A unified multi-activation (UMA) model of cell survival curves over the entire dose range for calculating equivalent doses in stereotactic body radiation therapy (SBRT), high dose rate brachytherapy (HDRB), and stereotactic radiosurgery (SRS)

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What was your motivation for initiating this study?

The linear-quadratic (LQ) model of in-vivo and in-vitro cell survival curves (CSCs) has been the foundation of standard fraction radiotherapy, typically in 2Gy per fraction treatments. The LQ model has been extrapolated for the calculation of equivalent dose in 2Gy fractions (EQD2) to the tumour and organs at risk (OAR) that receive hypofractionated radiotherapy, stereotactic body radiation therapy (SBRT), stereotactic radiosurgery (SRS), and high-dose-rate brachytherapy (HDRB). Such an extrapolation through use of the same parameters' ratio, validated at 2Gy fractions in the LQ model, might be inappropriate to predict cell survival at 7Gy to 20Gy per fraction located within the straight or almost straight portions of the observed CSC. In order to determine the EQD2 of hypofractionated large fractional dose treatments, investigators have modified the LQ model for an effective linear-quadratic-linear (LQL) model by several methods: by changing the parameter (and thus the ratio) as a function of time and repairing-rate constants [1, 2]; by adding a function of dose shift and constants [3]; or, for a universal survival curve (USC) model, by combining the LQ model at the low-dose domain, a multi-target (MT) model at the high-dose domain, and a transition dose point function between the two dose domains [4]. These new models are either inconvenient to use clinically as they involve complicated functions, theoretically difficult to explain for mechanism changes, or potentially uncertain to correlate outcomes with more parameters.

We were motivated to resolve the radiobiological discrepancies (or catastrophes) between the observed survival curves and model predictions, at either high-dose domain for bending curves by the LQ model or zero slope at zero dose by the MT model (which conflicts with the observed constant slopes at the low-dose domain for many cell lines to high linear energy transfer radiation). We aimed to achieve this through the introduction of a unified formula that precisely fitted any CSC over the entire dose range. The unified formula was empirically derived and numerically validated with many observed CSCs and their measurement errors were published in the literature. The unified multi-activation (UMA) model, which used only two dose-independent parameters, enabled us to estimate EQD2 and other quantities of interest for any fractional doses. A theoretical derivation of the same formula with no more assumptions, but which considers only multiple cell-death pathways that are initiated or activated by the ionising radiation, is currently under review.

What were the main challenges during the work?

There were three main challenges during the work:

(1) For over a century, radiobiologists, medical physicists, and clinicians who use ionising radiation for medical imaging and therapy have been searching for a simple formula to best describe the intrinsic radiosensitivities of cell lines to various doses. The LQ and MT models were widely accepted for their goodness of fit of CSCs at low and high doses, respectively. However, significant discrepancies (or catastrophes) remained between the observed CSCs and the predictions of the two models outside of their fitted dose ranges.

(2) After the discovery of the new UMA model, it is challenging to translate the lab-observed CSCs to tumour control and normal tissue complications of patients. We have to consider the systematic differences between uncontrollable variables of patient-disease systems to the controlled in-vivo and in-vitro cell cultures and measurements. The UMA model is applied for calculation of the EQD2 in order to correlate new fractionation regimens with clinical outcomes that are expected from standard 2Gy fractionation treatments. It is an advantage but also a challenge to prove that the UMA model enables us to directly calculate the EQD2 from the preclinical CSC modelling instead of adjusting the parameters to fit the clinical outcomes when using the LQ model for EQD2 calculation.

(3) It is extremely difficult to explain that the sub-lethal damage and repair (SLDR), potential lethal damage and repair (PLDR), and eventually the cell death and recovery (CDR) are universally included in our unified formula of $S = n/(e^{\frac{D}{D_o}} + n - 1)$ through multiple cell-death pathways that are activated by the ionising radiation. Li, the first author of this work, is producing a theoretical derivation and some interpretations of the unified formula with no more assumptions other than the kinetics of cell-death pathways, but publication of this work will require time for peer review and acceptance.

What is the most important finding of your study?

It is exciting that our proposed model has fitted survival curves of in-vivo and in-vitro tumour cells with R2 > 0.97 and global errors that are smaller than the experimental uncertainties, as shown in Fig. 1. We have found systematic differences between UMA and LQ predictions of EQD2, □□□□, and □□□ ratio. For example, the average EQD2 of 20Gy SRS for glioblastoma and melanoma metastatic to the brain, 10Gy x 5 SBRT for treatment of early-stage lung cancer, and 7Gy x 5 HDRB for endometrial and cervical carcinomas are 36.7Gy (24.3 - 48.5), 114.1Gy (86.6 - 173.1) and 45.5Gy (35 - 52.6), and these differ from the LQ model estimates of 50.0Gy, 90.0Gy, and 49.6Gy, respectively. The UMA-predicted EQD2 figures are closer to the clinical outcomes of low tumour control probability (TCP) in SRS, high TCP for SBRT of early stage non-small-cell lung cancer, and comparable TCP of HDRB (with or without 45Gy/25fx external beam radiotherapy) for endometrial and cervical carcinomas.

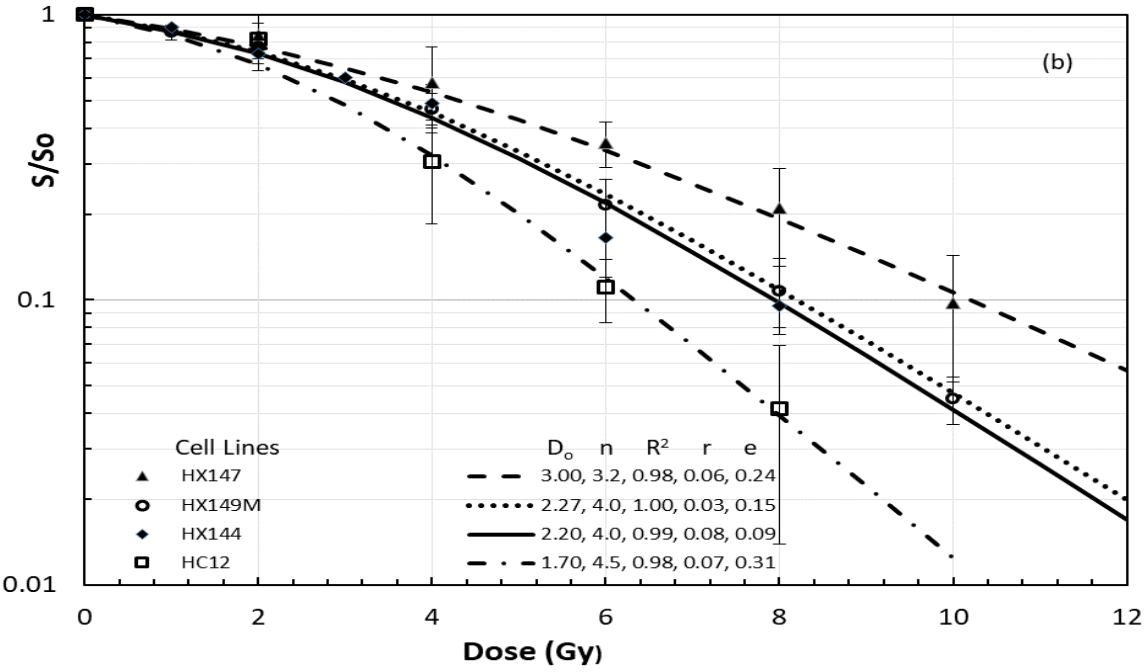

Fig. 1. In-vivo lung cancer redrawn data from [5] for HX147 - a large-cell carcinoma, HX149M - a variant small-cell carcinoma, HX144 – an adenocarcinoma, and HC12 - a classic small-cell lung cancer (SCLC). r – global regression errors. e –mean experimental uncertainty in 1 SD.

The unified formula indicates the same dose-response (or cell killing) mechanism among low doses when SLDR dominates and high doses when PLDR predominates. Having the same mechanism, it is reasonable to have a simple and fundamental quantification of radiosensitivity of cells. For this, the mean inactivation dose (MID) that was previously introduced for fractionated radiotherapy and brachytherapy by Fertil et al. [6] is analytically expressed as $MID = \frac{nLn(n)D_o}{n-1}$. Fig. 2 shows the change of D_o from 0.80Gy to 1.49Gy and n from 1.0 to 3.8 for the same breast cancer cell line irradiated with alpha particles and gamma-rays, respectively. The MID changes from 0.80Gy for alpha-particle irradiation to 2.7Gy for gamma-ray irradiation mainly due to the 3.8 time change of n. The number n that represents the cell death and recovery pathways plays an important role in defining shoulders of typical CSCs; hence our name for the new model of the unified multi-activation (UMA) model instead of the unified multi-target model.

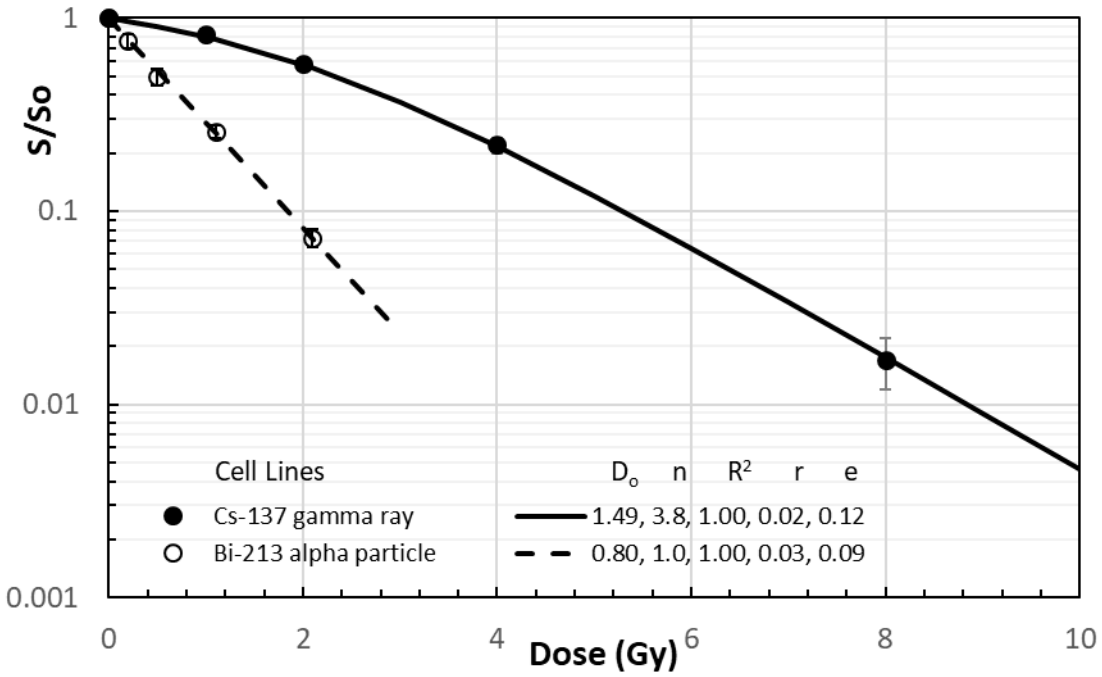

Fig. 2. Modelling of MDA-MB-231 cells - a human breast cancer, irradiated with Cs-137 γ- rays or Bi-213 α-particles. Redrawn data from Fig. 4 of reference [7].

The UMA model may assist clinicians as they make treatment decisions to choose an optimal dose fractionation scheme. For example, a CSC with n < 1 (which is likely from some metastatic cancer cell lines) should be treated with hyperfractionated twice-daily (BID) radiotherapy, while a CSC with n > 1 should be treated with hypofractionated radiotherapy. This can be analytically calculated or graphically illustrated as shown in Fig. 7 in the published paper.

What are the implications of this research?

Our UMA model, which fits CSCs over the entire dose range within their experimental errors, may reveal a common mechanism of cell killing with ionising radiation at all dose levels.

The unified formula, which is based on pre-clinical measurement of CSCs, appears to estimate EQD2 and other clinical quantities of interest at all dose levels. Thus, it could hold broad implications for clinical practice, particularly for alternative fractionation schemes such as hypofractionated radiotherapy. It may have application in the combination of radiotherapy with chemotherapy and hyperthermia.

The UMA model has been theoretically derived from cell-death pathways and it has been applied for typically hypofractionated radiotherapy procedures. Several facets remain to be explored: its clinical application and theoretical study of the mechanism of the synergistic effects when combined with chemotherapy, radiosensitisers for the tumour cells, radioprotectors for normal tissue, hyperthermia and immunotherapy, as well as the dose-rate effects such as in ultra-high dose rate in FLASH radiation, re-sensitisation from reoxygenation, repopulation and redistribution.

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