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European Association of Urology

Platinum Priority – Collaborative Review – Prostate Cancer

Editorial by Christopher J. Welty and Peter R. Carroll on pp. 1032–1033 of this issue

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

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Article info

Article history:
Accepted January 19, 2014
Published online ahead of print on January 28, 2014

Keywords:
Active surveillance
Expectant management
Histopathology
Markers
Prostate cancer
PSA
MRI
Urinary

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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0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2014.01.027

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