“Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis”

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This week’s research spotlight falls on a new research paper in Lancet Oncology on identifying predictive signatures of radiation response in prostate cancer. The authors draw a nice differential between prognostic signatures, those that forecast for the aggressiveness of the disease, and predictive signatures, those that predict tumors response to specific therapy. In their preliminary work, they could not identify any published works on predictive gene signatures or models for radiation therapy and prostate cancer. In order to look for signature that could predict response to radiation in prostate cancer, they used retrospective analysis of five studies, one study as a training set, and four others pooled into a larger validation set. Drawing on the inspiration from Oncotype DX, a gene signature that predicts breast cancer response to chemotherapy, they developed a gene set that was related to DNA damage and radiation. Starting with 1800 genes on the microarray platform, they analyzed the tumor samples from the training cohort, and ranked them according to “the univariate interaction value in a Cox proportional hazards model.” The ranked genes were utilized to train a ridge-penalised Cox model using distant metastasis as the endpoint. Expression of genes and presence of radiotherapy were the relevant variables. Following fancy statistics and analysis in the training set, they settled on the final 24 genes to compose their signature. The analysis of this signature was converted to binary scores (high or low, where 0 is no difference in outcomes) and named Post-Operative Radiation Therapy Outcomes Score (PORTOS).

The results should be exciting to anyone in the radiation field. By using PORTOS, and analyzing the samples with high or low PORTOS scores, the investigators found that patients with high PORTOS benefited significantly from radiotherapy, with only 4% of patients in the validation cohort experiencing distant metastasis at 10 years post-treatment. In contrast, 35% of patients with high PORTOS scores who did not receive radiotherapy experienced distant metastasis over 10 year follow up. Patients with low PORTOS scores did not appear to benefit from radiation, as 32% of both radiation-treated and untreated patients developed metastasis. The analysis matched patients for a number of clinicopathological characteristics, including PSA levels, Gleason score, positive surgical margins, seminal vesicle invasion, extracapsular extension, lymph node invasion, and androgen depravation therapy. Thus, it is unlikely an unaccounted pathological factor is influencing the analysis. Even so, prospective use of this signature will be necessary to make a final conclusion on its ability to identifying patients most likely to benefit from radiation therapy.

Why is this important? While radiation therapy is reasonably well tolerated, it does come with a host of side-effects, including skin burns, fatigue, and loss of physiological function in the irradiated area. Identifying which patients are likely to respond to radiotherapy and which are not, can drive adjuvant treatment selection and prevent radiation exposure for patients who are unlikely to derive benefit from the treatment. This would spare them radiation associated side effects and direct their physicians to select another treatment that is more likely to provide a positive outcome.

The full paper can be found at: http://www.sciencedirect.com/science/article/pii/S1470204516304910