Modelling Malignant Induction Probability in Medulloblastoma for Photon and Proton Therapy

A. M. Madkhali[1,5], C. L. Timlin[2], T. T. Sio[3], R. C. Miller[3], J. G. Loken[4], M. Partridge[1]

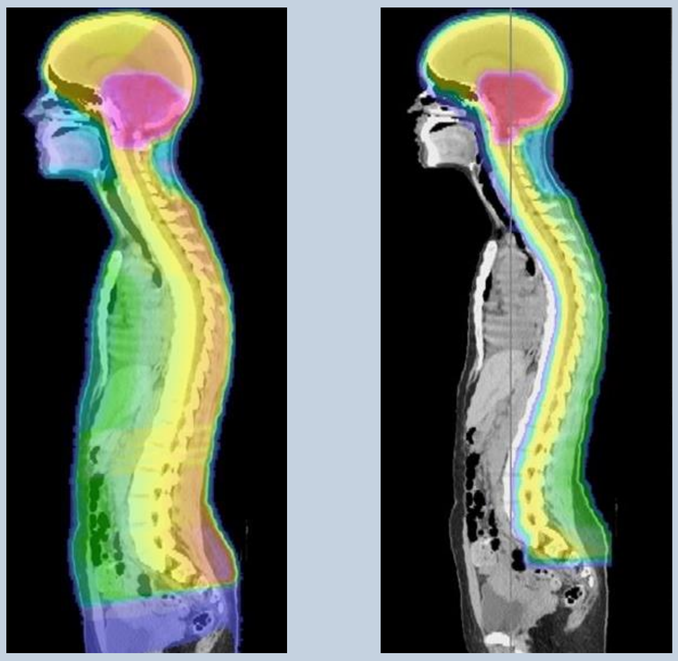
[1]University of Oxford, The Gray Institute, Oxford, UK; [2]University of Oxford, PTCRi, Oxford, UK; [3]Mayo Clinic, Radiation Oncology, Rochester, MN, USA; [4]University of Oxford, Physics, Oxford, UK; [5]King Saud University, Riyadh, Saudi Arabia.

Aim: More than half of cancer patients receive radiotherapy (RT) for radical or palliative purposes. Increasing survival rates in cancer patients makes it important to study side-effects. This work studies secondary cancer induction in medulloblastoma (MB) treated by RT using 3D conformal X-ray RT or actively scanned proton therapy. Malignant induction probability (MIP) and normal tissue complication probability (NTCP) are calculated in a voxel-by-voxel fashion using in-house developed code. The aim of the project is to compare the relative MIP of both modalities using different MIP models and, for each model and modality, to perform a sensitivity analysis to the pertinent radiobiological input parameters and to identify which organs' NTCPs are most sensitive to the choice of treatment modality.

Methods: A 3DCRT plan and an actively scanned proton therapy plan for an adult female MB patient were supplied by collaborators at Mayo Clinic. The prescribed dose was 36 Gy to the whole brain and spine with a 19.8 Gy boost to the posterior fossa (1.8Gy/fx). MIP is calculated using 4 models: linear-quadratic (LQ), linear (LIN), linear-no-threshold (LNT), and linear-with-threshold (LT). NTCP and biologically effective dose (BED) are also calculated.

All calculations are performed with a predefined priority list used to determine which structure each voxel is assigned to (and therefore which set of model parameters to apply). Using the voxel-wise calculation, BEDs were calculated for the clinical target volume (CTV) and gross tumour volume (GTV). NTCPs were calculated for right lung, left lung, small bowel, sigmoid colon, rectum and gallbladder. MIP was calculated for the whole body.

To assess the sensitivity of the MIP models to uncertainty in radiobiological parameters, an independent simulation done using a system capable of running multiple jobs in parallel, the program was utilized to calculate the MIP and the other outputs with changing the value of one parameter at time, while the value of the other parameters are fixed. The values ranged from 0.2 to 10.



The photon plan (left) and the proton plan (right). Notice the difference of the dose received by some of the anterior organs.

Results: BEDs for the target volumes of the two plans were compared and close agreement found in BED showing that comparisons of toxicity can be made. The MIP (photon) was 2.6, 3.3, 2.3 and 2.5 times higher than for MIP (proton) for each model respectively (Table 1 & Fig. 1). NTCP calculated for selected organs was lower for protons than for the photons, though the absolute numbers for both were very low. NTCP can be of more clinical relevance and importance in many clinical scenarios since the timeline of the expression of many normal tissue complications is much shorter than that needed to express secondary malignancy. The scan on the values of the parameters showed that though there are differences in MIP outcomes for each plan, the relative conclusion would be the same for most of the structures as well as the whole body MIP (Fig. 2).

Model	Photon	Proton	Relative MIP
LQ	0.262	0.100	2.606
LIN	0.042	0.013	3.265
LNT	0.335	0.145	2.320
LT	0.168	0.067	2.528

Table 1 : Whole body MIP values for both plans, and the relative MIP of both plans.

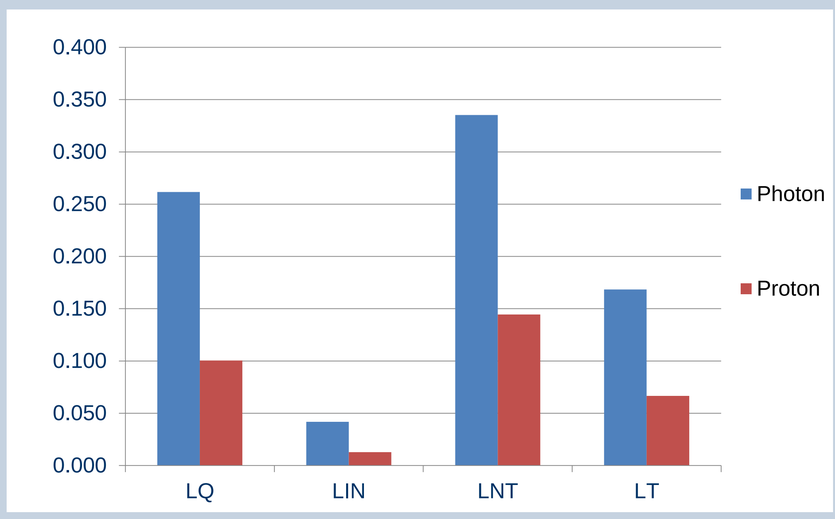


Fig. 1 : Whole body MIP values for both plans. Notice the difference in the values for each plan between the models.

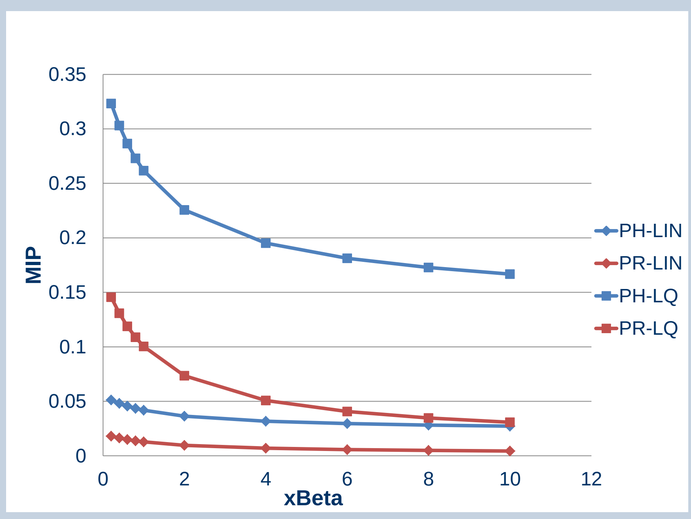


Fig. 2 : The effect on changing the value of **β** on whole body MIP values for both plans as calculated by the LIN and LQ models.

Conclusions: The 4 models produce quite different absolute MIP values, but the proton plan was shown to have smaller MIP than the photon for any given model, as expected from the decrease in radiation exposure outside treatment volumes in the proton case. The level of confidence in MIP models is associated with how accurately the doses to the organs are handled and the accuracy of the models. Currently, long-term follow-up data is being acquired to calibrate absolute MIP values of this work.
When the values of the parameters are varied, the MIP values for organs and subsequently the whole body changes. But the whole body MIP of the photon plan was almost always higher than that of the proton plan. This indicated that, even with the given uncertainty in the values of the parameters used; in this particular case, proton therapy is better than photon therapy.

The level of confidence in MIP models is associated with how accurately the doses to the organs are handled and the accuracy of the models used. Studies have been carried out in which a single dose value for an organ is taken into account to calculate MIP. This method, whether using the maximum, minimum, or the mean dose can be imprecise, as it does not account for heterogeneity in the organ dose distribution. An optimal MIP model should handle the dose on a voxel-by-voxel basis, which can take account of differences in the dose distribution across the organ or structure for which the calculations are being done.

To properly characterise MIP models, clinical trials with a follow-up period of 10-20 years, which should focus on monitoring quality of life of patients, their general health status as well as focusing on secondary malignancies and other possible therapy-related normal tissues complications are vital. Such long-term follow-up is the only way to truly validate and establish the clinical relevance of lifetime risk of secondary malignancies.

*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): MIP = $\mathbf{\mu D}$, 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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