Investigating Conversion Of Malignant Induction Probability To Cancer Mortality

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Purpose/Objective:

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 transforming modelled absolute malignant induction probabilities into life time excess relative risk estimates for cancer-related death (ERR) to allow comparison of the results with the relevant risk estimates in Life Span Study (LSS) report no. 14.

Materials & Methods:

Malignant induction probability (MIP) is calculated using the linear-quadratic (LQ), linear (LIN), linear-no-threshold (LNT) and linear-with-threshold (LT) models using in-house developed, voxel-wise code with individual organ weightings. We converted the MIP value from an adult female 1 Gy and 0.1 Gy exposures into lifetime excess relative risk of cancer-related death using population-averaged incidence and mortality figures from the Canadian Cancer Statistics 2013 report (ISSN0835-2976) for comparison with LSS report no. 14.

The Canadian Cancer Society in its 2013 Canadian Cancer Statistics report states that the lifetime probability of developing cancer is 46% for males and 41% for females (2007 data). This does not take individual behaviors and risk factors, as stated in the report. We assume, as an upper-bounds limit, that malignant induction events occur spontaneously in the whole population; the efficiency of this spontaneously occurring malignant induction evolving into a clinical expressed tumor can therefore be estimated using the numbers from the report (46% and 41%) and applied to our MIP predictions (table 1). On the other hand, the report estimates that the life-time probability of dying from cancer is 28% for men and 24% for females (Chapter 3, page 35). This may be used in a similar way to estimate a lower-bounds estimate for excess risk, given that cancer mortality, by definition, includes the expression of a clinical tumour and the progression of a malignantly induced cell(s) into a disease (table 1).

Model	MIP_{1Gy}	ERR Upper Limit	ERR Lower Limit	$MIP_{0.1Gy}$	ERR Upper Limit	ERR Lower Limit
LQ	0.570	0.234	0.137	0.038	0.016	0.009
LIN	0.045	0.018	0.011	0.005	0.002	0.001
LNT	0.051	0.021	0.012	0.005	0.002	0.001

Table 1: Upper and Lower limits for the ERR values using figures derived from the Canadian Cancer Statistics 2013 report

Results:

MIP values for a single 1 Gy uniform exposure from the four models were: 0.570 (LQ); 0.045 (LIN) and 0.051 (LNT). Allowing for uncertainties in describing disease progression, the models produced ERR estimates in the range: 0.234–0.137 (LQ); 0.018–0.011 (LIN) and 0.021–0.012 (LNT) (upper bound to lower bound).

MIP values for a single 0.1 Gy uniform exposure from the four models were: 0.038 (LQ); 0.005 (LIN) and 0.005 (LNT). Allowing for uncertainties in describing disease progression, the models produced ERR estimates in the range: 0.016–0.009 (LQ); 0.002–0.001 (LIN) and 0.002–0.001 (LNT) (upper bound to lower bound).

All the estimated lifetime excess relative risk figures in table 1 are notably lower than the figures in the LSS report no. 14 (0.47/Gy). The model which produced the closest estimate was the LQ model, which is just less than 1/3 of the LSS figures (further comparison with the LSS results is in progress). This analysis allows revision and modification of the choice of model and potential refinement of the radio-biological model parameters used to improve absolute predictive ability.

The ERR for cancer-related death for all solid cancers, according to LSS report no. 14, is linear with a slope of 0.47/Gy. Modelling malignant induction for individual subjects or patients is challenging due to uncertainties in models and parameters (due to uncertainties in exposure, genetic and environmental variations between populations among other factors). Transforming modelled outcomes into clinically-applicable figures can be done utilizing existing cancer registry data from different sources, and comparing them to other sources of data including, but not limited to, LSS.

Conclusions:

The results obtained by the methods used here demonstrate that there are considerable differences between the absolute risk estimates produced using different models. Although uncertainties of factor ~2 still remain in the risk estimates, these figures will allow refinement of the underlying model parameters. Further validation work and additional data are still required. Work is ongoing on modelling excess absolute risks and lifetime attributable risk using models published in the literature (BIER Report VII, Kellerer et al 2001).

*MIP Models used: The linear-quadratic malignant induction model (LQ): $\mathbf{MIP = n\,(\gamma d + \delta d^2)\, e^{-n(\alpha d+\beta d^2)}}$, The linear malignant induction model (LIN): $\mathbf{MIP = \mu D\, e^{-n(\alpha d+\beta d^2)}}$, Linear-no-threshold malignancy induction model (LNT): $\mathbf{MIP = \mu D}$, Linear-with-threshold malignancy induction model (LT) : $\mathbf{MIP = \mu (D - D_{threshold})}$ **if** $\mathbf{(D - D_{threshold}) > 0}$, **MIP = 0 otherwise.**

***SF** : the surviving fraction of cells given in (**n**) fractions of dose (**d**). **α** and **β**: the radiosensitivity parameters, are the linear and quadratic component of the curve, respectively. **γ** and **δ**: the malignant induction coefficients. **μ**: linear coefficient, **D** is the total dose.*

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