A metastatic biology gene expression assay to predict the risk of distant metastases in patients with localized prostate cancer treated with primary radical treatment.}

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**BACKGROUND**

- Approximately 20% of patients with organ-confined prostate cancer (PCa) will develop disease recurrence following radical treatment (surgery or external beam radiotherapy (EBRT)).
- We hypothesized that a molecular subgroup of early PCa may have metastatic potential at presentation, resulting in disease recurrence.
- These patients may benefit from intensification of treatment such as pelvic nodal irradiation, extended lymph node dissection, extended adjuvant androgen deprivation therapy (ADT), chemotherapy or novel agents.

**METHODS**

- Using unsupervised hierarchical clustering of gene expression from a Discovery PCa dataset of 126 formalin-fixed and paraffin-embedded (FFPE) radical prostatectomy resections including samples with known concomitant metastases, we identified a novel molecular subgroup with a transcriptional profile similar to metastatic disease (Fig. 1).
- We developed a 70-gene expression assay (Metastatic Assay) to prospectively identify patients within the subgroup from FFPE. Initial assessment found the assay to be predictive in three independent publicly available prostatectomy datasets (Fig. 2).
- We therefore assessed the prognostic value of the assay in FFPE radical prostatectomy samples collected from multiple international sites and FFPE biopsy samples collected from patients treated with radical EBRT. Tumor resections and tumor biopsy specimens were obtained from 322 surgical patients (n = 61, IPCRC, Republic of Ireland; n = 142, Oslo, Norway; n = 34, Surrey, UK; n = 85, Wales Cancer Bank, UK) and 248 patients treated with radical EBRT (n = 248, Belfast, UK). The regions of highest Gleason grade were identified for macrodissection, RNA extraction and gene expression analysis.
- Samples were dichotomized as Metastatic Assay positive or negative using a pre-specified cut-off. The association of assay results with biochemical failure (BF) and distant metastases (DM) was tested on multivariate analysis (MVA).

**RESULTS – Surgical Cohort**

- On MVA, the metastatic assay was significantly associated with BF (HR 1.59 [1.11-2.29], p=0.0128) and DM (HR 3.09 [1.70-5.51], p<0.0002) in the independent surgical cohort (n=322).
- In a combined model with CAPRA-S, the assay identified patients at high risk of BF (HR 2.47 [1.90-3.75], p<0.0001) and DM (HR 2.73 [1.43-13.73], p=0.0001) better than either model alone.

**RESULTS – Radiotherapy Cohort**

- On MVA, the metastatic assay was significantly associated with BF (HR 1.86 [1.07-3.22], p=0.0277) and DM (HR 2.83 [1.33-7.11], p=0.0273) in the radiotherapy cohort (n=248).

**CONCLUSIONS**

- The Metastatic Assay predicts BF and DM in PCa patients treated with either radical surgery or EBRT.
- This assay may help to select patients at low risk of relapse, who may benefit from an active surveillance approach, and to identify those patients at high risk of metastatic disease for additional treatment aimed at preventing disease recurrence.

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