



Predictive biomarkers for prostate brachytherapy – not there yet

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Brachytherapy has been used for the treatment of prostate cancer for nearly 100 years. Low dose rate brachytherapy, the permanent placement of radioactive seeds (e.g., Iodine-125 or Palladium-103) within the prostate, is an effective treatment for men with clinically localized low-risk prostate cancer. Brachytherapy can also be delivered by temporarily inserting high energy radioactive isotopes (e.g., Iridium-192) into the prostate. This technique is referred to as high dose-rate brachytherapy. The ability of brachytherapy to directly deliver radiation within the prostate while limiting the dose delivered to surrounding normal tissues is a significant advantage of this treatment (1).

Recent work by Molina and colleagues (2) reported on a study of biomarkers of biochemical recurrence in men treated with brachytherapy for prostate cancer. Although not explicitly stated, the clinically relevant goal of their work was to identify, prior to treatment, a group of patients in whom surgery (or potentially dose escalated radiotherapy) would offer improved cancer control due to intrinsic radiation resistance within their cancer. Previous work by multiple groups has led to a good understanding of prognostic factors for men with prostate cancer. For example, the extent of the primary tumor (i.e., T-stage), prostate specific antigen (i.e., PSA, including absolute value, PSA velocity, free PSA, and PSA doubling time) and Gleason score is accepted tumor-specific features that correlate with outcome. These factors have been combined into validated nomograms which can be used to predict biochemical control and/or prostate cancer mortality (3-6). Additional factors found to predict biochemical recurrence following brachytherapy include clinical stage, D90 and V100. The authors performed their work in order to improve upon these factors to better determine an

individual's risk of recurrence in low-risk prostate cancer. They hypothesized that the tumor's capacity for DNA repair may directly influence biochemical control following brachytherapy.

To fully interpret their data, it is necessary to briefly review the definitions of prognostic and predictive markers. Prognostic markers provide information on the likely course of the cancer in an individual. Prognostic markers are often used at the time of diagnosis to guide discussions about treatment goals and the likelihood of remission, cure, disease progression, and survival. Predictive markers, in contrast to prognostic markers, identify subpopulations of patients who are most likely to benefit from a given therapy. A classic example is mutations in the *KRAS* gene in colon cancer. Patients with wild-type *KRAS* benefit from cetuximab, an epidermal growth factor targeted therapy; those with mutated *KRAS* do not benefit from cetuximab (7,8). A biomarker is predictive if the treatment effect is different for biomarker positive patients than for biomarker negative patients. In order to describe a biomarker as predictive, two treatment groups must be available in order to test for interaction between the treatment and biomarker (9).

Molina *et al.* focused on the expression of proteins involved in non-homologous end-joining repair (NHEJR) of DNA double-strand breaks (DSBs). DSBs are a common cause of radiation-induced cell death. They hypothesized that tumors with an increased ability to repair DNA damage following radiation treatment would be more likely to recur. Ku70 and Ku80 dimerize and recruit DNA-dependent protein kinase catalytic subunit (DNA-PKcs) to the site of damage on the DNA. These proteins form the DNA-dependent protein kinase (DNA-PK) that functions in NHEJR (10) and have previously been shown to be

correlate with disease-free survival (11,12).

Molina *et al.* report on 167 men with prostate cancer treated at a single institution. All had Gleason scores ≤ 7 and were treated with ^{125}I brachytherapy to a dose of 160 Gy. In this analysis, there was no control group who received a different treatment (e.g., radical prostatectomy). Further complicating their analysis, half of these patients received short-term androgen deprivation therapy (ADT) prior to radiation treatment. The use of ADT for intermediate risk prostate cancer prolongs disease free survival and the time to biochemical recurrence. Tumor slides were scored for four markers by two independent uropathologists. Ku80, Ku70, and Ki67 were scored manually as a percentage of total cancer cells. DNA-PKcs was classified manually as 0 (absence of nuclear staining) or 1 (positive nuclear staining). Disagreements were rescored until a consensus was reached. Median follow-up for the study was <5 years. In all, 29 patients experienced biochemical recurrence (9 biochemical only, 8 locoregional recurrence, and 12 metastatic disease). They noted that 26 patients had a reclassified Gleason score after review resulting in upstaging of disease from Gleason ≤ 6 to 7 and that upstaging was associated with biochemical relapse. Known prognostic features identified in this cohort as correlating with biochemical relapse included clinical stage, pretreatment PSA level, and V100 values lower than 100%. They performed multiple statistical tests to identify potential correlations. Ku70 and Ku80 expression correlated with high proliferation; Ku80 (but not Ku70) expression correlated with a higher clinical stage; and Ku70 (but not Ku80) correlated with recurrence. Nuclear DNA-PKcs expression was observed in 74 of the 146 cases (21 patient samples could not be analyzed due to various factors). DNA-PKcs was strongly associated with Ku70, Ku80, and the proliferation marker Ki67. Interestingly, no association was observed between DNA-PKcs expression and known prognostic markers such as pretreatment PSA, Gleason score, or clinical stage. Their highlighted finding was that DNA-PKcs was significantly associated with biochemical recurrence ($P=0.003$).

There are multiple limitations of this study. The authors claim that the use of ADT was not significantly associated with recurrence ($P=0.06$). However, in our opinion, the follow-up period of this cohort is insufficient to make this claim due to the anticipated low failure rate in patients with low-risk prostate cancer. While they could have restricted their analysis to patients who did not receive ADT, it is likely that they would have lost the statistical power to identify the trends they wanted to see. In addition, they fail

to replicate their findings in an independent cohort in order to confirm the validity of their findings and do not evaluate the marker in a group of patients treated with an alternative approach. Additional, more minor concerns are that they used qualitative analysis of biomarker expression rather than utilizing more modern quantitative approaches and they use a heterogeneously treated cohort of patients who are at very low risk for recurrence and with known confounding factors (ADT treatment). Finally, they confuse their finding of a potentially prognostic marker to one of a predictive marker without providing any evidence that their marker of choice can be used to select a treatment for individual patients.

Overall they hope to convince the reader that DNA-PKcs expression and clinical stage can be used together to optimize the choice of treatment for men with low-risk prostate cancer. Their results should, at best, be interpreted as suggesting that DNA-PKcs may be a prognostic marker for low/intermediate risk prostate cancer and that further investigation is clearly needed.

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Footnote

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