PROSTATE CANCER: NOVEL PROGNOSTIC MARKERS
FOR POST-PROSTATECTOMY ADJUVANT CHEMOTHERAPY/RADIATION TREATMENT DECISION

OVERVIEW

• High unmet clinical need to identify post prostatectomy patients at increased risk of recurrence likely to benefit from adjuvant therapy.
• Prognostic markers 1 and 2 are independent of each other and clinical characteristics such as Gleason grade and PSA.
• The presence of high staining of both markers together provides the strongest association with biochemical progression post-prostatectomy.
• Further studies could investigate utility with biopsy samples to inform on radical prostatectomy decision.

THE OPPORTUNITY

Radical prostatectomy is the recommended treatment for aggressive prostate cancer, with 45% of US patients presenting with the disease ultimately receiving this treatment. Post-prostatectomy patients face a difficult decision to either receive adjuvant therapy with associated toxicities or opt for active surveillance. Current clinical practice uses, among other clinical characteristics PSA and Gleason grade to determine risk of recurrence. However this is sub-optimal and there is an unmet clinical need to better define risk of reoccurrence to help make a more informed adjuvant therapy treatment decision. Two novel prognostic biomarkers have now been identified and shown to be independent of Gleason grade and PSA. When combined with current clinical practice these markers could help better predict the risk of recurrence and enable more informed adjuvant therapy decision making.

Figure 1: Kaplan-Meier estimates of recurrence free survival by immunohistochemical staining of the two novel prognostic markers in 236 post prostatectomy samples.

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Currently, many clinicians make use of tables known as nomograms to calculate risk of recurrence and/or death following radical prostatectomy. Factors considered in the Memorial Sloan-Kettering nomogram include: pre-treatment PSA, age, Gleason grade at surgery and years since radical prostatectomy. Low risk patients normally receive observational follow up and forego adjuvant therapy as their recurrence risk is perceived to be low and hence the chemotherapy associated toxicities are not felt to be justified. Patients at intermediate risk of recurrence face the most difficult decision and may opt for either observation or adjuvant therapy, while high risk patients normally opt for adjuvant therapy.

Although clinical markers such as Gleason grade and stage have been shown to provide prognostic information, very few molecular markers are widely used for prognosis in clinical practice. Serum PSA at diagnosis can be used as a prognostic indicator but is sub-optimal and PSA immunohistochemistry of tumour samples is not of prognostic value.

Hayley Whitaker, lead scientist of the Biomarker Initiative at CRUK’s Cambridge Institute, has identified two markers as independent prognostic markers in a cohort of 236 post-prostatectomy cases.

Post radical prostatectomy tissue samples are analysed via H&E to determine clear margins and Gleason grade to help determine risk of recurrence and inform medical care post-prostatectomy. IHC staining of the two markers could be easily incorporated into the standard pathological analysis to provide additional prognostic information for inclusion into nomogram tables.

**BIOMARKER VALIDATION**

IHC staining of Prognostic Marker 1 & 2 was shown to be prognostic for recurrence even when hazard ratios (HR) were corrected for traditional clinical variables (Marker 1 HR - 1.8 & Marker 2 HR 1.9). This indicates that these markers provide additional prognostic information beyond Gleason grade and PSA. Further analysis also demonstrated that the markers were independent of each other and when combined they provide the strongest prediction of patients most likely to relapse post-prostatectomy Fig 1.

**COMMERCIAL OPPORTUNITY**

CRT has filed a patent application covering prognostics uses for Prognostic marker 1 and 2. We are now seeking a partner to develop an IHC-based test to identify patients at high risk of recurrence who may benefit from adjuvant treatment.

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Figure 2: **Clinical Practice**. In a post-prostatectomy setting patients face a difficult decision to either receive adjuvant treatment or risk proactive observation. Prognostics Markers 1 & 2 would be positioned into standard H&E work up post surgery to provide prognostic information in addition to Gleason grade and PSA. This will lead to better risk stratification and help inform adjuvant treatment decision.