Predictive biomarkers

Pan-cancer prediction of radiotherapy benefit using genomic-adjusted radiation dose (GARD): a cohort-based pooled analysis.

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BACKGROUND

Despite advances in cancer genomics, radiotherapy is still prescribed on the basis of an empirical one-size-fits-all paradigm. Previously, we proposed a novel algorithm using the genomic-adjusted radiation dose (GARD) model to personalise prescription of radiation dose on the basis of the biological effect of a given physical dose of radiation, calculated using individual tumour genomics. We hypothesise that GARD will reveal interpatient heterogeneity associated with opportunities to improve outcomes compared with physical dose of radiotherapy alone. We aimed to test this hypothesis and investigate the GARD-based radiotherapy dosing paradigm.

METHODS

We did a pooled, pan-cancer analysis of 11 previously published clinical cohorts of unique patients with seven different types of cancer, which are all available cohorts with the data required to calculate GARD, together with clinical outcome. The included cancers were breast cancer, head and neck cancer, non-small-cell lung cancer, pancreatic cancer, endometrial cancer, melanoma, and glioma. Our dataset comprised 1615 unique patients, of whom 1298 (982 with radiotherapy, 316 without radiotherapy) were assessed for time to first recurrence and 677 patients (424 with radiotherapy and 253 without radiotherapy) were assessed for overall survival. We analysed two clinical outcomes of interest: time to first recurrence and overall survival. We used Cox regression, stratified by cohort, to test the association between GARD and outcome with separate models using dose of radiation and sham-GARD (ie, patients treated without radiotherapy, but modelled as having a standard-of-care dose of radiotherapy) for comparison. We did interaction tests between GARD and treatment (with or without radiotherapy) using the Wald statistic.

FINDINGS

Pooled analysis of all available data showed that GARD as a continuous variable is associated with time to first recurrence (hazard ratio [HR] 0·98 [95% CI 0·97-0·99]; p=0·0017) and overall survival (0·97 [0·95-0·99]; p=0·0007). The interaction test showed the effect of GARD on overall survival depends on whether or not that patient received radiotherapy (Wald statistic p=0·011). The interaction test for GARD and radiotherapy was not significant for time to first recurrence (Wald statistic p=0·22). The HR for physical dose of radiation was 0·99 (95% CI 0·97-1·01; p=0·53) for time to first recurrence and 1·00 (0·96-1·04; p=0·95) for overall survival. The HR for sham-GARD was 1·00 (0·97-1·03; p=1·00) for time to first recurrence and 1·00 (0·98-1·02; p=0·87) for overall survival.

INTERPRETATION

The biological effect of radiotherapy, as quantified by GARD, is significantly associated with time to first recurrence and overall survival for patients with cancer treated with radiation. It is predictive of radiotherapy benefit, and physical dose of radiation is not. We propose integration of genomics into radiation dosing decisions, using a GARD-based framework, as the new paradigm for personalising radiotherapy prescription dose.