A Genetic Basis for Variation in the Vulnerability of Cancer to Ionizing Radiation

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Purpose/Objective(s): Clinical radiotherapy has made significant advances since its inception, growing into a tertiary specialty with significant contributions to curative and palliative treatments of cancer and health care costs. A major limitation to its appropriate application, however, has been the lack of measurable biological indicators, or biomarkers that can reliably identify patients with cancers that are more or less likely to respond to these treatments.

Materials/Methods: We conducted large-scale profiling of cellular survival after exposure to radiation in a diverse collection of 534 genetically annotated human tumor cell lines. Using data derived from a single, validated experimental platform we studied the genetic determinants of survival after radiation in 534 human cancer cell lines across 26 cancer types. We correlated radiation sensitivity and genomic parameters using a validated experimental platform we studied the genetic determinants of survival after exposure to radiation in a diverse collection of 534 genetically annotated human tumor cell lines. Using data derived from a single, validated experimental platform we studied the genetic determinants of survival after radiation in 534 human cancer cell lines across 26 cancer types. We correlated radiation sensitivity and genomic parameters using the information-based similarity index, which is sensitive to non-linear relationships and offers better resolution at the high end of the matching range.

Results: We showed that individual SCNA, gene mutations, and the basal expression of individual genes and gene sets correlate with radiation survival. By studying a large number of cancer types, we found that genetic correlates in any single cancer type can be found in other cancer types as well (e.g., Nrf2 activation in non-small cell lung cancer and hepatobiliary cancer and AR expression in prostate and breast adenocarcinomas). This supports the view that although diverse, cancer genomes reflect combinations of a limited number of functionally relevant events that can confer therapeutic resistance across cancer types.

Conclusion: We identified several new genetic determinants of response to DNA damage that can have predictive capacity by identifying the likelihood of response to therapy and, consequently, prognosis. The potential for stratification of patients from heterogeneous populations to genetically similar subgroups can help guide the transition of radiotherapy from a generic population-based approach to one that is more personalized.


Clinical Impact of Spatial Variations in Proton Relative Biological Effectiveness (RBE) Among Patients Receiving Radiation to the Prostate and Thorax


Purpose/Objective(s): Spatial variations in proton relative biological effectiveness (RBE) near beam edges and beyond the tip of the Bragg peak may potentially increase treatment complications or, alternatively, are a missed opportunity to enhance the therapeutic ratio. We used a newly implemented model in our treatment planning system to examine the impact of spatial variations in proton RBE on tumor targets and selected organs at risk (OAR) in 8 patients treated to the prostate or thorax with proton pencil beam scanning.

Materials/Methods: A research build of our treatment planning software combines a new dose algorithm with a published model for DNA double strand break (DSB) induction as a function of proton linear energy transfer (LET). Trends in the model computed RBE for DSB induction with proton LET is predictive of trends in reproductive cell survival in vitro. Dose and (RBE x dose) distributions were re-computed using our in-house treatment planning system for 8 patients (n = 4 to prostate, n = 4 to thorax). Dose-averaged RBE values were computed by dividing the (RBE x absorbed dose) for the tumor and OAR volume by the average absorbed dose to the same volume without corrections for spatial variations in proton RBE. The patient-specific RBE estimates were determined for the composite plan (all beams) as well as on a beam by beam basis. To identify putative biological hot and cold spots, plans that correct for spatial variations in proton RBE were compared to plans with a constant (spatially invariant) RBE of 1.1.

Results: The dose-averaged RBE for tumor targets ranged from 1.02 to 1.04 among prostate patients, whereas the dose-averaged RBE for OARs (bladder, rectum, femoral heads, penile bulb) ranged from 1.01 to 1.04.