Modelling recurrence and second cancer risks induced by proton therapy

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In the past few years, proton therapy has taken the centre stage in treating various tumour types. The primary contribution of this study is to investigate the tumour control probability (TCP), relapse time and the corresponding secondary cancer risks induced by proton beam radiation therapy. We incorporate tumour relapse kinetics into the TCP framework and calculate the associated second cancer risks. To calculate proton therapy-induced secondary cancer induction, we used the well-known biologically motivated mathematical model, initiation–inactivation–proliferation formalism. We used the available in vitro data for the linear energy transfer (LET) dependence of cell killing and mutation induction parameters. We evaluated the TCP and radiation-induced second cancer risks for protons in the clinical range of LETs, i.e. approximately 8 keV/μm for the tumour volume and 1–3 keV/μm for the organs at risk. This study may serve as a framework for further work in this field and elucidates proton-induced TCP and the associated secondary cancer risks, not previously reported in the literature. Although studies with a greater number of cell lines would reduce uncertainties within the model parameters, we argue that the theoretical framework presented within is a sufficient rationale to assess proton radiation TCP, relapse and carcinogenic effects in various treatment plans. We show that compared with photon therapy, proton therapy markedly reduces the risk of secondary malignancies and for equivalent dosing regimens achieves better tumour control as well as a reduced primary recurrence outcome, especially within a hypo-fractionated regimen.

Keywords: tumor control probability; recurrence; secondary malignancy; linear energy transfer; mutation rate; relative risk.

1. Introduction

In the last few decades, external beam radiation therapy has seen drastic technological improvements in both the palliative and the curative clinical settings. One of the primary reasons for this improvement is the administration of radiation to patients in a conformal manner. Survival rates have increased due to better dose conformity and more targeted dose distribution in the tumour volume. There are several types of external beam radiotherapy techniques administered clinically, including high-energy photons (e.g. 3D conformal radiotherapy and intensity-modulated radiotherapy) and particle therapy (e.g. protons, alpha particles and heavy ions). In current radiation therapy planning paradigms, heterogeneous dose distributions are used to treat the tumour. The probability that all the cancerous cells are removed from the system is known as the tumour control probability (TCP) (O'Rourke *et al.*, 2009). The therapeutic index of any radiation treatment plan can be understood to some extent (if not completely) through TCP values. These values can be further used to design radiation protocol for a given patient. Interestingly, in spite of apparent appropriate tumour control, many clinical studies have reported relapses after radiation treatment

FIG. 1. A schematic diagram displaying diagnosis of primary tumour, relapse of primary tumour and radiation-induced second tumour. (a) Patient diagnosed with primary tumour, Hodgkin's lymphoma (tumour at lymph nodes); (b) disease-free (i.e. completely cured); (c) tumour relapse; and (d) radiation-induced second tumour in breast tissue. dots denote the tumour bed.

of the primary tumour, e.g. early and late relapses are observed in Hodgkin's lymphoma patients (Gaudio *et al.*, 2011). The recurrence of the primary tumour is likely a function of several (pre)clinical variables, e.g. tumour grade, stage, micro-environment, patient risk factors and (epi)genetics. Additionally, the recurrence risk of the primary tumour likely is strongly dependent upon the modality by which it was treated, such as radiotherapy, surgery, chemotherapy or a combination in an adjuvant or neoadjuvant setting.

The clinical management of primary diagnosis and follow-up is shown in Fig. 1.

A patient diagnosed with primary tumour, Hodgkin's lymphoma (HL), has three possible scenarios that could potentially occur after administration of (radiation and/or chemotherapy) treatment: (a) disease-free, i.e. complete elimination of tumour; (b) relapse of the tumour; and (c) treatment-induced second tumour.

Although there is a gain in the clinical management of primary tumour, with aggressive radiotherapy, there is a delayed effect on normal tissues in the form of radiation-induced secondary malignant neoplasms, which typically appear many years after the treatment. The latency time for these therapy-induced second cancers is generally 5–20 years (Henry-Amar & Somers, 1990; Cosset *et al.*, 1991; Mauch *et al.*, 1995; Lee *et al.*, 2000; Hodgson *et al.*, 2007a,b). It is widely accepted that secondary malignancies are due to the irradiation of healthy tissue in the vicinity of tumour volume, affecting in particular the 'organs at risk' identified during radiotherapy planning (Xu *et al.*, 2008). Numerous case-control and cohort studies have reported the appearance of secondary malignancies post-radiation therapy. Epidemiological studies such as childhood cancer survivors' cohorts and atomic bomb survivors' data clearly indicate that ionizing radiation induces secondary cancers in the organs at risk during radiotherapy (Gilbert *et al.*, 2003; Travis *et al.*, 2003; Veiga *et al.*, 2012). Radiation therapy has improved the survival rate of cancer (e.g. in HL) patients to few more decades treated with

FIG. 2. Radiation-induced second cancer dynamics (taken from [Manem, 2014](#)).

radiation therapy, it is of great importance to evaluate secondary cancer risks induced by radiation. Furthermore, the childhood cancer survivors' study has indicated that there is an increased risk of secondary breast, lung and thyroid cancers in HL cancer survivors ([Gilbert *et al.*, 2003](#); [Travis *et al.*, 2003](#); [Veiga *et al.*, 2012](#)). Recent clinical studies have suggested that children treated with radiation therapy have a high incidence of radiation-induced second cancers ([Gilbert *et al.*, 2003](#); [Travis *et al.*, 2003](#); [Veiga *et al.*, 2012](#)). Due to the prevalence of second cancers, it is of clinical importance to investigate the risks of second cancers associated with current clinical paradigms.

The dynamics of second tumour evolution post-radiation treatment is shown in Fig. 2.

The DNA damage occurs to healthy tissue surrounding the tumour bed due to radiation, and the cell acquires further mutations and transforms itself into a malignant phenotype, termed as a radiation-induced secondary malignancy.

When photons traverse the tissue, they deposit energy both along their path and also at points away from the path. Photons deliver a larger integral dose to the target volume, and the exit dose might potentially damage healthy tissues around the tumour. However, this is not the scenario with protons, because they have a finite range and deposit bulk of their energy in the target volume. The point where the maximum energy is released is known as the 'Bragg peak'. One of the main advantages of proton radiation over photon radiation is that the clinician can control the range of protons and the position of the Bragg peak ([Xu *et al.*, 2008](#)). Comprehensive experimental studies have been carried out by various authors in the literature for clonogenic cell survival and mutation induction following radiotherapy ([Belli *et al.*, 1989, 1992, 1998](#)). These studies have clearly indicated that radiobiological parameters and mutation induction frequency depend on the type of radiation (e.g. protons, alpha particles or ions) used in clinical practice. The two most important parameters in modelling TCP and second cancer risks are cell kill and mutation induction rate. There is enough experimental data in the literature, which suggest cell kill and mutation frequency depend on dose-averaged linear energy transfer (LET). The LETLET is defined as the amount of energy that gets transferred to the biological tissue. The dose-averaged LET is defined as follows:

$$\langle \text{LET} \rangle = \frac{\sum_i D_i \text{LET}_i}{\sum_i D_i}. \quad (1.1)$$

In the above equation, i denotes dosimetric particle tracks and D_i represents the corresponding dose. Clinically relevant LET values are used to model TCP and second cancer risks. To model TCP, we choose the radiobiological parameter and mutation induction rate as a function of LET approximately 8 keV/ μ m (see Paganetti, 2014, fig. 4). Second cancer risks are modelled in the plateau region of the ‘Bragg peak’. The plateau region is defined as the region where particles are moving fast and LET is lower, which eventually leads to the Bragg peak. The value of LET in this plateau region is approximately 1–3 keV/ μ m (see Paganetti, 2014, fig. 4). To simplify the mathematical framework, we assume the following in our formalism: (a) the model does not consider the variations in LET along the particle track in the plateau region; (b) additionally, this framework does not account for the contribution of second cancer risks from neutrons; and (c) uniform dose distribution in tumour and organs at risk is considered for this model.

In the literature, several authors have modelled the effect of photons on TCP, relapse and second cancer risks (e.g. Lindsay *et al.*, 2001; Sachs & Brenner, 2005; O’Rourke *et al.*, 2009; Schneider *et al.*, 2010; Manem *et al.*, 2014, 2015). In this study, we model TCP, relapse and second cancer risks in HL patients, parameterized for breast tissues in the context of proton therapy, and compare these results to analogous findings for photon therapy. The main goal of this study is to model the efficacy of proton therapy incorporating two risk factors together, namely, relapse of primary tumour and the risk of radiation-induced secondary malignancy. In particular, we investigate the following: (a) estimate TCP for a conventional, hypo-fractionation regimen treated with proton therapy; (b) incorporate relapse kinetics into the TCP framework and calculate the relapse time of primary tumour; and (c) estimate the associated secondary cancer risks. To compare photons against protons, we chose a relative biological effectiveness (RBE) = 1.1 (Paganetti, 2014) to convert photon dose to Cobalt-Gray equivalent (CBE). The novelty of this work relies in extracting parameters for radiosensitivity and mutation rates as a function of LET in a proton therapy setting.

2. Materials and methods

2.1 TCP and recurrence

The tumour control probability within this work is calculated as a Poisson statistic, representative of the underlying stochasticity of the cellular dynamics of the tumour being irradiated. That is, the TCP within this work is calculated as the Poisson-distributed probability that all cells within a tumour are eradicated, given the ‘average’ number of cells, computed deterministically. Thus, the TCP is given in (2.1) as (O’Rourke *et al.*, 2009):

$$TCP = e^{-N \cdot S}, \quad (2.1)$$

where N is the average number of clonogens in the system and S is the survival fraction of cells after a given acute dosage D . Moreover, the survival fraction S is computed based on the linear quadratic model of cellular survival post-irradiation for a uniform dose D , taken in unit of Gray over K fractions, such that:

$$S = e^{-\alpha D - \beta(D^2/K)}. \quad (2.2)$$

In the above, α (1/Gy) and β (1/Gy²) are the cellular radiosensitivity parameters, taken to denote the action of direct lethal cell killing and two track action where damage from two different radiation tracks interact to inactivate the cell via a double-strand break in the DNA respectively (Chadwick & Leenhouts,

1981). The survival fraction of cells is tissue specific and taken into account through the ratio α/β . The value of α/β is high for tissues with early effects and low for tissues with late effects; the quadratic term is more important, so fractionation also becomes more relevant.

Because cell killing induced by radiation is clinically a stochastic process, there is a non-zero probability that there exists a small number of cancerous cells at the end of the treatment, equal to the TCP subtracted from unity. This can be used to give an average number of cells surviving at the end of treatment. Then, we assume that these remaining cancerous cells grow according to logistic growth, for simplicity. A recurrence of the primary malignancy is assumed to have occurred if the cell population reaches the order of 10^6 . That is, in determining an average time to relapse, we determine the time point at which the tumour population level reaches a threshold of 99.9% of 10^6 . This is then used as the post-treatment time to recurrence, and the logistic growth equation governing this dynamics is:

$$\frac{dn_r}{dt} = \lambda n_r \left(1 - \frac{n_r}{N}\right); \lambda > 0. \quad (2.3)$$

Note that n_r is the expected number of tumour cells remaining at the end of the treatment. The output of the TCP model determines the initial conditions for the relapse dynamics framework.

We note that for proton therapy, published works have shown that the dose of radiation may be compared with photon therapy with the comparative unit known as CGE. This is taken within this work to be such that:

$$\text{CGE} = \text{Proton Dose (Gy)} \times 1.1. \quad (2.4)$$

Thus, any dose quoted for proton therapy, when used in the above equations (which we suppose hold for photon therapy) is converted to cobalt-Gray units.

2.2 Second cancer risk framework

There are several types of risks used in the literature to represent radiation-induced carcinogenic risks. In the current study, we use excess relative risk (ERR) to estimate proton-induced second cancer risks. A widely used biological-based mathematical formalism, called the initiation–inactivation–proliferation model, is used to estimate radiation-induced carcinogenic risks (Sachs & Brenner, 2005). This model incorporates three biological phenomena that occur during radiation treatment, namely, inactivation (cell killing due to radiation), initiation (radiation-induced cell mutation) and proliferation (repopulation of cells during and after radiation). The organ-specific second cancer incidence due to ionizing radiation is assumed to be proportional to the yield of radiation-induced pre-malignant cells at the end of treatment, which is defined as follows (Sachs & Brenner, 2005):

$$\text{ERR} = M \times B, \quad (2.5)$$

where ERR is given by the product of the number of initiated cells remaining at the end of the treatment (M) and a proportionality factor (B). The proportionality factor takes into account gender, demographic variables, age at diagnosis and so on.

The evolutionary dynamics of normal ($n(t)$) and pre-malignant ($m(t)$) stem cells during and at the end of the treatment is considered in the model. One of the important assumptions in the framework is that the repopulation mechanism is active between administration of fractions in the treatment regimen

and also at the end of the treatment. Due to the homeostatic regulation of cells the healthy tissue, the pre-malignant cells reach a steady-state number N after the treatment. Let the average dose per fraction for the organ be denoted by d (Gy) and the number of fractions be K , so that the total integral dose is given by $D = Kd$.

We let n^- , m^- , n^+ and m^+ denote the number of normal and initiated cells just before a dose fraction and immediately after the dose fraction respectively. Suppose $k = 1, 2, \dots, K$, then the surviving fraction of cells due to dose d is given by (ignoring the quadratic term) (Sachs & Brenner, 2005):

$$S = e^{-\alpha d}, \quad (2.6)$$

where α (1/Gy) is the cellular radiobiological parameter.

The fraction of healthy cells that are not initiated as mutated cells is given by (Sachs & Brenner, 2005):

$$P = e^{-\gamma d}, \quad (2.7)$$

where γ (1/Gy) is the mutation induction parameter.

Therefore, the healthy and initiated cells that survive the k th dose fraction are (Sachs & Brenner, 2005)

$$n^+(k) = S P n^-(k), \quad m^+(k) = S [m^-(k) + (1 - P) n^-(k)]. \quad (2.8)$$

We assume that the repopulation mechanism of normal and pre-malignant cells during and after radiation to follow logistic growth kinetics, where λ and $r\lambda$ are the repopulation rates of normal cells and pre-malignant cells, respectively. Thus, the repopulation dynamics for healthy and initiated cells is given by (Sachs & Brenner, 2005):

$$n^-(k+1) = \frac{N}{1 - e^{-\lambda T} [1 - N/n^+(k)]}, \quad m^-(k+1) = m^+(k) \left[\frac{n^-(k+1)}{n^+(k)} \right]^r. \quad (2.9)$$

The number of initiated cells after the last dose, and until the normal cells cease to repopulate in the system, is given by (Sachs & Brenner, 2005):

$$M = m^+(k) \left[\frac{N}{n^+(k)} \right]^r. \quad (2.10)$$

The initial conditions to solve the above discrete set of equations (2.6–2.9) are $n^-(1) = N$ and $m^-(1) = 0$, from which we obtain the yield of pre-malignant cells at the end of the treatment (and until the proliferation of normal cells tend to reaches its steady state).

2.3 Parameters

The dependency of proton LET using V79 cells (*in vitro*) on the radiobiological parameters and on mutation frequency is discussed in this section. There are two models that are proposed in the literature to fit the radiobiological parameter with the LET, namely, non-linear and linear model (Wilkens & Oelfke, 2004; Chen & Ahmad, 2012). In the current study, we use a linear dependence for α on the LET as

FIG. 3. Linear radiosensitivity coefficient as a function of LET. Experimental data taken from Chen & Ahmad (2012). Solid line indicates linear fit using (2.11).

follows (Wilkins & Oelfke, 2004),

$$\alpha = \alpha_1 + \alpha_2 (\text{LET}), \quad (2.11)$$

where $\alpha_1 = 0.1$ (1/Gy) and $\alpha_2 = 0.02$ (Gy keV/μm)⁻¹ (Wilkins & Oelfke, 2004). Figure 3 displays the dependence of α on proton LET.

One of the most important biological end points to model second cancer risk is the radiation-induced mutation frequency. In a biological sense, mutation frequency is defined as the fraction of radiation-induced mutated cells within a given cell culture. And, mutation rate is defined as the rate at which mutations occur in a given time scale. In this article, we make a simplifying assumption that the mutation frequency is proportional to the mutation rate. Due to the availability of biological data on Chinese hamster V79 cells, we have used it in the current investigation. Several authors have investigated the effects of mono-energetic proton beams on Chinese hamster V79 cells on the mutation frequency (Belli *et al.*, 1989, 1992, 1998). Figure 4 shows the mutation frequency induced by protons for various 7, 11, 20 and 30.5 keV/μm dose-averaged LET values and for different doses. Hence, we used this available *in vitro* data for this specific cell line to emphasize the influence of proton LET on the TCP, relapse and second cancer risks (Belli *et al.*, 1989, 1992, 1998).

We then took various values of slope from Fig. 4 and plotted them as a function of LET, which is shown in Fig. 5.

The summary of parameters used in the mathematical model and their interpretations are presented in Table 1.

3. Results

To illustrate our mathematical framework on proton-induced TCP, relapse and second cancer risks, the case of HL, a haematopoietic malignancy primarily occurring in children will be considered. Clinically, this malignancy is treated with radiotherapy, and related second cancers in organs at risk have been reported in a number of survivors of this disease. Often, the irradiated lymph nodes in HL are those in the

FIG. 4. Linear fit of mutation frequency as a function of dose. Experimental data taken from [Belli *et al.*, 1989, 1992, 1998](#) and the solid line indicates linear fit.

FIG. 5. Mutation frequency as a function of LET using a linear fit.

infraclavicular chain, anatomically in close proximity to developing breast tissue, lung apices and thyroid tissue. Within this work, we mathematically model the risk of secondary malignancy in breast tissue. However, it should be noted that a similar analysis (with appropriate parameterization) could compute analogous values for lung and thyroid tissues, which is also an organ at risk in this case.

Parameter values used in this study are summarized below in Table 2. We have considered subclinical disease, i.e. intermediate (to small)-sized tumours in HL patients. The ratio α/β is chosen to be 10 ([Vlachaki & Kumar, 2010](#)). We have chosen the doubling time to be 75 days for a slow-growing tumour ([Tubiana, 1989](#)). Radiobiological parameter for protons was calculated using (2.11) with an LET = 8. In one of the previous works ([Manem *et al.*, 2014](#)), the authors have shown that the perturbation in the growth rate is insensitive to the TCP and relapse, due to higher cell killing in fractionation, giving an α equal to 0.26.

TABLE 1 *Summary of parameters and their interpretations used in the current study*

Parameters (units)	Interpretation
N_0	Initial number of tumour cells
α (1/Gy)	Radiobiological parameter in linear quadratic model
β (1/Gy ⁻²)	Radiobiological parameter in linear quadratic model
t_{dou} (days)	Doubling time of cancerous cells (pretreatment)
λ_1 (1/day)	Growth rate of cancer cells during treatment
λ_2 (1/day)	Growth rate of cancer cells post-treatment
λ (1/day)	Growth rate of normal cells (in healthy tissue)
r	Relative growth rate of pre-malignant cells in breast
γ (1/Gy)	Radiation-induced mutation induction rate
B (breast)	Proportionality factor for secondary breast cancer risk

TABLE 2 *Summary of parameters used in TCP and relapse framework*

Parameter	Value
N_0	10^6 cells
α	0.26/Gy (proton); 0.25/Gy (photon)
β	0.026/Gy ⁻² (proton); 0.025/Gy ⁻² (photon)
t_{dou}	75 days
λ_1	$\ln(2)/75 \text{ days}^{-1}$
λ_2	$\ln(2)/75 \text{ days}^{-1}$
λ	$\ln(2)/75 \text{ days}^{-1}$

One of the subtypes of HL is the nodular lymphocyte predominant HL (NLPHL), which is reported to be of slow-growing variants compared with the classical HL (Diehl *et al.*, 1999; Hawkes *et al.*, 2012). Clinically, it still remains unclear regarding the reasons for the slow progressiveness of the NLPHL. In addition, there are no biological data available for the doubling time of NLPHL tumour cells. In the literature, the mean doubling time for intermediate and slow-growing breast tumours has been calculated as around 26–75 days and 76 days or longer, respectively. Hence, in our current study, we have assumed 75 days as the tumour doubling time for these slow-growing variants of HL disease.

Within this work, in order to model the treatment of HL, two radiation schedules are considered, namely conventional and hypo-fractionation schedules of radiation, summarized in Table 3. These describe the clinical dose distribution of the administered radiation for both proton and photon-based therapy. It should be noted that as is done clinically, the modelled radiation schedule is administered 5 days/week, with weekends excluded and treatment beginning on a Monday. It is supposed that the treatment is administered at the same time every day.

3.1 TCP and relapse

The sensitivity analysis of tumour doubling time is presented in Fig. 6 for photon and proton radiation in the context of conventional and hypo-fractionation regimens. This is important to understand the influence

TABLE 3 *Summary of fractionation protocols*

Protocol	Fractionation scheme
Conventional regimen	30 Fractions
Hypo-fraction regimen	20 Fractions

FIG. 6. Sensitivity of TCP for photon therapy to doubling time, for the considered cases of α for proton and photon therapy, over different radiotherapy schedules. In both the cases, the α (photon) = 0.25, α (proton) = 0.26, $\alpha/\beta = 10$.

of fast- and slow-growing tumours on the tumour control probability for various fractionation protocols. To add further confidence to the presented data, we have included a plot below of the sensitivity of the TCP to changes in the doubling time for the clinically relevant parameters we consider in the article. We present below the TCP over a range of doubling times between 5 days and 100 days, encompassing a wide variety of possible doubling times. The contour plot displays the TCP for a given doubling time and dose. Figure 6 shows the relative insensitivity of the TCP to this parameter for this choice of clinically relevant parameters. Therefore, for slow-growing tumours with doubling time >70 days, such as the NPLHL, proton radiation is superior to photon radiation.

Model results depicting the tumour control probability for the parameters listed in Table 2 are shown in Fig. 7, which shows the comparative tumour control probabilities during radiotherapy for both conventional and hypo-fractionation treatment schedules, in the cases of both proton and photon therapy.

These results indicate that a hypo-fractionation treatment regimen produces a greater degree of tumour control, regardless of modality, as well as a reduced average time to recurrence, as summarized in Table 4. Moreover, comparing the results of the TCP for proton and photon therapy, it is evident that proton therapy

FIG. 7. Comparison of the tumour control probability for various schedules of photon and proton radiotherapy; $\alpha(\text{photon}) = 0.25$, $\alpha(\text{proton}) = 0.26$, $\alpha/\beta = 10$, and tumour doubling time = 75days in both cases.

TABLE 4 Average simulated relapse times for various schedules of photon and proton radiotherapy, for the case where $\alpha_{\text{photon}} = 0.25$, $\alpha_{\text{proton}} = 0.26$ and tumour doubling time is taken as 75 days

Schedule	Modality	Average time to relapse (days)
Conventional	Photon	~2671
	Proton	~3000
Hypo-fractionation	Photon	~2851
	Proton	~3194

produces, generally greater tumour control and a slightly earlier time to an equivalent photon tumour control, perhaps due to the 10% increased RBE of protons over photons.

3.2 Second cancer risks

The organs at risk in HL patients are breast, lung and thyroid tissues. As stated above, we study the impact of protons on secondary breast cancer risks, but analogous calculations for lung and thyroid specific parameters can be done. The mathematical formalism does not consider any specific treatment plan but only demonstrates the impact of LET in the proton therapy-induced second cancer risks. Table 5 presents the parameters used in this investigation.

The prediction of the mathematical framework has been done by Sachs and Brenner on the historical data of secondary breast and lung cancers for photons (Sachs & Brenner, 2005). In their study, mutation induction parameter was derived from the atomic bomb survivor studies. We have used the same parameter

TABLE 5 *Summary of parameters used in second cancer risk framework*

Parameters	Value	References
N	10^6	Sachs & Brenner (2005)
α	Using equation (13)	Sachs & Brenner (2005)
λ	0.4	Sachs & Brenner (2005)
r	0.76	Sachs & Brenner (2005)
γ	$\gamma_{pr} = \gamma_0 = 0.185 \times 0.1307 \mu\text{m} (\text{keV Gy})^{-1} \times \text{LET} \times 10^{-5}$	Experimental data
B (breast)	0.18	Sachs & Brenner (2005)

FIG. 8. Conventional regimen (30 fractions). Radiation-induced relative risk of breast tissue for varying values of LET.

set in evaluating proton therapy-induced second cancer risks, except for cell kill and mutation induction parameters. The clinical value of proton LET in the plateau region of the Bragg peak is around 1–3 (keV/μm) (Paganetti, 2014). We considered LET values of 1, 2 and 3 (keV/μm) to estimate ERR for breast tissue. Figures 8 and 9 present ERR for conventional and hypo-fractionation regimens in breast tissue, respectively.

In the low- and intermediate-dose region, mutation induction is dominated by the cell killing mechanism, and at higher doses, the cell killing mechanism dominates over the mutation induction. We notice that the relative risk approaches zero, indicating a reduction in cancer risk, which is due to cell overkill. Therefore, we have assumed the dose range of [0, 50] Gy (since, clinical doses do not exceed 50 Gy to healthy organs) and evaluated radiation-induced relative risk of breast cancer. Below are the plots for: (a) conventional and (b) hypo-fractionation protocols.

From Figs 8 and 9, it is evident that hypo-fractionation protocol reduces second cancer risks compared with a conventional regimen in a proton therapy setting. In addition, proton therapy-induced second cancer risks are lower compared with photon-induced risks (see Sachs & Brenner, 2005, fig. 3b). For example, when a patient is treated with a conventional regimen with an integral dose of 40 Gy, then the corresponding photon- and proton-induced second cancer risks are approximately 18

FIG. 9. Hypo-fractionation regimen (with 20 fractions). Radiation-induced relative risk of breast tissue for varying values of LET.

(see [Sachs & Brenner, 2005](#), fig. 3b) and 14.8 (for conventional protocol), respectively. Mutation induction and cell killing mechanisms dominate in different dose ranges. Our results also indicate that theoretically hypo-fractionation protocol seems a better regimen to reduce secondary cancer risks.

4. Discussion

Clinically, the results presented above suggest that for the parameter cases tested in HL, a conventional treatment protocol may be less effective theoretically than a hypo-fractionation protocol with regard to the level of tumour control obtained at the end of therapy, as well as the relapse rate in long-term follow-up. Interestingly, these results hold for both proton and photon therapy and are consistent with the work presented in [Manem *et al.* \(2014\)](#), where for photon therapies, a hypo-fractionation protocol was shown to be theoretically more efficacious. Furthermore, we note that with regard to the risk of secondary malignancy, hypo-fractionation protocol shows superior results, which is consistent with another study ([Schneider *et al.*, 2010](#)). However, we note that while theoretically and mathematically such results are shown as improved, it remains a clinical question as to whether these dosing schedules would truly be optimal or even tolerable in therapy. That is, we note for instance, in hypo-fractionation therapy, a greater dose per fraction is administered, perhaps increasing the rate of acute radiation-related side effects, such as skin erythema, mucositis or gastritis. With regard to photon therapy, although the dose would be more targeted, it is still possible that local inflammatory reactions may occur during treatment, leading to dose toxicity and an inability to tolerate a highly hypo-fractionation schedule of radiotherapy.

In spite of the limitations of assessing treatment protocol efficacies theoretically, we emphasize that the clinical significance of this work is the novel consideration of proton therapy as well as the simplified approach used within to compare treatment protocols and modalities. In particular, this work shows that for a clinically relevant parameter set, proton therapy is superior to photon therapy for a number of reasons. That is, regardless of the schedule of administration, it leads to a superior TCP because of its greater RBE, and because of its greater ability to be targeted to tissue, it has a minimal modelled risk for secondary malignancy. Further, quantifying this degree of improved treatment with the TCP suggests that equivalent tumour controls to photon therapy may be possible with reduced doses of radiation, along

with a reduced rate of induction of pre-malignant cells. This may lead to shorter, but still efficacious radiotherapy regimens, ultimately making these therapies more tolerable for patients.

We do note, however, that this model is not without its limitations. That is, we have shown in our previous work (Manem *et al.*, 2014) that the solution space of this system for clinically relevant parameters (which also holds in the case of proton therapy, with an increased effective dose) is quite stable. Thus, the results would remain consistent within some degree of inter-tumour and inter-patient variability, but for significantly different parameters or radiation schedules, these results may not hold. For this reason, we feel that the precise values of the parameter sets used are not of great importance in this work, but the overarching observation is that qualitatively, photon therapy is able to achieve greater tumour controls. This is because of its greater biological efficacy and significantly reduced risks of primary recurrence and secondary malignancy, as compared to proton therapy, and especially for a hypo-fractionation regimen. Lastly, we emphasize the importance of the theoretical framework highlighted in this work and in previous works (Manem *et al.*, 2014), which serve to highlight the theoretical interplay between the TCP and risk of recurrence, as well as the critical comparison between recurrence risk and secondary malignancy risk when planning radiotherapy, which can be modelled over long time scales.

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