



Genome-based modeling for adjusting radiotherapy dose (GARD)-a significant step toward the future of personalized radiation therapy

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Radiation therapy (RT) is an integral part of treatment for the majority of patients diagnosed with cancer in the United States. While significant advancements are being made in radiation oncology technology and physics with increasing utilization of stereotactic techniques, couches with 6° of freedom, and particle beam therapy, radiation oncology lags far behind its medical oncology counterpart with regard to personalized cancer care based on tumor biology and genomics. Specifically, in-depth understanding and subsequent utilization of the concepts of differential individual patient tumor intrinsic radiosensitivity remains elusive. Advancement of this understanding promises to move RT into the realm of personalized medicine where radiation dose, fractionation, and possibly treatment volumes can be individualized based on tumor gene expression profile.

Current clinical understanding of differential radiation effects is based primarily on the 4 R's of radiobiology: repair of DNA damage (influenced by radiation dose/fractionation schedules), redistribution of cells in the cell cycle, repopulation (affected by cell proliferation rate), and reoxygenation of hypoxic tumors (1). The biologic effect of treating a tumor to a high total dose using conventional fractionation (1.8–2 Gy per fraction) is relatively equivalent to treating to a lower total dose using larger doses per fraction. The concept of biologically effective doses (BEDs), which may be used to quantify the impact of RT on both tumors and normal tissues, is derived from the linear

quadratic (LQ) model for RT (first described in 1946) (2). The LQ model takes into account DNA damage from both single (which are non-repairable and linearly related to RT dose, αD , α = linear cell kill) and double radiation tracts (which are repairable and quadratically related to RT dose, βD^2 , β = quadratic cell kill). This model is often utilized clinically to help guide radiation dose and fractionation. A significant downfall of this model, however, is that it treats all tumors of a particular type the same based on a universal concept of global alpha/beta ratios (the point at which linear cell kill is equivalent to quadratic cell kill) for tumor type or malignancies in general with no ability to determine relative alpha/beta ratio for individuals. Additionally, proven available assays to predict individual tumor response such as *in vitro* therapeutic assessment of cultured patient cancer cells, determination of *in vivo* tumor oxygen levels, and assessment of tumor proliferative potential are cumbersome, time-consuming, and often low yield making them clinically impractical. Consequently, RT remains dependent on clinical and histologic features with the utilization of a one size fits all philosophy for treatment.

Since the dawn of full genome MicroArray and high throughput molecular techniques, multiple groups have attempted to determine genetic molecular profiles that are predictive of radiation therapeutic effect, though with arguably limited results (3,4). To date the most well-documented and validated molecular signature for tumor intrinsic radiation sensitivity consists of a ten gene

expression profile as originally reported by Eschrich *et al.* (cJun, HDAC1, RELA, PKC-beta, SUMO-1, cAbl, STAT1, AR, CDK1, and IRF1). A linear regression model containing these ten genes has been developed to generate a Radiosensitivity Index (RSI, high index = resistant) (5). Since its initial discovery, RSI has been validated to predict patient outcome following RT in multiple clinical cohorts including esophageal cancer, colon/rectal cancer, head and neck squamous cell carcinoma, pancreas cancer, breast cancer, and glioblastoma (6-10). By contrast, RSI did not predict outcome in patients treated without RT. Despite the ability of RSI to predict patient outcomes across various malignancies, its predictive value in and of itself does not allow for application in radiation treatment planning with regard to alteration of dose or fractionation to maximize patient benefit.

In the current study entitled “A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study” by Scott *et al.*, the authors attempted to combine the two validated gene-expression-based RSI and the LQ model into a single calculation, namely the genomic adjusted radiation dose (GARD) score, to enable adjustment of radiotherapy dose and to predict RT effect (10). The calculation for GARD is similar to BED [= $nd(\alpha + \beta d)$, $n=1$, $d=2$ Gy, $\beta=0.05/\text{Gy}$], except that patient-specific α is derived by substituting RSI for survival. A higher GARD value predicts a higher RT effect. In total, GARD scores were determined and analyzed for 8,271 patients with significant heterogeneity in both GARD score and radiation dose provided for patients within each cohort. Additionally, GARD scores within each radiation dose level analyzed were heterogeneous as well, signaling variation in RSI amongst the patients. As might be postulated, GARD scores appeared to correlate well with patient outcome both on an individual and cohort basis with the highest median GARD scores noted in patients with cervical cancer and oropharyngeal cancer and relatively low GARD scores found in patients with glioma and sarcomas, mimicking relative treatment efficacy amongst these patient populations. On multivariate analysis, GARD scores were also noted to be significantly associated with distant relapse free survival in breast cancer patients, local control in lung cancer patients, and overall survival in patients with glioblastoma or pancreas cancer.

Additionally, the authors took this concept a step further in an attempt to determine a threshold GARD score associated with improved clinical outcomes in a single reported breast cancer cohort (Erasmus Breast Cancer

Cohort) in the hope that this might signal individual patients who could benefit from radiation dose escalation. Kaplan-Meier survival analysis revealed that patients with a GARD score at or above the 75th percentile (score of >38.9) within this patient group had a significant improvement in distant metastasis free survival than those with a GARD below 75th percentile ($P=0.0058$). Further, upon multivariate analysis, GARD score was the only independent predictor of distant recurrence. Based on these findings, the authors predict that dose escalation within a clinically relevant dose range of 45–75 Gy would allow achievement of a GARD score of at least 38.9 and thus may be associated with improved patient outcomes in a subset of patients.

Prior to this publication, clinical application of genome sequencing and mutational analytics have been largely ignored by the field of radiation oncology, being primarily relegated to potential prognostic tools alone. While genetic/molecular indications of individual patient radiosensitivity clearly potentiate that patients with relatively radioresistant tumors may benefit from dose escalation and that those with more radiosensitive tumors may not require doses as high as that are currently provided, it is in the combining of this concept with radiation dose/fractionation information to create an easily interpretable score that will allow it to become truly clinically relevant. In this, the current manuscript by Scott *et al.* represents a significant step towards individualized tumor dosimetry to optimize treatment outcomes and away from the one-size-fits all approach currently employed in radiation therapy.

Despite its significant promise, utilization of GARD score in the design of personalized radiation treatment plans remains far from ready for general use as multiple studies have still yet to be conducted. Firstly, while GARD scores appear to correlate with patient outcomes across several malignancies, and determination of a GARD score threshold associated with improved outcomes to guide radiation dose escalation has been provided for the tested patients, further investigation into this concept amongst other malignancies is necessary to understand its universal applicability and ability to extrapolate to patients in clinic. Additionally, while RSI, and ultimately GARD score, are based on radiosensitivity of a patient's primary tumor, it has been noted that metastatic tumors may be slightly more radiation resistant than primaries and there are differences in RSIs amongst different anatomical sites of metastases. Furthermore, it remains unclear how RSI and GARD score relate to relative radiosensitivity of

the surrounding healthy tissues. Investigation into this relationship is necessary as healthy tissue toxicity may preclude the desired dose escalation indicated by a lower GARD score. Also, as all patients treated in the respective cohorts received conventional fractionation of their radiation therapy, assessment of RSI and GARD score using hypofractionated radiation therapy is required as the genes associated with radiosensitivity per RSI [calculated based on tumor surviving fraction at 2 Gy (SF2) may not remain relevant at high fractional radiation doses]. We do not know if RSI that is calculated based on cellular clonogenic survival after 10 Gy (SF10) or other hypofractionation regimen will predict tumor response to stereotactic body radiotherapy the same way as RSI (calculated based on SF2) predicts tumor response to conventional fractionation of RT. In addition, the currently presented GARD model ignored the potential effect of systemic chemotherapy on RT and the potential differential repair (using constant β), proliferation and reoxygenation capacity of tumors. Nevertheless, the current study provides a framework to design future more effective, genomically-guided clinical trials which will push forward personalized medicine in radiation oncology. We very much look forward to further studies regarding both GARD score and associated concepts in the near future as this path of research undoubtedly signals where radiation oncology, and medicine in general, are rapidly heading.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

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