Genomic biomarkers for precision radiation medicine

Radiotherapy provides local control and cure for many tumour types. Precision radiation medicine seeks to improve the therapeutic ratio of radiotherapy through greater local control and reduced toxicity. Modern radiotherapy techniques already use considerable physical precision, bolstered by technological advances and computational power; however, biological precision has lagged. Radiotherapy dose is currently guided primarily by tumour histology and local anatomy, and genomic features are not commonly considered.

Tumour radiophenotype is influenced by numerous factors, including the number of tumour clonogens, DNA damage response, cell cycle phase, immunogenicity, and tissue oxygenation. The possibility that genomic biomarkers can reflect a common radiophenotype in distinct tumour types has long intrigued investigators. Eschrich and colleagues,[1] devised the gene-expression-based radiosensitivity index using heterogeneous 2 Gy clonogenic survival data (SF2) generated from multiple laboratories on 48 NCI-60 cell lines. The authors' validation study of the 12 remaining NCI-60 cell lines showed an inverse relationship between predicted and reported SF2 (r=–0·57, two-sided p=0·06).[1] Concerns have already been raised by other investigators regarding radiosensitivity index performance in vitro with the use of modern gene expression platforms.[2] Its application to clinical cohorts has corroborated some prognostic associations, but radiosensitivity index has not reliably predicted local control, including in cohorts tested by the investigators themselves.[3,4]

In the study published in *The Lancet Oncology*, Jacob Scott and colleagues[5] applied radiosensitivity index to a large Total Cancer Care (TCC) cohort (in the absence of clinical outcome data) and to five smaller clinical cohorts. In each clinical cohort, patients received surgery or chemotherapy, or both, in addition to radiotherapy; none were treated with radiotherapy alone. Genomic-adjusted radiation dose (GARD) was derived from the linear-quadratic model (describing cell killing from radiotherapy-induced DNA double-strand breaks) by adjusting the linear component with radiosensitivity index. The quadratic component, which is susceptible to differences in cellular proficiency of DNA repair, was not adjusted. Thus, GARD does not appear to adequately account for DNA repair, despite the radiosensitivity index's inclusion of genes that affect the radiophenotype by enhancing DNA repair (eg, androgen receptor). Within the TCC cohort, distinct tumour types showed a strong bimodal distribution of GARD scores, which could have readily informed natural cutoffs for GARD in the five clinical cohorts. Instead, the chosen strategy to choose cutoffs appeared ad hoc and poorly justified. The most relevant endpoint, local control, was included for only one of the five clinical cohorts (Moffitt Lung Cancer Cohort: hazard ratio [HR] 3·4, 95% CI 1·3–9·1; p=0·016) and was excluded from the analyses even when available. Focusing on one other clinical cohort, Scott and colleagues argued that GARD was superior to radiotherapy dose in predicting outcome (Erasmus Breast Cancer Cohort: GARD values [HR 2·11, 95% 1·13–3·94; p=0·018] but not biologically effective dose [0·7, 0·45–1·09; p=0·1131] were associated with longer 5-year distant-metastasis-free survival), but this analysis was notably absent for the other cohorts, and for any cohort reporting local control.

In combining a genomic biomarker with radiotherapy dose, Scott and colleagues have proposed a new framework for the advancement of precision radiation medicine. They should be applauded for their effort. However, there are substantial limitations to this work. We would, therefore, strongly caution against the use of this radiosensitivity index-derived GARD within any clinical trials in the absence of rigorous validation in pre-clinical and additional clinical settings with a focus on local control.

SVB is co-inventor on a patent "Identification and use of circulating tumor markers" 14/209,807 licensed to Roche, and a patent "Methods and compositions for assessing patients with non-small cell lung cancer" PCT/US2015/020244. All other authors declare no competing interests.

Scott V Bratman, Michael F Milosevic, Fei-Fei Liu, Benjamin Haibe-Kains
scott.bratman@uhnresearch.ca

Princess Margaret Cancer Centre, University Health Network, Toronto, ON M5G1L7, Canada (SVB, MFM, F-FL, BH-K); Department of Radiation Oncology (SVB, MFM, F-FL), Department of Medical Biophysics (SVB, F-FL, BH-K), and Department of Computer Science (BH-K), University of Toronto, Toronto, ON, Canada; and Ontario Institute of Cancer Research, Toronto, ON, Canada (BH-K)

1 Eschrich S, Zhang H, Zhao H, et al. Systems biology modeling of the radiation sensitivity network: a biomarker discovery platform. *Int J Radiat Oncol Biol Phys* 2009; **75:** 497–505.
2 Hall JS, Iype R, Senra J, et al. Investigation of radiosensitivity gene signatures in cancer cell lines. *PLoS One* 2014; **9:** e86329.
3 Speers C, Zhao S, Liu M, Bartelink H, Pierce LJ, Feng FY. Development and validation of a novel radiosensitivity signature in human breast cancer. *Clin Cancer Res* 2015; **21:** 3667–77.
4 Torres-Roca JF, Fulp WJ, Caudell JJ, et al. Integration of a radiosensitivity molecular signature into the assessment of local recurrence risk in breast cancer. *Int J Radiat Oncol Biol Phys* 2015; **93:** 631–38.
5 Scott JG, Berglund A, Schell MJ, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. *Lancet Oncol* 2017; **18:** 202–11.