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Title **Use of Classical and Novel Biomarkers as Prognostic Risk Factors for Localized Prostate Cancer: A Systematic Review**

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Aim

To provide an evidence-based perspective on the prognostic value of novel markers in localized prostate cancer; to identify the best prognostic model including the 3 classical markers; and to investigate whether models incorporating novel markers are better.

Conclusions and results

This review reveals poor quality and heterogeneity of studies, which render many of the results inconclusive. Only a small share of reported models are based on patient cohorts with a mean or median follow-up of at least 5 years, making long-term predictions unreliable. Prostate-specific antigen (PSA) velocity stood out in terms of the strength of evidence supporting its prognostic value and the relatively high hazard ratios. PSA velocity is of interest as a monitoring tool for active surveillance, but no consensus exists on its use or the threshold indicating the need for radical treatment. Of the 30 papers that met the inclusion criteria, 28 reported on prognostic novel markers and 5 on prognostic models. In total, 21 novel markers were identified from the 28 novel marker studies. Findings varied widely, the quality of the studies was generally poor, and some categories had a shortage of studies. The marker with the strongest evidence for its prognostic significance was PSA velocity (or doubling time). A particularly strong association was found between PSA velocity and prostate cancer death in both clinical and pathological models. In the clinical model, the hazard ratio for death from prostate cancer was 9.8 (95% CI 2.8–34.3, $p<0.001$) in men with an annual PSA velocity above 2ng/ml versus an annual PSA velocity of 2ng/ml or less; similarly, the hazard ratio was 12.8 (95% CI 3.7–43.7, $p<0.001$) in the pathological model. The quality of the prognostic model studies was adequate and overall better than the quality of the prognostic marker studies. All of the prognostic model studies dealt poorly with inclusion of established markers and consideration of the possible biases from study attrition. Given the models' heterogeneity, they are not comparable. Two models did not include a novel marker, and one of these included several demographic and comorbidity variables to predict all-cause mortality. Two models reported a measure of model performance, the *C*-statistic, but neither calculated it in an external data set. It was not possible to assess whether the models that included novel markers performed better than those without.

Recommendations

This review highlighted the poor quality of studies and the heterogeneity between studies, rendering the results of much of this research inconclusive. Hence, it is not possible to make recommendations for service provision. See Executive Summary link at www.hta.ac.uk/project/1614.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1614.asp.

Further research/reviews required

Conducting retrospective cohort studies in an organized and scientific manner would better enable identification of the most promising prognostic markers. Many of the studies appear ad hoc and poorly designed. Specific recommendations are: 1) Data could be collected prospectively for later retrospective studies. If this is combined with storage of biopsy and pathological material, new markers could be rapidly assessed with existing long-term follow-up data. 2) Larger patient cohorts are needed. For data to be combined from different centers, the parties need to agree on common definitions of PSA and clinical disease recurrence so that outcomes are not ambiguous. 3) Analysis and reporting of prognostic marker studies must be improved, following guidelines such as REMARK.

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