (93%) but low specificity (40%) for progression (defined as PSA velocity >1 ng/ml per year or Gleason $>3 + 4$, or $>50\%$ of cores involved on repeat biopsy).

In summary, many studies are available on the value of MRI within AS, although none use MRI as an indication for treatment. MP-MRI generally shows a very high NPV for the intermediate end point of disease upgrading. Favourable MRI findings on a good-quality MP-MRI may therefore be used for selection and follow-up of patients during AS and might obviate the need for repeat biopsies. MRI might be less useful after extensive biopsy protocols. The PPV of MRI for higher risk disease seems to be considerably lower in the selected population of patients with low-risk cancers and may be caused by reporter bias with more false positives in AS cohorts who are known to have PCa. The reported range of percentages of tumours identified in AS candidates is very wide (50–98%). Furthermore, MRI lesions do not always correspond with guided biopsy or RP specimen findings. This suggests that lesions seen on MRI should ideally be

confirmed on guided biopsy rather than being an indication for radical treatment. ADC holds important additional predictive information (ROC up to 0.83). Rosenkrantz et al. recently described the diffusional kurtosis imaging technique to have more value as a marker of adverse final pathologic outcome among AS candidates [38]. Discrepancies between MRI study findings may be due to variation in MRI specifications, grading standards, (single or multiple) parameters graded [39], different patient selection criteria, and timing of MRI with respect to biopsy. Significant interobserver variability is seen in some studies, and results may not be applicable in the community setting. The use of a TRUS biopsy (with its sampling error) as the reference test by which to validate imaging findings is an important limitation of these studies.

3.2.2. Serum markers

Tosoian et al. retrospectively related PSA isoforms to unfavourable findings (Gleason ≥ 7 , three or more cores, $>50\%$ involvement) on annual biopsy in AS patients ($n = 167$) [22]. Free and bound forms of PSA as well as different PSA protein isoforms can be found in serum. Biopsy reclassification was associated with baseline and longitudinally measured ratio of free PSA (fPSA) to total PSA (tPSA; %fPSA), ratio of $[-2]$ proPSA to fPSA ($[-2]$ proPSA), ratio of $[-2]$ proPSA to %fPSA, and Prostate Health Index (ϕ ; defined as $[([-2]proPSA \text{ pg/ml}) / (fPSA \text{ ng/ml})] \times [tPSA \text{ mg/ml}]^{0.5}$). The mean baseline ϕ for patients with, and without, biopsy reclassification was 37.45 (SD: 18.21) versus 27.99 (SD: 10.07) ($p = 0.0002$), respectively.

Makarov et al. assessed PSA isoforms in serum and also in PCa and adjacent tissue areas with quantitative immunohistochemistry ($n = 71$) [23]. The results were analysed with respect to unfavourable repeat biopsy findings during AS (Gleason ≥ 7 , three or more cores, $>50\%$ involvement). The ratio of $[-2]$ proPSA to %fPSA in serum at diagnosis was higher in men developing unfavourable repeat biopsy. $[-5/-7]$ proPSA in tissue staining was more intense, with greater fractional area in this group. The mean ratio of $[-2]$ proPSA to %fPSA for favourable versus unfavourable repeat biopsy outcomes was 0.65 (SD: 0.36) versus 0.87 (SD: 0.44) ($p = 0.02$), respectively.

Two studies retrospectively focused on the value of fPSA in AS patients. Van As et al. found in multivariate analysis that T stage and %fPSA remained significant predictors of transition to radical treatment during AS ($n = 326$) [24]. Classifying patients into groups using the median values as a threshold, patients with both favourable PSA and %fPSA, one favourable or both unfavourable, had an active treatment rate at 3 yr of 0%, 27%, and 55%, and histologic progression rates of 0%, 28%, and 35%, respectively. ROC for %fPSA as a predictor of radical treatment within 2 yr was 0.83.

Khan et al. found that besides tPSA and gland volume, %fPSA at diagnosis predicted unfavourable findings at repeat biopsy ($n = 67$) [25]. The diagnostic accuracy of combined variables ranged from 75% to 84%, and the area under the ROC curve was 0.83.

Finally, Venkitaraman et al. did not find a relation of serum levels of α - and γ -tocopherol, α - and β -carotene,

lycopene, retinol, and selenium with disease progression (adverse histology on repeat biopsy Gleason grade ≥ 4 , $>50\%$ positive cores) or radical treatment for high PSA velocity ($n = 104$) [26].

Several studies indicate that fPSA and PSA isoforms add to classical parameters for predicting intermediate AS end points; however, the overlap between values in favourable and unfavourable groups makes it difficult currently to use these as stand-alone criteria for AS selection and follow-up.

3.2.3. Urinary markers

Lin et al. assessed the value of post-DRE prostate cancer antigen 3 (PCA3) and TMPRSS2:ERG (gene fusion related to promotion of PCa) within the Canary Foundation Prostate Active Surveillance Study ($n = 387$) [27]. Median value of PCA3 and TMPRSS2:ERG increased with both increasing number of positive cores and Gleason score. The AUC for Gleason ≥ 7 disease of both new biomarkers combined (0.66) was smaller than that of PSA alone (0.68). Combined, AUC was 0.70.

Tosoian et al. also studied the value of PCA3 scores within the John Hopkins surveillance program ($n = 294$) [28]. Mean PCA3 scores were not different between patients with stable disease or patients showing biopsy upgrading or upstaging (60.0 vs 50.8; $p = 0.131$). AUC of PCA3 alone for predicting biopsy progression was 0.59.

Whelan et al. obtained expressed prostatic secretion (EPS) preoperatively in patients who were also considered to be suitable for AS according to the National Comprehensive Cancer Network guidelines ($n = 216$) [29]. Secretion capacity biomarkers total RNA and EPS specimen volume and the RNA expression biomarkers TXNRD1 mRNA, PSA mRNA, TMPRSS2:ERG fusion mRNA, and PCA3 mRNA were measured. Two high-performing models were identified, one featuring two TMPRSS2:ERG variants (type III and type VI), and one featuring two secretion capacity biomarkers. The best performing model was associated with a reduced risk of upstaging, and of both upstaging and Gleason upgrading, by 7.8- and 5.2-fold, respectively, with 52% of all potential AS candidates meeting the model criteria.

Nakanishi et al. found PCA3 to correlate with tumour volume and to outperform PSA and biopsy characteristics ($n = 59$ before biopsy; 83 before RP) [30]. A PCA3 score threshold of 25 yielded the highest diagnostic accuracy for predicting tumour volume <0.5 ml (sensitivity: 63.0%; specificity: 81.2%; PPV: 56.7%; NPV: 84.3%; accuracy: 76.0%). Median PCA3 score was 36.2. PCA3 was also significantly different between Gleason 6 and higher grade PCa but not analysed in multivariate analysis.

Ploussard et al. retrospectively tested the performance of PCA3 in patients with low-risk PCa who underwent RP ($n = 106$) [31]. A PCA3 score threshold of 25 was significantly associated with tumour volume and improved on the predictive value of biopsy criteria (odds ratio for volume >0.5 ml was 3.19). Only 28% of patients had a PCA3 score <25 . No relation between PCA3 and disease stage was found.

Novel EPS biomarkers may hold additional predictive value, especially for tumour volume. The value of PCA3

seems limited due to the lack of a consistent association with disease stage or Gleason score. Only a minority of patients have the low PCA3 scores that show the best predictive accuracy. If surveillance were restricted to those with such a low PCA3 score, many patients would be excluded from AS who may have in fact been suitable.

3.2.4. Histopathology markers

Makarov et al. studied 12 nuclear morphometric descriptors (such as shape and size of nucleus) within patients in a PCa expectant management program ($n = 75$) [32]. Of these, 30 showed unfavourable biopsy (Gleason >6 , more than two biopsy cores, $>50\%$ of cores involved) during follow-up. A model with clinical parameters and morphometric descriptors had an AUC of 0.88 versus 0.68 for a model incorporating clinicopathologic variables alone.

Isharwal et al. analysed DNA content and optical density of prostate biopsy tissue ($n = 71$) [33]. Abnormal optical density of benign and cancer tissue were significant predictors of unfavourable results (Gleason >7 , more than two positive cores, $>50\%$ cancer involvement) during annual biopsy on multivariate analysis. Other DNA content measurements showed trends towards significance. In the same group, serum phi ratio ($p = 0.003$) and ratio of $[-2]$ proPSA to %fPSA ($p = 0.004$) were found to be significant predictors of unfavourable biopsy; phi and ratio of $[-2]$ proPSA to %fPSA improved prediction in combination with DNA content [34].

Jhavar et al. used tissue microarrays of prostate biopsies of patients on AS to test immunohistochemical markers ($n = 60$) [35]. Ki-67 (a nuclear protein indicating growth fraction) labelling index was found to be a significant ($= 0.03$) predictor of progression to treatment ($\geq 4 + 4$ or $>50\%$ positive cores on repeat biopsy).

The studies just cited on morphometric biopsy characteristics and DNA content show interesting pilot data, but they are hampered by small sample size, the use of intermediate end points, lack of prospective validation, and possible sampling error of biopsies.

3.2.5. Germline genetic markers

Data on genetic evaluation of AS patients are scarce. Goh et al. studied the predictive value of 29 cancer risk-associated

single nucleotide polymorphisms and family history in AS patients ($n = 471$) [36]. This retrospective study found no association with the intermediate end points, adverse repeat biopsy findings, and time to treatment.

McGuire et al. assessed the association between carrier status of 35 risk alleles in patients who had received RP but had also been suitable for AS ($n = 263$) [37]. Carriers of one and two of three specific risk alleles had a twofold (95% CI, 1.2–5.3) and sevenfold (95% CI, 2.7–19.4) risk of adverse characteristics at RP (Gleason ≥ 7 and/or stage $\geq pT2b$), respectively (not adjusted for clinical parameters). Maximal AUC was limited to 0.66. Repetitive testing could have led to apparently significant associations. Prospective validation in larger cohorts is indicated.

There is currently no good evidence that germline genetic markers have clinical utility for patient selection for AS or monitoring during AS.

3.3. Discussion

This review aims to provide insight into the value of novel markers that could be of use in AS selection and follow-up. Figure 2 presents a schematic representation of the place of novel tools in AS to improve selection and decrease the switch to active therapy. The quality of studies varied, and most did not fully comply with Standards for Reporting of Diagnostic Accuracy criteria [40]. The review focuses on the AS setting only and not on predicting insignificant disease in general. Several of these novel markers have the potential to improve our practice of AS. In our view, the use of high-quality MP-MRI shows particular promise because of the very high NPV reported with respect to significant PCa. If validated, a favourable MRI might obviate the need for repeat biopsy during AS. The addition of PSA isoform measurement to current AS criteria may also provide added value. Prospective studies are needed to study the performance of these novel markers, using template prostate mapping biopsies and MR-targeted biopsy protocols. Standards for study design to avoid common bias in biomarker evaluation have been proposed [41].

Two studies did not meet the criteria for inclusion in the review, but they deserve attention because of their

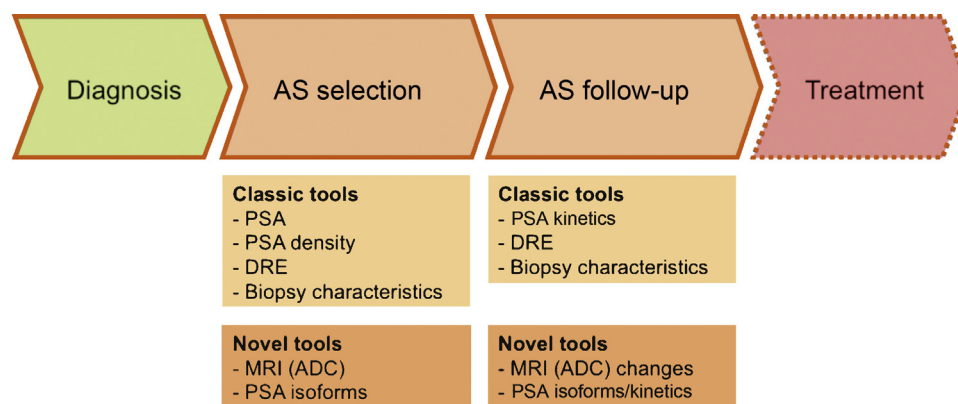


Fig. 2 – Schematic representation of the place of novel tools in active surveillance to improve selection and decrease switch to active therapy. ADC = apparent diffusion coefficient; AS = active surveillance; DRE = digital rectal examination; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

potential value in AS programs. First, the Oncotype DX Genomic Prostate Score (GPS; Genomic Health, Inc., Redwood City, CA, USA) was recently presented [42]. It is derived from RNA expression levels of a set of 17 cancer-related genes in PCa tissue, normalised to 5 reference genes. The score was originally developed to predict clinical recurrence after RP using prostatectomy specimen tissue ($n = 441$), but a strong association with adverse pathology was confirmed when analysing biopsy tissue from patients with low- to intermediate-risk disease ($n = 167$). The GPS was validated in biopsies of patients suitable for AS and strongly predicted ($p = 0.005$) high-grade and/or pT3 disease after adjusting for pretreatment factors ($n = 395$). It remains unclear whether the GPS would provide additional value independent of MP-MRI and PSA isoforms.

Second, the cell cycle progression (CCP) score derived from RNA expression levels of 31 genes in PCa biopsy tissue has also been suggested as a predictor of PCa outcomes ($n = 349$) [43]. In multivariate analysis, CCP score was the strongest predictor (HR of 1.65 for one CCP score point increase; 95% CI, 1.31–2.09; $p < 0.001$) for death from PCa. Gleason score and PSA also contributed significantly. CCP scores >3 , $2-3$, $1-2$, $0-1$, and <0 were seen in 16, 50, 114, 133, and 36 patients, respectively. Although these data are promising, the CCP score has not been tested in the context of low-risk disease on AS.

The literature on novel markers as applied to AS has a number of important limitations. No consideration has been given to cost effectiveness, only to clinical utility. No data are available with respect to longer term end points such as time to metastasis or disease-specific mortality [44]. Rather, marker studies are limited to intermediate end points such as repeat biopsy findings, treatment-free survival, or RP specimen characteristics. It remains to be seen whether the results of any of the markers discussed turn out to be a useful indicator of longer term outcomes.

Another important caveat is that the tumour size and grade criteria for clinical significance are arbitrary. The most widely used definition of so-called clinically insignificant disease is based on a study of 139 cystoprostatectomy specimens by Stamey et al. [45]. When applying the lifetime probability of 8% (11 of 139) of being diagnosed with PCa to the 55 (40%) cancers found, the largest 11 tumours ranged in volume from 0.5 to 6.1 ml, leading to the conclusion that tumours <0.5 ml were insignificant. This approach was repeated by Winkler et al., who studied 97 men who underwent radical surgery for bladder cancer between 2000 and 2005 [46]. Fifty-eight of 97 cases (60%) were found to have PCa. Using the same approach towards defining the pathologic characteristics of clinically insignificant disease gave a tumour volume cut-off of 1.09 ml. The Stamey criteria for insignificant disease thus may be too restrictive in terms of selecting cases with a likely indolent natural history. Furthermore, the definition of insignificant PCa should be dynamic instead of static; in practice one cannot use the same volume/grade criteria for significance in all patients. A cancer that would be significant in a 50-year-old man may not be significant in a 75-year-old man.

The need for AS arises from overdiagnosis, together with our inability to accurately predict individual PCa behaviour. If initial diagnostic tests gave a 100% certain estimation of tumour behaviour, surveillance would not be needed. Rather we would treat those destined to cause harm and we would not need to even follow up men with harmless cancers (and possibly even relabel these as nonmalignant) [47]. AS accepts a certain risk that patients with what appears to be indolent disease may actually harbour higher risk disease. Monitoring aims to correct for this understaging and undergrading, and also to detect biologic progression. The choice between treatment and observation is essentially the same choice, whether it is made at the time of diagnosis or after an initial period of AS. The stricter the inclusion criteria for AS, the less failure will be seen during follow-up. It follows that the better the risk estimation at the start of AS, the less strict the follow-up protocol needs to be, possibly leading to higher acceptance of AS.

4. Conclusions

Diverse novel markers are available that may further improve current AS protocols. The added value of MP-MRI and PSA isoforms should be assessed in prospective studies. Risk assessment, with the acceptance of a certain amount of uncertainty, will always remain inherent to AS, as in many other aspects of PCa management. The definition of indolent disease remains disputable. The use of novel markers that improve PCa risk assessment may not only increase the number of patients suitable for surveillance but also reduce the burden of monitoring during AS.

Author contributions: Roderick C.N. van den Bergh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: van den Bergh, Parker.

Acquisition of data: van den Bergh.

Analysis and interpretation of data: van den Bergh, Parker.

Drafting of the manuscript: van den Bergh, Parker.

Critical revision of the manuscript for important intellectual content:

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References

- [1] Ganz PA, Barry JM, Burke W, et al. National Institutes of Health State-of-the-Science Conference: role of active surveillance in the management of men with localized prostate cancer. *Ann Intern Med* 2012;156:591–5.

- [2] Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent—update 2013. *Eur Urol* 2014;65:124–37.
- [3] Cary KC, Cowan JE, Sanford M, et al. Predictors of pathologic progression on biopsy among men on active surveillance for localized prostate cancer: the value of the pattern of surveillance biopsies. *Eur Urol*. In press. <http://dx.doi.org/10.1016/j.eururo.2013.08.060>
- [4] Dall'Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate cancer: a systematic review of the literature. *Eur Urol* 2012;62:976–83.
- [5] Bul M, Zhu X, Rannikko A, et al. Radical prostatectomy for low-risk prostate cancer following initial active surveillance: results from a prospective observational study. *Eur Urol* 2012;62:195–200.
- [6] Stattin P, Holmberg E, Johansson JE, et al. Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. *J Natl Cancer Inst* 2010;102:950–8.
- [7] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
- [8] Lee DH, Koo KC, Lee SH, et al. Tumor lesion diameter on diffusion weighted magnetic resonance imaging could help predict insignificant prostate cancer in patients eligible for active surveillance: preliminary analysis. *J Urol* 2013;190:1213–7.
- [9] Lee DH, Koo KC, Lee SH, et al. Low-risk prostate cancer patients without visible tumor (T1c) on multiparametric MRI could qualify for active surveillance candidate even if they did not meet inclusion criteria of active surveillance protocol. *Jpn J Clin Oncol* 2013;43:553–8.
- [10] Guzzo TJ, Resnick MJ, Canter DJ, et al. Endorectal T2-weighted MRI does not differentiate between favorable and adverse pathologic features in men with prostate cancer who would qualify for active surveillance. *Urol Oncol* 2012;30:301–5.
- [11] Turkbey B, Mani H, Aras O, et al. Prostate cancer: can multiparametric MR imaging help identify patients who are candidates for active surveillance? *Radiology* 2013;268:144–52.
- [12] Ploussard G, Xylinas E, Durand X, et al. Magnetic resonance imaging does not improve the prediction of misclassification of prostate cancer patients eligible for active surveillance when the most stringent selection criteria are based on the saturation biopsy scheme. *BJU Int* 2011;108:513–7.
- [13] 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;188:1732–8.
- [14] Fradet V, Kurhanewicz J, Cowan JE, et al. Prostate cancer managed with active surveillance: role of anatomic MR imaging and MR spectroscopic imaging. *Radiology* 2010;256:176–83.
- [15] 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.
- [16] Vasarainen H, Lahdensuo K, Savolainen R, Ruutu M, Taari K, Rannikko A. Diffusion-weighted magnetic resonance imaging in prostate cancer patients on active surveillance one year after diagnosis and before repeat biopsy. *Scand J Urol* 2013;47:456–61.
- [17] Margel D, Yap SA, Lawrentschuk N, et al. Impact of multiparametric endorectal coil prostate magnetic resonance imaging on disease reclassification among active surveillance candidates: a prospective cohort study. *J Urol* 2012;187:1247–52.
- [18] Mullins JK, Bonekamp D, Landis P, et al. Multiparametric magnetic resonance imaging findings in men with low-risk prostate cancer followed using active surveillance. *BJU Int* 2013;111:1037–45.
- [19] van As NJ, de Souza NM, Riches SF, et al. A study of diffusion-weighted magnetic resonance imaging in men with untreated localised prostate cancer on active surveillance. *Eur Urol* 2009;56:981–8.
- [20] Somford DM, Hoeks CM, Hulsbergen-van de Kaa CA, et al. Evaluation of diffusion-weighted MR imaging at inclusion in an active surveillance protocol for low-risk prostate cancer. *Invest Radiol* 2013;48:152–7.
- [21] Morgan VA, Riches SF, Thomas K, et al. Diffusion-weighted magnetic resonance imaging for monitoring prostate cancer progression in patients managed by active surveillance. *Br J Radiol* 2011;84:31–7.
- [22] Tosoian JJ, Loeb S, Feng Z, et al. Association of [-2]proPSA with biopsy reclassification during active surveillance for prostate cancer. *J Urol* 2012;188:1131–6.
- [23] Makarov DV, Isharwal S, Sokoll LJ, et al. Pro-prostate-specific antigen measurements in serum and tissue are associated with treatment necessity among men enrolled in expectant management for prostate cancer. *Clin Cancer Res* 2009;15:7316–21.
- [24] van As NJ, Norman AR, Thomas K, et al. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. *Eur Urol* 2008;54:1297–305.
- [25] Khan MA, Carter HB, Epstein JI, et al. Can prostate specific antigen derivatives and pathological parameters predict significant change in expectant management criteria for prostate cancer? *J Urol* 2003;170:2274–8.
- [26] Venkitaraman R, Thomas K, Grace P, et al. Serum micronutrient and antioxidant levels at baseline and the natural history of men with localised prostate cancer on active surveillance. *Tumour Biol* 2010;31:97–102.
- [27] Lin DW, Newcomb LF, Brown EC, et al. Urinary TMPRSS2:ERG and PCA3 in an active surveillance cohort: results from a baseline analysis in the Canary Prostate Active Surveillance Study. *Clin Cancer Res* 2013;19:2442–50.
- [28] Tosoian JJ, Loeb S, Kettermann A, et al. Accuracy of PCA3 measurement in predicting short-term biopsy progression in an active surveillance program. *J Urol* 2010;183:534–8.
- [29] Whelan C, Kawachi M, Smith DD, et al. Expressed prostatic secretion biomarkers improve stratification of NCCN active surveillance candidates: performance of secretion capacity and TMPRSS2:ERG models. *J Urol* 2014;191:220–6.
- [30] Nakanishi H, Groskopf J, Fritsch HA, et al. PCA3 molecular urine assay correlates with prostate cancer tumor volume: implication in selecting candidates for active surveillance. *J Urol* 2008;179:1804–9.
- [31] Ploussard G, Durand X, Xylinas E, et al. Prostate cancer antigen 3 score accurately predicts tumour volume and might help in selecting prostate cancer patients for active surveillance. *Eur Urol* 2011;59:422–9.
- [32] Makarov DV, Marlow C, Epstein JI, et al. Using nuclear morphometry to predict the need for treatment among men with low grade, low stage prostate cancer enrolled in a program of expectant management with curative intent. *Prostate* 2008;68:183–9.
- [33] Isharwal S, Makarov DV, Carter HB, et al. DNA content in the diagnostic biopsy for benign-adjacent and cancer-tissue areas predicts the need for treatment in men with T1c prostate cancer undergoing surveillance in an expectant management programme. *BJU Int* 2010;105:329–33.
- [34] Isharwal S, Makarov DV, Sokoll LJ, et al. ProPSA and diagnostic biopsy tissue DNA content combination improves accuracy to predict need for prostate cancer treatment among men enrolled in an active surveillance program. *Urology* 2011;77:763.
- [35] Jhavar S, Bartlett J, Kovacs G, et al. Biopsy tissue microarray study of Ki-67 expression in untreated, localized prostate cancer managed by active surveillance. *Prostate Cancer Prostatic Dis* 2009;12:143–7.

- [36] Goh CL, Saunders EJ, Leongamornlert DA, et al. Clinical implications of family history of prostate cancer and genetic risk single nucleotide polymorphism (SNP) profiles in an active surveillance cohort. *BJU Int* 2013;112:666–73.
- [37] McGuire BB, Helfand BT, Kundu S, et al. Association of prostate cancer risk alleles with unfavourable pathological characteristics in potential candidates for active surveillance. *BJU Int* 2012;110:338–43.
- [38] Rosenkrantz AB, Prabhu V, Sigmund EE, Babb JS, Deng FM, Taneja SS. Utility of diffusional kurtosis imaging as a marker of adverse pathologic outcomes among prostate cancer active surveillance candidates undergoing radical prostatectomy. *AJR Am J Roentgenol* 2013;201:840–6.
- [39] Dickinson L, Ahmed HU, Allen C, et al. Scoring systems used for the interpretation and reporting of multiparametric MRI for prostate cancer detection, localization, and characterization: could standardization lead to improved utilization of imaging within the diagnostic pathway? *J Magn Reson Imaging* 2013;37:48–58.
- [40] Bossuyt PM, Reitsma JB. Standards for Reporting of Diagnostic Accuracy. The STARD initiative. *Lancet* 2003;361:71.
- [41] Pepe MS, Feng Z, Janes H, Bossuyt PM, Potter JD. Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: standards for study design. *J Natl Cancer Inst* 2008;100:1432–8.
- [42] Klein EA. A genomic approach to active surveillance: a step toward precision medicine. *Asian J Androl* 2013;15:340–1.
- [43] Cuzick J, Berney DM, Fisher G, et al. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *Br J Cancer* 2012;106:1095–9.
- [44] Selvadurai ED, Singhera M, Thomas K, et al. Medium-term outcomes of active surveillance for localised prostate cancer. *Eur Urol* 2013;64:981–7.
- [45] Stamey TA, Freiha FS, McNeal JE, et al. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. *Cancer* 1993;71(Suppl):933–8.
- [46] Winkler MH, Livni N, Mannion EM, Hrouda D, Christmas T. Characteristics of incidental prostatic adenocarcinoma in contemporary radical cystoprostatectomy specimens. *BJU Int* 2007;99:554–8.
- [47] Ahmed HU, Arya M, Freeman A, Emberton M. Do low-grade and low-volume prostate cancers bear the hallmarks of malignancy? *Lancet Oncol* 2012;13:e509–17.

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