

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



European Association of Urology



Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Molecular Subgroup of Primary Prostate Cancer Presenting with Metastatic Biology

Steven M. Walker^{a,b}, Laura A. Knight^b, Andrena M. McCavigan^b, Gemma E. Logan^b, Viktor Berge^d, Amir Sherif^e, Hardev Pandha^f, Anne Y. Warren^g, Catherine Davidson^a, Adam Uprichard^a, Jaine K. Blayney^a, Bethanie Price^b, Gera L. Jellema^b, Christopher J. Steele^b, Aud Svindland^h, Simon S. McDade^a, Christopher G. Edenⁱ, Chris Foster^j, Ian G. Mills^{a,d,k,l}, David E. Neal^m, Malcolm D. Masonⁿ, Elaine W. Kay^c, David J. Waugh^a, D. Paul Harkin^{a,b}, R. William Watson^o, Noel W. Clarke^p, Richard D. Kennedy^{a,b,*}

^a Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, UK; ^b Almac Diagnostics, Craigavon, UK; ^c Department of Pathology, RCSI, Beaumont Hospital, Dublin, Ireland; ^d Department of Urology, Oslo University Hospital, Oslo, Norway; ^e Department of Surgical and Perioperative Sciences, Urology and Andrology, Umea University, Umea, Sweden; ^f Department of Microbial Sciences, University of Surrey, Guildford, UK; ^g Department of Pathology, Addenbrooke's Hospital, Cambridge, UK; ^h Department of Pathology, Oslo University Hospital, Oslo, Norway; ⁱ Department of Urology, Royal Surrey County Hospital, Guildford, UK; ^j Institute of Translational Medicine, University of Liverpool, Merseyside, UK; ^k Department of Molecular Oncology, Oslo University Hospital/Institute for Cancer Research, Oslo, Norway; ^l Prostate Cancer Research Group, Centre for Molecular Medicine Norway (NCMM), University of Oslo and Oslo University Hospitals, Forskningsparken, Oslo, Norway; ^m Uro-oncology Research Group, Cambridge Research Institute, Cambridge, UK; ⁿ Wales Cancer Bank, Cardiff University, School of Medicine, Health Park, Cardiff, UK; ^o UCD School of Medicine, Conway Institute, University College Dublin, Belfield, Dublin, Ireland; ^p Christie NHS Foundation Trust, Manchester, UK

Article info

Article history:

Accepted March 17, 2017

Associate Editor:

James Catto

Keywords:

Prostate cancer
Prognostic
Recurrence
Progression
Metastatic assay

Abstract

Background: Approximately 4–25% of patients with early prostate cancer develop disease recurrence following radical prostatectomy.

Objective: To identify a molecular subgroup of prostate cancers with metastatic potential at presentation resulting in a high risk of recurrence following radical prostatectomy.

Design, setting, and participants: Unsupervised hierarchical clustering was performed using gene expression data from 70 primary resections, 31 metastatic lymph nodes, and 25 normal prostate samples. Independent assay validation was performed using 322 radical prostatectomy samples from four sites with a mean follow-up of 50.3 months.

Outcome measurements and statistical analysis: Molecular subgroups were identified using unsupervised hierarchical clustering. A partial least squares approach was used to generate a gene expression assay. Relationships with outcome (time to biochemical and metastatic recurrence) were analysed using multivariable Cox regression and log-rank analysis.

Results and limitations: A molecular subgroup of primary prostate cancer with biology similar to metastatic disease was identified. A 70-transcript signature (metastatic assay) was developed and independently validated in the radical prostatectomy samples. Metastatic assay positive patients had increased risk of biochemical recurrence (multivariable hazard ratio [HR] 1.62 [1.13–2.33]; $p = 0.0092$) and metastatic recurrence (multivariable HR = 3.20 [1.76–5.80]; $p = 0.0001$). A combined model with Cancer of the Prostate Risk Assessment post surgical (CAPRA-S) identified patients at an increased

* Corresponding author. Centre for Cancer Research and Cell Biology, Queen's University of Belfast, 97 Lisburn Road, Belfast, BT9 7BL, UK.
E-mail address: r.kennedy@qub.ac.uk (R.D. Kennedy).

risk of biochemical and metastatic recurrence superior to either model alone (HR = 2.67 [1.90–3.75]; $p < 0.0001$ and HR = 7.53 [4.13–13.73]; $p < 0.0001$, respectively). The retrospective nature of the study is acknowledged as a potential limitation.

Conclusions: The metastatic assay may identify a molecular subgroup of primary prostate cancers with metastatic potential.

Patient summary: The metastatic assay may improve the ability to detect patients at risk of metastatic recurrence following radical prostatectomy. The impact of adjuvant therapies should be assessed in this higher-risk population.

© 2017 European Association of Urology. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Although prognosis for localised prostate cancer patients following radical prostatectomy is very good, 4–25% (dependent upon disease stage and use of population prostate-specific antigen [PSA] screening) will develop metastatic disease within 15 years [1,2]. In addition, patients with low- and some intermediate-risk prostate cancers are best treated by active surveillance; however, there is clinical uncertainty about progression in this population [3]. Progression in low/intermediate risk may be due to a more biologically aggressive genotype of primary tumours, whilst in clinically higher risk groups there may be undetected micrometastatic disease at presentation [4]. This could be treated by adjuvant approaches including pelvic radiotherapy [5], extended lymph node dissection [6], adjuvant hormone therapy [7], or chemotherapy [8].

Presently, metastatic risk is estimated from histopathologic grade (Gleason score [GS] and clinical grade grouping), tumour stage, and presenting PSA level. These prognostic factors have limitations; 15% of lower-grade prostate cancer patients (Gleason ≤ 7) experience disease recurrence [9], whereas 74–76% of higher-grade patients (Gleason > 7) do not develop metastatic disease following surgery [10]. For Gleason 7 tumours, dominant lesion grade affects prognosis, 40% of Gleason 4 + 3 patients developing recurrence by 5 years compared with 15% for Gleason 3 + 4 [11]. Clearly, there is a need to identify additional prognostic factors to guide adjuvant treatment. Current approaches can broadly be classified as mathematical risk models using clinical factors such as Cancer of the Prostate Risk Assessment (CAPRA) [12] and CAPRA-surgery (CAPRA-S) [13] scoring, or biomarkers measured from tumour tissue. Regarding biomarkers, researchers have taken immunohistochemical approaches such as high Ki67 expression [14] or PTEN loss to indicate metastatic potential [15]. Others have used multiplexing approaches where a gene expression [16–18] or proteomic signature [19] has been trained against known outcomes to predict high- and low-risk disease using archived material.

It is recognised that malignancies originating from the same anatomical site can represent different molecular entities [20]. We hypothesised that a unique molecular subgroup of primary prostate cancers may exist that has a gene expression pattern associated with metastatic disease. We took an unsupervised hierarchical clustering approach using primary localised prostate cancer, primary prostate cancer presenting with concomitant metastatic disease, lymph node metastasis, and normal prostate samples to

identify a novel “metastatic subgroup”. A 70-transcript signature (metastatic assay) was developed using this approach and independently validated in a cohort of radical prostatectomy samples for biochemical and metastatic recurrence.

2. Patients and methods

2.1. Study design

Study design followed the reporting recommendations for tumour marker prognostic studies (REMARK) guidelines as outlined in the criteria checklists (Supplementary Table 1 and Appendix A) and REMARK study design diagram (Supplementary Fig. 1).

2.2. Patients

Formalin-fixed paraffin-embedded (FFPE) sections from 126 samples (70 primary prostate cancer specimens from radical prostatectomy resections including those with known concomitant metastases, 31 metastatic disease in lymph nodes, and 25 histologically confirmed normal prostate samples that did not display hypertrophy, sourced from bladder resections) were collected from the University of Cambridge and the Institute of Karolinska for molecular subgroup identification (Supplementary Table 2). A secondary training dataset of 75 primary resection samples was collected, of which 20 were profiled in duplicate, to aid in the selection of the final signature length (Supplementary Table 3). For independent *in silico* validation, three public datasets were identified [17,21,22]: GSE25136 ($n = 79$; Supplementary Table 4), GSE46691 ($n = 545$; Supplementary Table 5), and GSE21034 ($n = 126$; Supplementary Table 6). A total of 322 FFPE prostatectomy samples from four sites were collected for independent validation of the assay (Supplementary Table 7). Biochemical recurrence was defined as a post-prostatectomy rise in PSA of > 0.2 ng/ml followed by a subsequent rise. Metastatic recurrence was defined as radiologic evidence of any metastatic disease, including lymph node, bone, and visceral metastases. Inclusion criteria were T1a–T3c NX M0 prostate cancers treated by radical prostatectomy, no previous systemic adjuvant or neoadjuvant treatment in non-recurrence patients, and at least 3-yr follow-up. Ethical approval was obtained from East of England Research Ethics Committee (Ref: 14/EE/1066).

2.3. Metastatic subgroup and assay discovery

The 126 discovery samples were analysed for gene expression using a cDNA microarray platform optimised for FFPE tissue. Unsupervised hierarchical clustering, an unbiased statistical method to discover structure in data, was applied to the gene expression profiles. Genes were selected using variance-intensity ranking and then an iterative procedure of clustering with different gene lists to determine the optimal set for reproducibility. Data matrices were standardised to median gene expression and agglomerative two-dimensional hierarchical clustering was performed, using Euclidean

Download English Version:

<https://daneshyari.com/en/article/5693945>

Download Persian Version:

<https://daneshyari.com/article/5693945>

[Daneshyari.com](https://daneshyari.com)