Calibrating absolute malignant induction probabilities into life-time attributable risk

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Aim:

More than half of cancer patients receive radiotherapy for radical or palliative purposes. Increasing survival rates in cancer patients make it important to study late side-effects, including secondary radiation-induced cancers. Although a number of predictive models exist, the absolute accuracy of these models in the radiotherapy dose range is limited partly due to scarcity of data and partly by extrapolation beyond historical data bounds. The aim of this work is to investigate conversion of malignant induction probabilities, which provide useful *relative* risk estimates, into absolute life time attributable risk estimates (LAR) and excess *absolute* risk (EAR) by calibrating and benchmarking our models using published outcome data.

Materials & Methods:

An in-house modelling tool, which calculates voxel-wise risk estimates from patient-specific 3D dose distributions, was modified to generate linear-no-threshold (LNT) model-based risk estimates for the whole body and per organ using organ-equivalent dose. Second cancer risk was calculated for uniform whole-body exposure of 0.1 Gy for comparison with tabulated BEIR VII data [1]. Model parameters initially used were taken from existing published reports for the relevant models. The calculated LAR was then compared to the BEIR VII results and the linear coefficient, λ, was adjusted to make the model prediction better match the BEIR VII result. A similar calibration of parameters was then performed for the linear quadratic (LQ) and linear model (LIN) malignant induction models. The calibrated λ was then used to calculate LAR and EAR for a 3DCRT plan and an actively scanned proton therapy plan for a case of adult medulloblastoma.

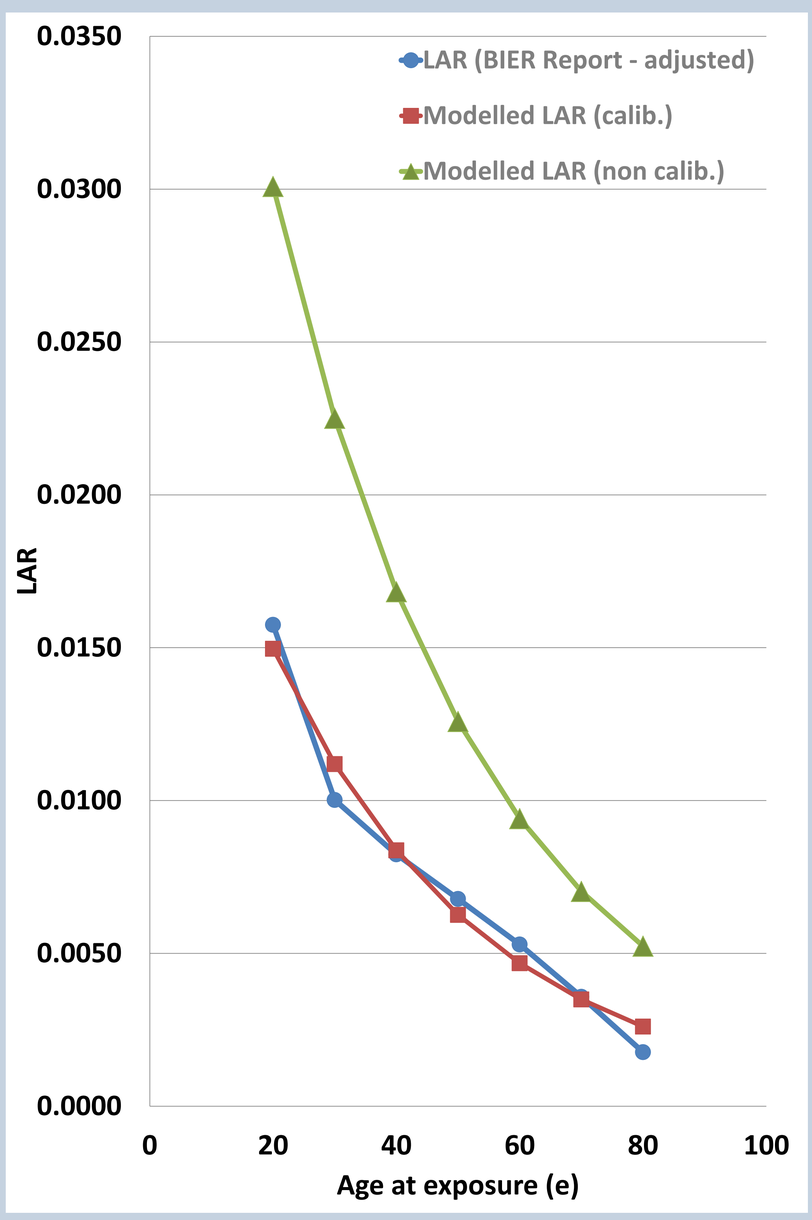

Figure 1: LAR from BEIR VII report and modelled LAR for a single uniform exposure of 0.1 Gy, using a non-calibrated λ and a calibrated λ .

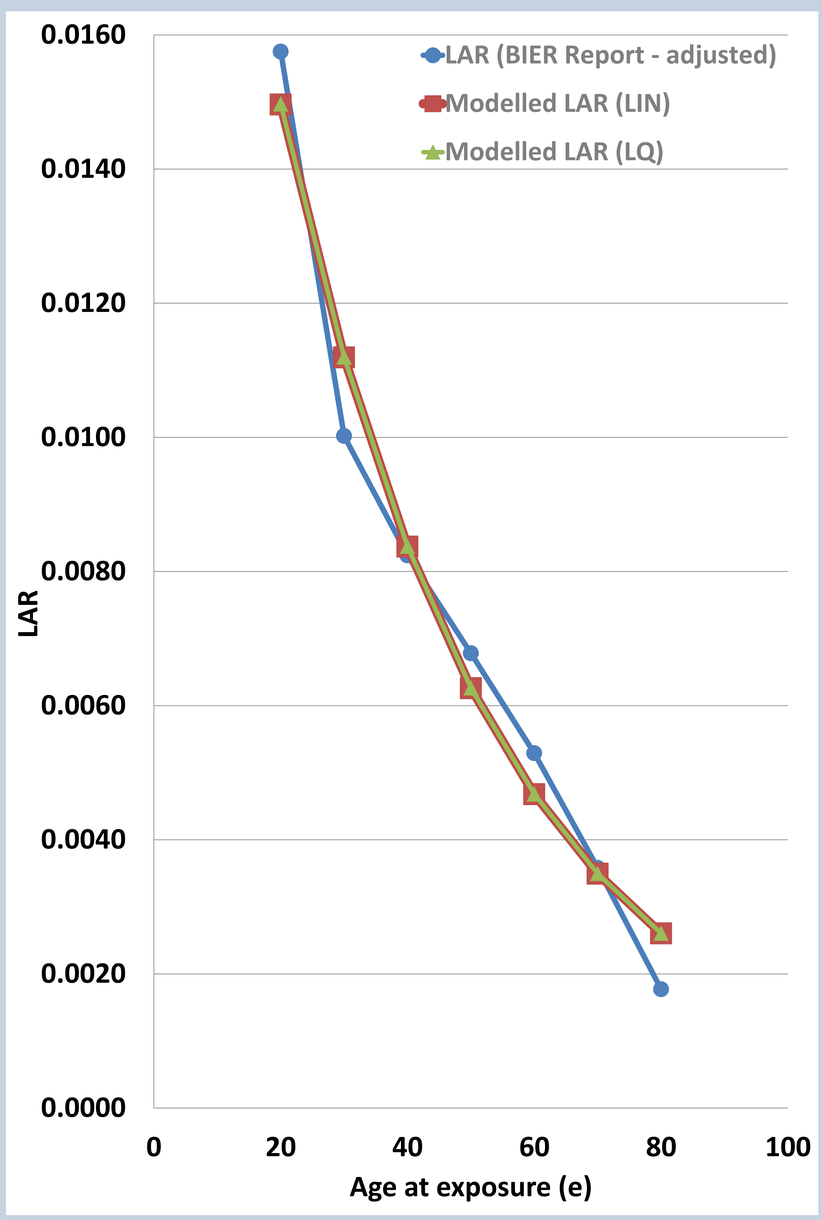

Figure 2: LAR from BEIR VII report and modelled LAR for a single uniform exposure of 0.1 Gy, using a calibrated λ, α,β for LIN model, and γ and δ for the LQ model.

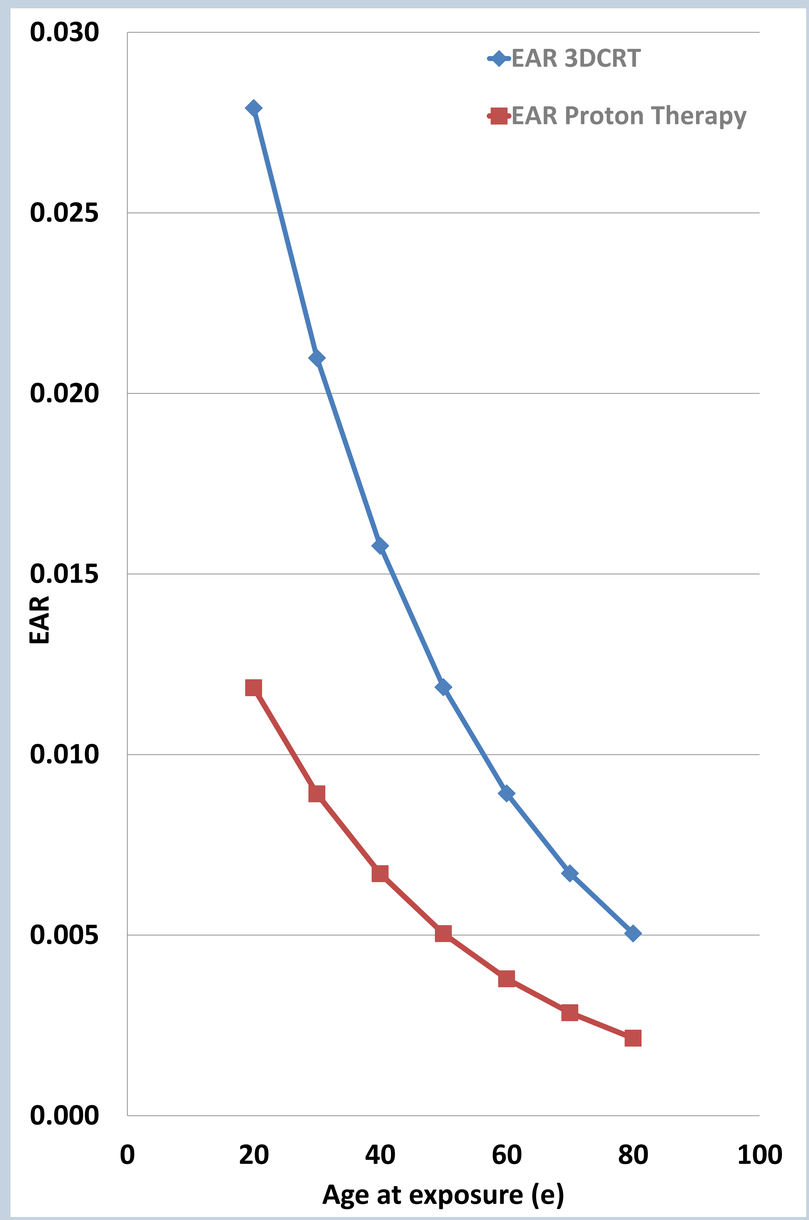

Figure 3: EAR calculated using the LNT model for an adult patient with MB for a 3DCRT plan and an actively scanned proton therapy plan with CSI dose of 36 Gy and boost dose to the posterior fossa of 19.8 Gy.

Results:

Initial calculations of LAR for single uniform exposure of 0.1 Gy produced an LAR of 1683 cases per 100,000 for an exposure at age of 40, in comparison to 824 cases per 100,000 according to BEIR VII report After calibration, calculations of LAR for single uniform exposure of 0.1 Gy produced a value of 837 cases per 100,000 for an exposure at age of 40. Averaging over ages at exposure of 20 to 80 produced a value within 5% of the BEIR VII report (figure 1). Calculations of EAR for a dose range relevant to RT of 1-6 Gy using the LIN model were always within the range of uncertainty due to differences in RBE neutron value in the independent published Hodgkin Lymphoma data (Schneider et al, 2008). Calibration was also done for LIN and LQ model and improved fits were produced (figure 2). EAR was calculated for 3DCRT plan actively scanned proton therapy plan for a case of adult medulloblastoma. 3DCRT was predicted to have higher EAR than actively scanned protons (figure 3), which reinforces previous relative modelling results of MIP. The same trend was seen with LQ and LIN models.

Conclusions:

Our results show that our models can produce absolute lifetime attributable risk estimates for secondary cancer which are consistent with the values reported in the BEIR VII report for uniform irradiation to 0.1 Gy. The comparison of our results of EAR using LIN model to published data showed agreement with independent published data of HL. The models can then be used to predict LAR for voxelized model taking into consideration heterogeneity in both the radiosensitivity and the 3D dose distribution.

Malignant induction models: Linear-no-threshold: $MIP_{LNT} = \lambda D$ λ is the linear coefficient, *D* is the total dose, linear quadratic model: $MIP_{LQ} = n(\gamma d + \delta d^2)\, e^{-n(\alpha d+\beta d^2)}$,

linear model: $MIP_{LIN} = \lambda D\, e^{-n(\alpha d+\beta d^2)}$ n is the number of fractions, d is the dose per fraction , γ and δ are the malignant induction coefficients, α and β are radiosensitivity parameters.

SCR $\mu = \beta$ OED μ EAR $= \beta$ OED μ $\mu = \exp\left[\gamma_e(e-37) + \gamma_a \ln\left(\frac{a}{46}\right)(1 \pm s)\right]$ $LAR_{D,e} = EAR_{D,e,a}\frac{S(a)}{S(e)}$

[1] BEIR VII: Health Risks from Exposure to Low Levels of Ionizing Radiation, National Academies Press, 500 Fifth Street, NW, Washington, DC 20001.

[2] Schneider U, Walsh L (2008) Cancer risk estimates from the combined Japanese A-bomb and Hodgkin cohorts for doses relevant to radiotherapy. Radiat Environ Biophys (2008) 47:253–263

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