Classical and novel biomarkers as prognostic risk factors for localised prostate cancer

Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review

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Executive summary

Health Technology Assessment 2009; Vol. 13: No. 5
DOI: 10.3310/hta13050

Health Technology Assessment
NIHR HTA Programme
www.hta.ac.uk

Executive summary

Background

Prostate cancer is the most prevalent malignancy in men worldwide and is a leading cause of cancer death. Many men with early localised prostate cancer (i.e. clinical or pathological stage TI–T3N0M0 or Jewett–Whitmore system stages A, B, C) will never suffer any symptoms or adverse effects of the disease, but because of the difficulties in identifying this group of patients the majority do receive radical local treatment, which can result in erectile dysfunction and urinary leakage. The problem for clinicians is deciding which men have fast-growing cancers that need essential treatment and which men have slow-growing cancers that will never trouble them. Prognostic markers may help to avoid unnecessary treatment and identify patients with poor outcomes who would be candidates for trials of adjuvant treatment.

Objectives

The current systematic review aims to provide an evidence-based perspective on the prognostic value of novel markers. Through systematic, explicit and rigorous methods of identifying, critically appraising and synthesising evidence, systematic reviews are considered a useful and appropriate means of identifying and combining existing evidence. The focus of the review was on novel prognostic markers (as opposed to classical markers) and prognostic models.

The first objective was to identify and evaluate novel prognostic markers. The second was to identify the best prognostic model(s) that include(s) the three classical markers and to see if any models incorporating novel markers are better than these.

Methods

Search strategies

The search aimed to identify all references relating to novel markers and prognostic models. One search was conducted to cover both topics as a large overlap in the literature exists.

Eight electronic bibliographic databases were searched during March–April 2007. In addition, the reference lists of relevant articles were checked and various health services research-related resources were consulted via the internet.

Generic inclusion criteria

Population

Males with a diagnosis of early localised prostate cancer (i.e. clinical or pathological stage TI–T3N0M0 or Jewett–Whitmore system stages A, B, C) before treatment (radical or not) or at the time of radical treatment (prognostic markers were measured before or at treatment).

Study end points

All reported measures of the prognostic value of individual or combinations of markers that predict the following outcomes:

- overall survival
- disease-specific survival
- disease-free survival
- biochemical [prostate-specific antigen (PSA)] recurrence
- biochemical (PSA) freedom from recurrence
- clinical recurrence.

Results

Search results

A total of 30 papers met the inclusion criteria after full paper sift. Of these, 28 were concerned with prognostic novel markers and five with prognostic models. Note that three papers were included in both the novel markers and the prognostic models sections.

Novel prognostic markers

A total of 21 novel markers were identified from the 28 studies that met the inclusion criteria for this section.

The considerable variability in results reported within the prognostic marker categories, the poor quality of studies and the lack of studies for

some categories have made it difficult to provide clear conclusions as to which markers might offer the most potential as prognostic parameters for localised prostate cancer. These reasons also meant that it was not possible to quantitatively synthesise the results. Key quality issues that commonly affected the potential to draw conclusions on the novel markers were the lack of classical markers in the statistical models and insufficient events per variable.

Nevertheless, on the available evidence the 21 prognostic markers were placed into one of three categories depending on the direction and strength of the evidence for each in terms of adding prognostic value to the established markers: (1) promising; (2) not promising; and (3) inconclusive. The novel markers featuring in each of the three categories are listed below:

1. Promising:
   i. acid phosphatase level
   ii. Gleason pattern in Gleason score 7 (4 + 3 versus 3 + 4) (non-classical use of Gleason measurements)
   iii. amount of high-grade cancer (non-classical use of Gleason measurements)
   iv. PSA kinetics (PSA velocity/PSA doubling time)
   v. percentage positive biopsy cores (proportion cancer).
2. Not promising:
   i. β-catenin expression
   ii. creatinine
   iii. germ-line genetic variation in the vitamin D receptor
   iv. maximum tumour dimension (tumour size)
   v. tumour volume (tumour size).
3. Inconclusive:
   i. percentage cancer in surgical specimen (proportion cancer)
   ii. androgen receptor: CAG repeats
   iii. DNA ploidy
   iv. CYP3A4 genotypes
   v. modified Gleason score (non-classical use of Gleason measurements)
   vi. Ki67 LI
   vii. Bcl-2
   viii. p53
   ix. syndecan-1
   x. CD10
   xi. Stat5 activation status.

The marker with the strongest evidence for its prognostic significance, and which also has relatively large hazard ratios, is PSA velocity.

Prognostic models

In the review of prognostic models only five papers reporting eight models met the inclusion criteria, all of which developed new models. In general, the quality of the prognostic model studies, as assessed by our criteria, was adequate and overall was better than the quality of the prognostic marker studies. Nevertheless, there were two issues that were poorly dealt with in most or all of the prognostic model studies: inclusion of established markers and consideration of the possible biases from study attrition.

Given the heterogeneity of the models, particularly in terms of the outcomes predicted and whether they included only clinical variables or also pathological variables, the models cannot be considered comparable. Only two models did not include a novel marker, and one of these included several demographic and co-morbidity variables to predict all-cause mortality. Only two models reported a measure of model performance, the *C*-statistic, and for neither was it calculated in an external data set. It was not possible to assess whether the models that included novel markers performed better than those without. In addition, in terms of the need for external model validation, a key recommendation is that the uncertainty around model predictions should be reported.

Discussion

The main sources of uncertainty for the results of the novel prognostic marker review were the heterogeneity between studies, the small number of studies and the poor quality of the studies, which made it difficult to reach firm conclusions on the prognostic value of the novel markers. Similar issues, as well as the lack of external validation and lack of a well-established measure of performance for prognostic models, affected the conclusions that could be reached on the prognostic models. The poor evidence base is a key finding of this review. Other reviews of prognostic markers and models have also highlighted this problem.

The review inclusion criteria of a minimum sample size of 200 and follow-up of a mean or median of at least 5 years were intended to select the studies that were most likely to yield the best quality evidence. However, they also had the effect of limiting the markers and prognostic models that were included in the review.

Given the expected variation in quality an emphasis was put on quality assessment to identify factors that needed to be taken into account when interpreting the results of each study. Key failings were lack of classical markers in the statistical models and too few events.

Conclusions

Implications for service provision

Novel markers

This review has highlighted the poor quality of studies and the heterogeneity between studies, which make the results of much of this research inconclusive. As a result it is not possible to make any immediate recommendations for service provision. However, one marker, PSA velocity (or doubling time), did stand out, not only in terms of the strength of the evidence supporting its prognostic value but also in terms of the relatively high hazard ratios. There is great interest in PSA velocity as a monitoring tool for active surveillance but there is as yet no consensus on how it should be used, and, in particular, what threshold should indicate the need for radical treatment.

Models

This review highlights the small proportion of models reported in the literature that are based on patient cohorts with a mean or median follow-up of at least 5 years. Users of models need to be aware that long-term predictions may be unreliable. We note that our inclusion criteria, for pragmatic reasons, were somewhat arbitrary. It is possible that some large cohorts with a follow-up of less than 5 years that were excluded from this review may have had as many patients at risk at 5 years as some smaller studies with a longer follow-up that were included. When using any form of prediction tool, model users should look at the confidence intervals around the survival estimates. None of the models in this review were externally validated.

Implications for future research

Much more could be achieved to identify the most promising prognostic markers with retrospective cohort studies if the research was conducted in an organised and scientific manner. Many of the current studies appear ad hoc and poorly designed. Some specific recommendations are as follows:

- 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.
- Larger patient cohorts are needed. For data to be combined from different centres an agreement needs to be reached on common definitions of PSA and clinical disease recurrence, so that outcomes are not ambiguous.
- Analysis and reporting of prognostic marker studies must be improved, following guidelines such as REMARK.

Publication

Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al*. Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review. *Health Technol Assess* 2009;**13**(5).

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The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

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First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Second, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA Programme as project number 06/27/01. The contractual start date was in November 2006. The draft report began editorial review in November 2007 and was accepted for publication in March 2008. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NCCHTA.

Printed on acid-free paper in the UK by the Charlesworth Group.