# Temporally-Feathered Intensity Modulated Radiation Therapy: A technique to reduce normal tissue toxicity

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## Abstract

**Purpose/Objective:** We introduce a novel strategy of radiation therapy planning using canonical radiobiology principles and leveraging time to further decrease normal tissue complication probability (NTCP). Temporally feathered radiation therapy (TFRT) is presented as a strategy to reduce radiation-induced toxicity, and is compared with conventionally fractionated radiotherapy an *in silico* model of normal tissue radiation response.
**Material/Methods:** As a first choice to compare conventional and temporally feathered plans, we consider the biologically equivalent dose (BED), which is the most common model used to compare different fractionation schemes in radiotherapy. We formulated a mathematical model to simulate normal tissue radiation-induced damage and recovery induced by different fractionation regimens. This model considers tissue recovery as a dynamic process rather than a static probability. Radiation response is determined by the Linear-Quadratic (LQ) model, which is widely used in radiobiology.
**Results:** TFRT is shown to be beneficial in reducing radiation-induced toxicity to normal tissues compared to conventional treatment schedules. BED is not suitable to evaluate the success potential of TFRT because of its static nature in time, the proposed dynamical NTCP model however, demonstrates that there exists a window of opportunity for temporally feathering organs at risk whereby toxicity can be reduced without affecting tumor dosing. The high and low fractional doses delivered by temporally feathered plans to organs at risk allow increased damage recovery despite higher total doses compared to standard plans. The clinical benefit of temporally feathered plans not only depends on the combination of fractional doses considered, but also on the organ-specific recovery rate of radiation damage. In particular, we found that when comparing temporally feathered and standard plans, for each recovery rate a certain range of standard fractional doses exists in which TFRT reduces toxicity. Although the potential benefit of TFRT over conventionally fractionated radiotherapy is always higher in those ranges, there exists an optimal standard fractional dose in which toxicity induced by the temporally feathered plan is minimum.
**Conclusions:** Our novel TFRT methodology opens a yet unexplored avenue for planning optimization in radiotherapy. Application of this technique to carefully selected cases will not only potentially allow reduction in normal tissue toxicity, but also allow dose escalation to the tumor thereby enhancing the therapeutic ratio.

## Introduction

Currently, it is estimated that about half of cancer patients benefit from curative or palliative radiation therapy at some point during the course of their disease[1]. Its use has continued to grow in popularity with the growing understanding of radiation planning, delivery and effects. Historically, the delivery of therapeutic radiotherapy has been limited by the ratio of tumor control probability (TCP):normal tissue complication probability (NTCP) ratio, termed the therapeutic ratio[2]. Research efforts have been directed at maximizing tumor control while minimizing damage to local normal tissue by way of improving physical dose distributions, and optimizing radiation dose and fractionation schema[3]. Physical dose distribution has been improved with the evolution from 2D to 3D conformal planning and now intensity modulated radiation therapy (IMRT)[4–6]. Preferential tumor kill has been attempted with radiosensitizers and optimizing oxygen distribution[7] and normal tissue sparing has been explored

using radioprotectants[8,9], but are not in routine clinical use, and carry the risk of side effects. Various dose and fractionation schemes have been clinically studied including conventional fractionation, hyperfractionation, accelerated hyperfractionation, hypofractionation, and stereotactic body radiation therapy/stereotactic radiosurgery[10–12], each of which offers benefit to tumor control in specific clinical scenarios. The efficacy of various fractionation schedules have been optimized according the tumor's inherent radiosensitvity (i.e. $\alpha/\beta$ ratio to be discussed below), and more recently, genomic methods have been postulated[13]. In current practice, fractionated radiation therapy with 1.8 to 2.0 Gy per fraction, remains standard for the majority of cases.

Through these advancements in radiation oncology, the four pillars of radiobiology have remained the foundation to our understanding of radiation effect on tissue: (1) repair of sublethal damage, (2) reassortment of cells within the cell cycle, (3) repopulation, and (4) reoxygenation. Repair is the main contributor to reducing acute normal tissue toxicity. This provides the rationale for fractionated radiotherapy in which a consistent low dose of radiotherapy is delivered on a daily basis allowing time for normal tissue recovery between fractions. The cumulative dose of radiotherapy ultimately delivered to the tumor achieves clinical outcomes[14]. The concept of daily fractionation has been optimized for logistical delivery of radiation therapy in the clinic setting to accumulate radiation-induced damage in cancer cells whilst allowing for sufficient time for sublethal damage recovery in normal tissues. Clinically, acute toxicities often still manifest mid-way or toward the end of most treatment courses, and chronic, or late effects, are common and contribute to the morbidity of cancer therapy. This proves that sublethal repair is not complete with an inter-fraction interval of 24 hours. Furthermore, repopulation of normal tissue following peak acute toxicity can take weeks to months. Historically, late toxicities have been deemed to be more dependent on fractional dose of radiation whereas early toxicities have been proven to be sensitive to changes in the fractional dose as well as time over which radiation is delivered[14]. Both acute and late toxicities can be dose-limiting when considering radiation planned to be delivered to the target. Often acute toxicities are reversible, however dose-limiting acute toxicities may impede patients from undergoing the full prescribed course of radiotherapy and in this way compromise tumor control. In particular, treating head and neck malignancies have been challenging for acute toxicities[15]. Late toxicities are often irreversible, and stem from permanent radiation-induced damage. The goal of this study is to introduce an innovative treatment planning strategy using basic radiobiology principles by leveraging time to further decrease toxicity without compromising tumor control.

Present day IMRT treatment algorithms produce fractionated radiotherapy plans to deliver a consistent fractional dose of radiation to the target. Surrounding organs at risk also receive a constant dose of radiation, which have been optimized based on the many evidence-based constraints[2,16], and carefully computed beam angles shapes. However these fractional doses delivered to normal tissue are often sufficient to produce truly sublethal damage - and even clinically dose-limiting toxicity, especially in cases with suboptimal anatomy or large primary tumors. We propose a novel technique to treatment planning in which dose to tumor is unchanged, but the delivery to organs at risk (OARs) is temporally 'feathered' to allow for normal tissue repair. We discuss a dynamic NTCP model that simulates the recovery of an OAR, and use the temporally feathered technique to improve radiation therapy outcomes.

## Methods

### Temporally Feathered Radiotherapy

Fractionated radiotherapy provides relative sparing of normal tissue despite consistent tumor cell kill. This is in part due to repair of sublethal damage and repopulation of normal cells. To reduce toxicity of normal tissue, we present a novel treatment planning algorithm referred to as temporally feathered radiotherapy (TFRT). The daily fractional dose of radiation delivered to organs at risk is altered to allow for increased normal tissue recovery by way of repair and repopulation. Let us denote normal tissue recovery by $\mu$ (day$^{-1}$), which is an organ-specific parameter.

A TFRT plan is generated as a composite of several iso-curative (same tumor dose) plans each with altered constraints on particular OARs of interest. In each of these plans, a single OAR is deprioritized, allowing the optimization algorithm to reduce dose and thereby toxicity to all other OARs. In practice, consider a target volume with 5 surrounding OARs of interest prescribed a dose of 70 Gy in 35 fractions, similar to that commonly implemented in treating head and neck cancers. Consider that 5 plans are developed, wherein each of the 5 OARs receives a relatively high fractional dose ($d_H$) compared to the conventional fractional dose ($d_S$) once weekly, i.e. 2.0Gy. A relatively lower ($d_L$) fractional dose is then delivered the remaining 4 days of the week (Figure 1). With this, though greater sublethal damage is induced by $d_H$, it is offset by the lower fractional dose, $d_L$, delivered over a greater amount of time during the remaining 4 days. We compare the composite of $d_H$ and $d_L$ to the corresponding standard fractional dose $d_S$ delivered to each OAR in a conventional radiotherapy plan. In this example case, a TFRT plan composed of 35 fractions, the OAR of interest will receive 28 fractions of $d_L < d_S$ and 7 fractions of $d_H > d_S$. For demonstrative purpose we focus analysis to a single OAR of 5 considered, however TFRT could be applicable to any number of OARs simultaneously (Figure 1).

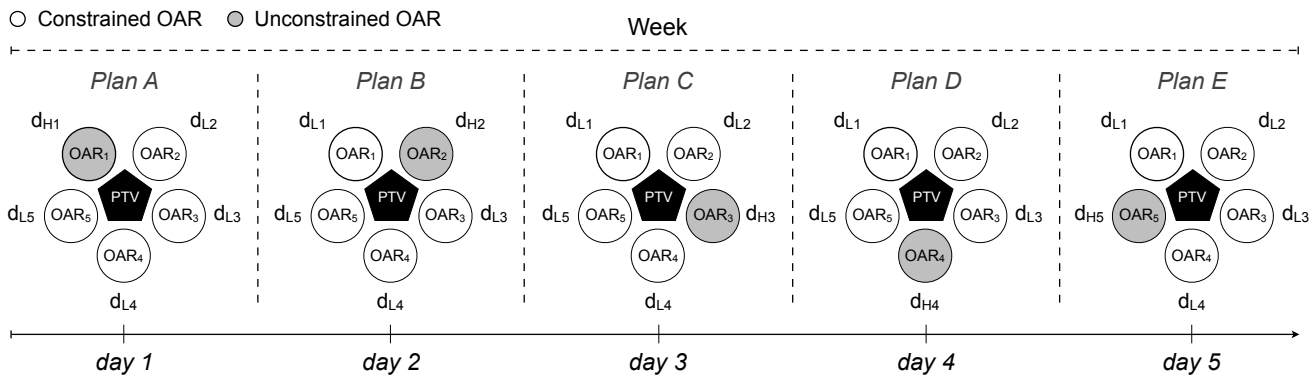


**Figure 1.** Schematic representation of temporally feathered radiation therapy (TFRT), in which the planning target volume (PTV) is in close proximity to 5 OARs. Each OAR $i$ receives a higher fractional dose once weekly, $d_{H_i}$, followed by lower fractional doses for the remaining four fractions, $d_{L_i}$. $1 \leq i \leq 5$. The PTV is represented as a black pentagon, and surrounding OARs are represented by circles. White: constrained OAR; Gray: unconstrained OAR.

## Biologically Effective Dose (BED) Model

The current mathematical model fit to observed *in vitro* cell survival experiments allows modeling of surviving fraction following exposure to radiation. This model incorporates the linear-quadratic behavior of observed cell survival curves[17]. The linear behavior describes direct cell kill whereas the quadratic model describes indirect kill[14]. The surviving fraction (SF) of cells after $n$ fractions of a radiation dose $d$ is given by

$$\mathrm{SF(d)} = e^{-nd(\alpha+\beta d)} \tag{1}$$

where $\alpha\left(\mathrm{Gy}^{-1}\right)$ and $\beta\left(\mathrm{Gy}^{-2}\right)$ are tissue-dependent radiosensitivity parameters. It follows directly from the LQ-model that the biological effect ($E$) of $n$ equally sized fractions of dose $d$ is given by $E = nd(\alpha+\beta d)$. This equation can be manipulated to derive biologically effective dose (BED) calculations, which is a standard quantity which allows comparison of various fractionation schemes. BED is dependent on inherent biologic radiosensitivity of tissues, which is termed as the $\alpha$ to $\beta$ ratio, $\alpha/\beta$. This is also borrowed from the linear-quadratic (LQ) model[18,19]. The biologically effective dose [20] is given by

$$\mathrm{BED} = nd\left[1+\frac{d}{\alpha/\beta}\right]. \tag{2}$$

The BED equation above applies to conventional radiation plans in which a constant fractional dose is delivered daily. The BED for a standard constant daily fraction $\mathrm{BED_S}$ is

$$\mathrm{BED_S} = n_S\, d_S\left[1+\frac{d_S}{\alpha/\beta}\right]. \tag{3}$$

The BED of temporally feathered plans $\mathrm{BED_{TF}}$ is defined as

$$\mathrm{BED_{TF}} = n_L\, d_L\left[1+\tfrac{d_L}{\alpha/\beta}\right] + n_H\, d_H\left[1+\tfrac{d_H}{\alpha/\beta}\right], \tag{4}$$

where $n_S$ is the number of fractions and $d_S$ is the radiation dose per fraction delivered in a conventional fractionation. In temporally feathered plans, $n_L$ and $n_H$ refer to the number of lower dose fractions and number of higher dose fractions respectively. Lower dose fractions deliver a dose less than what would be delivered in a conventional plan, low dose $d_L < d_S$ and similarly higher dose fractions deliver a dose higher than the fractional dose of conventional plans, $d_H > d_S$. We consider that doses $d_L$ and $d_H$ remains unaltered during the treatment, and for this initial treatment, we consider dose to each structure to be homogeneous. Importantly, the total number of fractions and their time of delivery remains the same in conventional and temporally feathered plans, i.e. $n_S = n_L + n_H$, and we are not changing tumor dose, only dose to OARs. The difference in the BED of a temporally feathered plan compared to a conventional plan is defined as $\Delta\mathrm{BED} = \mathrm{BED_S} - \mathrm{BED_{TF}}$.

### Dynamic NTCP Modeling

Given that temporally feathered plans allow more time for repair of normal tissue following a higher dose $d_H$, we use a non-spatial dynamic model to simulate normal tissue response to radiation. This is a form of normal tissue complication probability modeling (NTCP), which are quantitative measures for the expected negative side effects on healthy tissue[21–25]. The model is formulated as a logistic differential equation that describes the recovery of normal tissues $(N)$ from sublethal radiation damage given by

$$\frac{dN}{dt} = \mu\, N(t)\,(1-N(t)) - \delta(t_i)\ \mathrm{RT(d)}\ N(t)\,(1-N(t)), \tag{5}$$

where $\mu > 0$ is the recovery rate of normal tissues. Let us consider the case that before radiation, the OAR is at tissue homeostasis with a 1% turnover rate, $N(0) = 0.99$. Then $N(t) < N(0)$ represents the level of normal tissue damage by radiotherapy (small values of $N(t)$ relate to severe damage), and $(N(0) - N(t))$ is used as an indication of the radiation-induced toxicity. Further, we denote by $\Delta$NTCP as the difference between the degrees of normal tissue toxicity (radiation damage) induced by a standard $N_{\mathrm{S}}(t)$ and a temporally feathered $N_{\mathrm{TF}}(t)$ plan at the end of treatment. This means that positive values $\Delta\,\mathrm{NTCP} > 0$ favor temporally feathered over standard fractionated plans.

The effect of radiation is included by the loss term $\delta(t_i)\,\mathrm{RT(d)}$ in equation (5), where $\delta(t_i)$ is a characteristic function equal to 1 at the time of irradiation $t_i$, and zero in other case. The function $\mathrm{RT(t)} = \left(1 - e^{-\alpha d - \beta d^2}\right)$ is based on the radiobiological LQ model in equation (1). More precisely, RT(d) represents the effect of a fractional dose $d$ on the normal cell population. We assume that both the delivery of each fraction and response to radiation are instantaneous. It should be noted that similar models have been previously proposed to simulate the effect of radiation on brain[26] and lung tumors[27], as well as to define an organ specific normal tissue complication probability model[28].

## Results

### BED Model Simulations

We simulate BED delivered to normal tissues for temporally feathered and conventional treatment schedules under varying conditions. Comparisons between TFRT plans and standard fractionation protocols delivering the same dose every fraction are made using equations (3) and (4). Figure 2 illustrates the differences in the BED between conventional plans and temporally feathered plans, defined as $\Delta\,\mathrm{BED} = (\mathrm{BED_S} - \mathrm{BED_{TF}})$. This simulation is conducted for tissues with presumed $\alpha/\beta = 3$ Gy, and represents 35 total fractions (28 $n_L$ with a low dose $d_L < d_S$ and 7 $n_H$ with a high dose $d_H > d_S$ in TF plans). Irrespective of $d_S$, temporally feathered plans only result in a lower BED when the total dose delivered to the OAR $(28d_L + 7d_H)$ is less compared to the standard plan $(35d_S)$. Further, there exists also combinations of $d_L$ and $d_H$ that result in $\mathrm{BED_{TF}} > \mathrm{BED_S}$ even when the total dose by TFRT plans is smaller than in the standard plan. These results hold irrespective of the $\alpha/\beta$ ratio characterizing the OAR of interest (see the supporting Figure 1). Thus, due to the fact that the BED formulation does not consider the effect of inter-fractional normal tissue repair of radiation damage, we demonstrate that this is not a suitable model

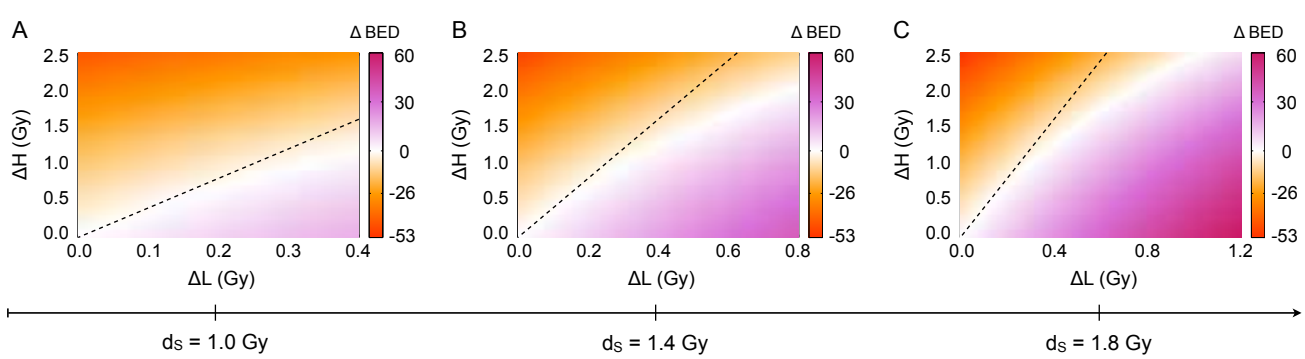


**Figure 2. BED model simulations comparing conventional and temporally feathered treatment plans.** Change in the BED is determined by $\Delta\,\mathrm{BED} = \mathrm{BED_S} - \mathrm{BED_{TF}}$. **(A-C)** From *left to right* representations of BED delivered to OAR depending on various $d_S$ per fraction delivered to OAR. The x- and y-axes represent $\Delta L = d_S - d_L$ and $\Delta H = d_H - d_S$ respectively. Each combination of doses $d_L$ and $d_H$ remains unaltered during the treatment. The dashed line shows the plot at which the total dose of the temporally feathered and conventional plans are equal $(\Delta H = 4\Delta L)$. The region below (above) the dashed line represents combinations of $d_L$ and $d_H$ in which TF plans deliver lower (higher) total doses compared to a conventional plan, keeping $d_S$ constant.

to evaluate the potential benefit of temporal feathering with respect to conventional fractionation. This highlights the need for models considering the dynamic of tissue repair between treatment fractions to assess the success potential of TFRT.

## Dynamic NTCP Model Simulations

We simulate normal tissue complication probability of TFRT schedules compared to conventionally planned fractionated radiation therapy. For that purpose, we use the dynamic model of normal tissue response to radiotherapy in equation (5). In this model, the normal tissue recovery rate is determined by an organ-dependent parameter $\mu$, and radiation cell kill described by the linear-quadratic (LQ) model in equation (1). Proof of principle exists in the particular case investigated as follows. We consider a conventionally fractionated plan delivering $d_S$ for 35 fractions and TFRT plans consisting of 28 fractions of $d_L < d_S$ and 7 fractions of $d_H > d_S$. Further, we consider an OAR of interest at a physiologic equilibrium and characterized by a $\alpha/\beta$ ratio of 3 Gy (simulations for varying $\alpha/\beta$ ratios is available in the supplementary material).

Simulations conducted using the dynamic NTCP model reveal a range of conditions in which TFRT plans reduce radiation-induced toxicity to OARs compared to conventionally fractionated plans. These conditions are dependent on $d_L$ and $d_H$, as well as organ-specific recovery rates, $\mu$, associated with radiation damage. This is demonstrated in Figure 3 and Figure 4, which illustrate the difference between standard and temporally feathered plans ($\Delta$NTCP) with varying values of $\mu$. For each $\mu$ the bottom panels represents $\Delta$NTCP resulting from a standard plan with a constant daily dose $d_S$, and combinations of $d_L$ and $d_H$ in TFRT plans varying in the ranges $[d_S - 0.5, d_S]$ and $[d_S, d_S + 2.5]$ respectively. We found that certain combinations of $d_L$ and $d_H$ may deliver higher total doses in TFRT plans as compared to conventional plans $(28 \cdot d_L + 7 \cdot d_H > 35 \cdot d_S)$ but yet still reduce the overall OAR toxicity at the end of treatment. This is depicted by the region above the dashed line (*red*: $\Delta$NTCP $> 0$) in the bottom panels of Figure 3. This particular scenario emphasizes the opportunity of reducing OAR toxicity using TFRT despite increased total dose to the OAR, and also suggests technical feasibility.

A first important finding is that the therapeutic gain by TFRT increases as the treatment progresses. This is shown in the top plots of Figures 3 and 4, where, irrespective of the values of $\mu$ and standard doses $d_S$ considered, the difference in the radiation induced damage by standard and TFRT plans progressively increases with increasing number of treatment fractions. Figure 3 illustrates the utility of TFRT in reducing toxicity in OARs with low recovery rates ($\mu$) when compared to conventionally

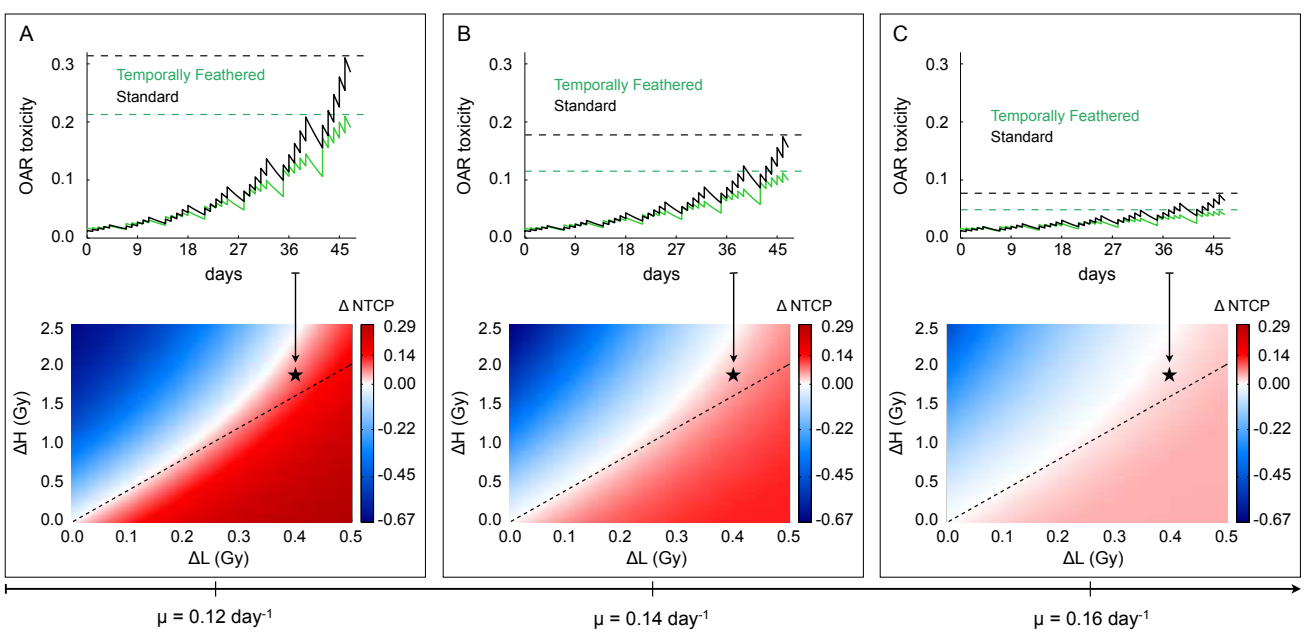


**Figure 3. Comparison and representation of NTCP and OAR toxicity of conventional and TFRT plans with varying recovery rates.** NTCP modeling follows equation (5) and is simulated for OAR $\alpha/\beta = 3$ Gy. The x- and y-axes represent $\Delta L = d_S - d_L$ and $\Delta H = d_H - d_S$ respectively. Each combination of doses $d_L$ and $d_H$ remains unaltered during the treatment. **(A-C)** Bottom panels from *left* to *right* $\Delta$NTCP are obtained for increasing recovery rates, $\mu$, under conditions of $d_S = 1.2$ Gy, $n_L = 28$ and $n_H = 7$. The dashed line shows the plot at which the total dose of the temporally feathered and conventional plans are equal. The region below (above) the dashed line represents combinations of $d_L$ and $d_H$ in which TFRT plans deliver lower (higher) total doses compared to a conventional plan, keeping $d_S$ constant. Top sub-figures show the time-evolution of OAR toxicity induced by the conventional (*black*) and TFRT (*green*) plans corresponding to the location marked by stars in bottom panels. Dashed lines represent the time points at which NTCP of standard and TFRT plans are compared.

fractionated plans delivering $d_S = 1.2$ Gy per fraction. Furthermore, reduction in OAR toxicity by TFRT plans is greater when compared to standard fractionation protocols delivering higher doses $d_S$ to the OAR of interest with $\mu = 0.15$ day$^{-1}$, as shown in Figure 4. However, previous results strongly depend on the particular combination of $\mu$ and $d_S$ where a close relationship exists. More precisely, there exist optimal success potentials and maximum benefits that can be achieved with TFRT as $d_S$ or $\mu$ change. While keeping constant any of those parameters and varying the other, we found that the potential benefit of TFRT increases until a maximum value and then decreases again.

To better assess the potential benefits of TFRT as a method of normal tissue toxicity reduction, Figure 5 summarizes how normal tissue and treatment parameters impact success potential of TFRT. For each combination of $\mu$ and $d_S$ we calculate $\Delta$NTCP of the standard plan delivering $d_S$ and the temporally feathered plan with $(d_S - 0.5) \leq d_L \leq d_S$ and $d_S \leq d_H \leq (d_S + 2.5)$. Figure 5(A) summarizes the overall success potential of TFRT plans compared to conventional fractionated radiotherapy, referred to as $\mathrm{OPB_{TF}}$, and obtained as the ratio of temporally feathered plans resulting in ($\Delta$NTCP $> 0$) and delivering higher total doses $(28d_L + 7d_H > 35d_S)$ than the corresponding standard plan to all simulated plans. The maximum success potential of a temporally feathered plan, referred as $\mathrm{MAX_{TF}}$, is shown in Figure 5(B). $\mathrm{MAX_{TF}}$ is obtained as the maximum $\Delta$NTCP $> 0$ of TF plans delivering higher total doses than the corresponding standard plan.

Considering the entire parameter space reveals the limits of TFRT benefit, and also gives us an opportunity to use retrospective data to parameterize individual OAR $\mu$, and to appropriate select patients in the future. We leave this to future work however. Supplementary Figures 2 and 3 show that $\mathrm{OPB_{TF}}$ and $\mathrm{MAX_{TF}}$ also depend on the specific $\alpha/\beta$ ratio of the OAR. However, TFRT continues to be a possible, valuable alternative to reduce radiation induced OAR damage.

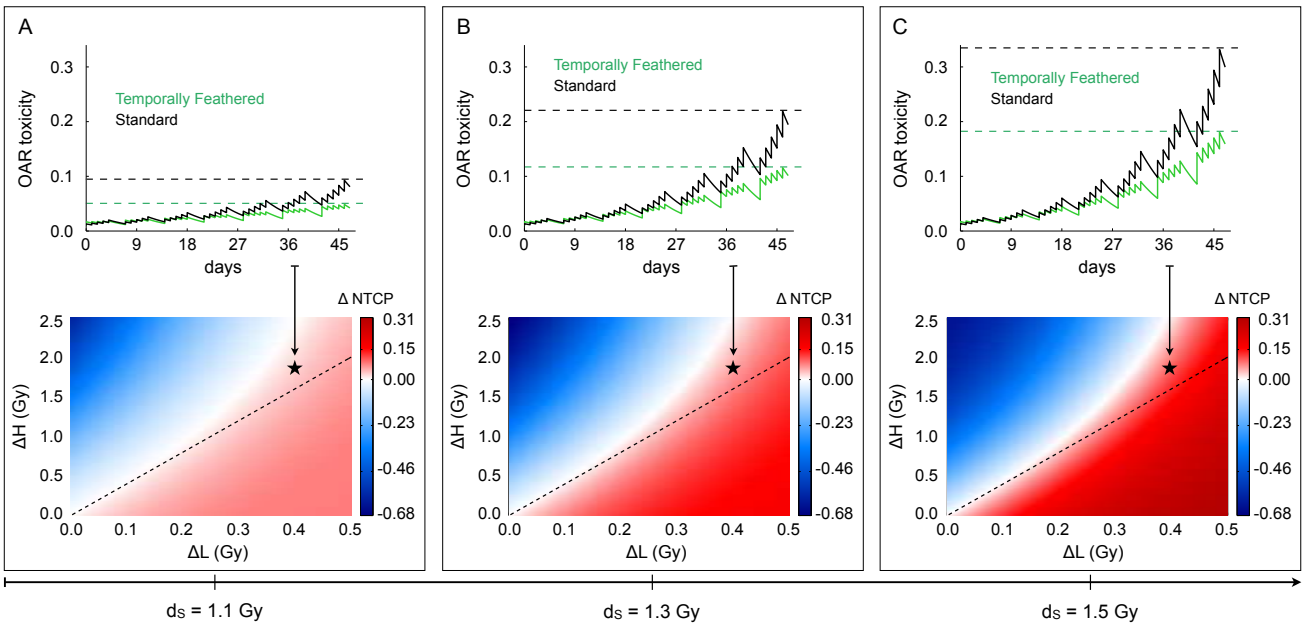


**Figure 4. Comparison and representation of NTCP and OAR toxicity of conventional and TFRT plans with varying standard fractional dose.** NTCP modeling follows equation (5) and is simulated for OAR late toxicity ($\alpha/\beta = 3$ Gy). The x- and y-axes represent $\Delta L = d_S - d_L$ and $\Delta H = d_H - d_S$ respectively. Each combination of doses $d_L$ and $d_H$ remains unaltered during the treatment. **(A-C)** Bottom panels from *left* to *right* $\Delta$NTCP are obtained for increasing standard fractional doses, $d_S$, under conditions of $\mu = 0.15$ day$^{-1}$, $n_L = 28$ and $n_H = 7$. Top sub-figures show the time-evolution of OAR toxicity induced by the conventional (*black*) and temporally feathered (*green*) plans corresponding to the location marked by stars in bottom panels. Dashed lines represent the time points at which NTCP of standard and TFRT plans are compared.

## Discussion

Radiation therapy is delivered within the therapeutic ratio at which tumor control probability is balanced against normal tissue toxicity. Through the years, researchers in the field of radiation oncology and medical physics have been innovating new ways of widening this therapeutic window by either increasing tumor control probability or decreasing normal tissue complication probability. In this paper, we focus on the latter. We introduce TFRT as a new concept that alters fractional doses of radiation delivered to organs at risk to maximize normal tissue recovery through the course of radiotherapy. For this purpose, we have

then used a dynamic NTCP model which accounts for normal tissue recovery. The basis of this treatment planning technique is capitalizing on the non-linearity of normal tissue recovery - allowing non-intuitively for more sublethal damage repair and repopulation even in the face of higher total dose. In this process, tumor control probability remains unchanged as equal doses of radiation are delivered to the target. Clinically, reducing OAR toxicity would $(i)$ improve the quality of life issues for patients that are dealing with both acute and late complications of radiation-induced toxicity, and $(ii)$ could enable dose escalation to the tumor for patients currently failing radiation.

We have also provided "success potential" maps to help gauge the potential of TFRT plans in reducing toxicity as compared to conventional radiation plans (see Figure 5 and Supplementary Figures 2 and 3). Success potential is dependent on recovery rates of OAR of interest and dose/fractionation delivered to OAR. It is important to note that this technique has the most potential to reduce toxicity in carefully selected patients whereas the gain might not be substantial for all comers treated with IMRT. The ideal patient is likely to be one where traditionally achieved doses to OARs are near their tolerance and recovery rates are average to low. Regardless of the inherent radiosensitivity of the normal tissue (i.e. $\alpha/\beta$ ratio), TFRT plans can be a superior treatment choice (see Supplementary Figures 2 and 3). Future work will be focused on studying individual dosimetric plans, comparing standard IMRT versus TFRT, creating an optimized work flow for temporally feathered plan and eventually

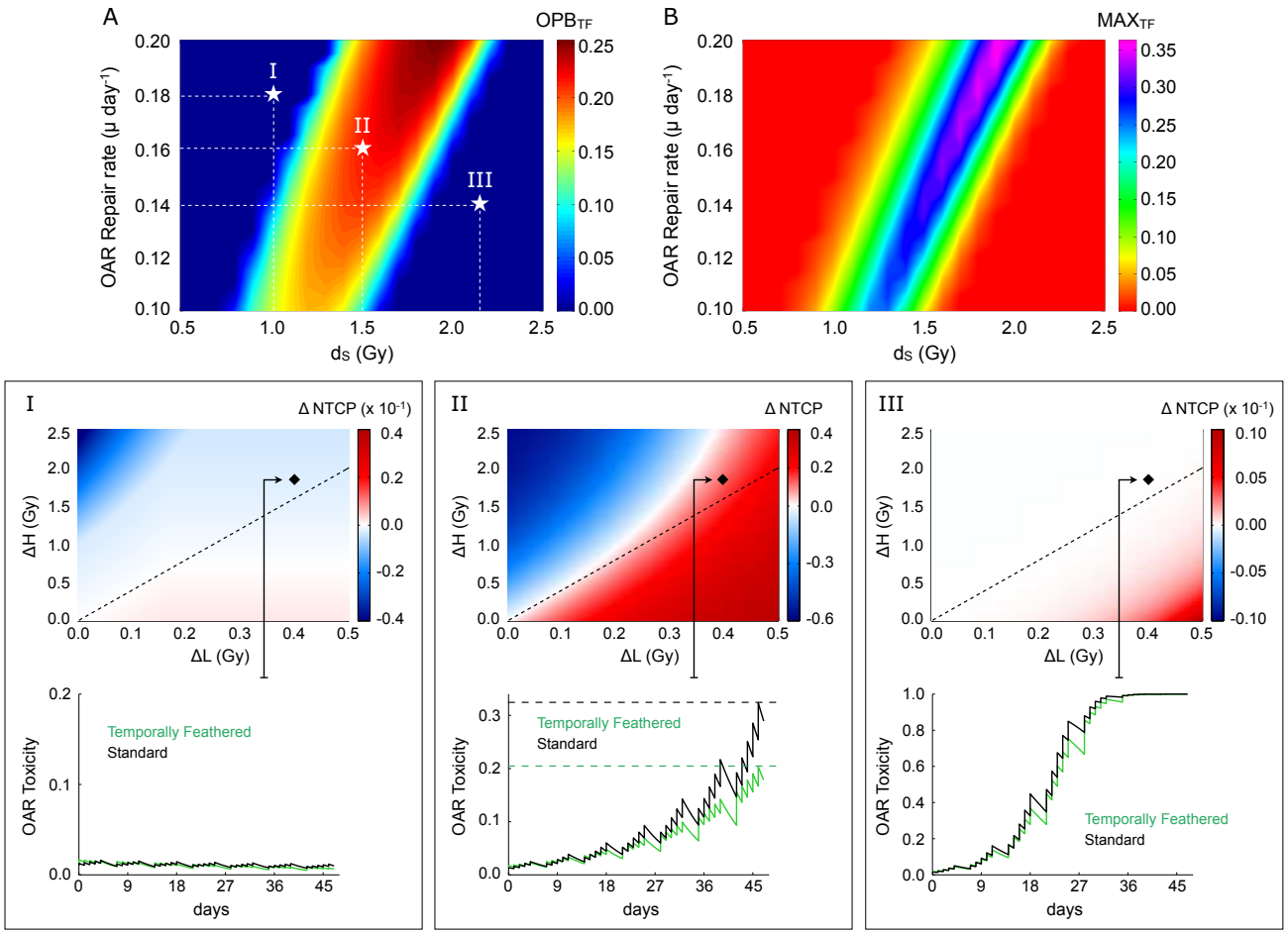


**Figure 5. Overall potential benefit of TF plans over conventional fractionated radiotherapy with respect to the standard fractional dose $d_S$ and OAR repair rate $\mu$.** Parameters $\alpha/\beta = 3$ Gy, $n_L = 28$ and $n_H = 7$ were considered. For each combination of $\mu$ and $d_S$, $\Delta$NTCP values are obtained as a result of comparing a standard plan delivering $d_S$ per fraction, and TFRT plans with $(d_S - 0.5) \leq d_L \leq d_S$ and $d_S \leq d_H \leq (d_S + 2.5)$. Each combination of doses $d_L$ and $d_H$ remains unaltered during the treatment. **(A)** OPB$_{\mathrm{TF}}$ is defined as the ratio of TFRT plans resulting in $\Delta$NTCP $> 0$ and delivering higher total doses than the corresponding standard plan to all simulated plans. **(B)** Maximum benefit (MAX$_{\mathrm{TF}}$) that can be achieved from the TFRT plans resulting in $\Delta$NTCP $> 0$ and delivering higher total doses than the corresponding standard plan. Top panels in *I*, *II* and *III* represent the single cases marked by stars in (A). The x- and y-axes represent $\Delta L = d_S - d_L$ and $\Delta H = d_H - d_S$ respectively. Bottom sub-figures show time-evolution of OAR toxicity induced by the conventional (*black*) and TFRT (*green*) plans corresponding to the location marked by diamonds in the top panels.

translating the lessons learned to the clinic as a phase I feasibility study. An automated planning algorithms could be generated with input factors for dose/fractionation delivered to OAR and recovery rates $\mu$ for OAR of interest. Additionally, efforts will need to be directed toward elucidating recovery rates of normal tissues. Based on radiobiological properties of the OARs involved, the introduced TFRT technique has the potential to inform us about the optimal sparing frequency and combinations of OARs to be considered on each daily treatment plan, as well as how many plans are required for individual radiotherapy patients. These models can be fit to clinical toxicity data to create a definition of $\mu$.

The next steps beyond TFRT dose is its combination with spatial information. With the evolution of developing radiation dose constraints, focus has been redirected away from looking at organs in their entirely, and instead moreso as partial volumes. Gradiations of dose across the normal tissue of interest has been emphasized[29]. We hope to use data points beyond simple dose volume histogram data in predicting the risk of toxicity does not take into consideration spatial, anatomic, or biologic effects of where dose is actually distributed. Dividing OAR into sub-volumes may better estimate and characterize the toxicity induced by each treatment plan.

## Conclusions

Our current understanding of BED does not account for normal tissue recovery. However, our basic radiobiologic principles predict a degree of normal tissue recovery between fractional doses of radiation delivered. We propose a new technique of altering fractional doses of radiation delivered to normal tissues, termed temporally-feathered radiation therapy (TFRT). Normal tissue complication probability can be predicted by a mathematical model that incorporates a radiation damage recovery term, $\mu$. Reduction of normal tissue complication probability is clinically valuable in reducing radiation-induced toxicity. Furthermore, isotoxic radiation doses can be determined as an avenue for radiation dose escalation to the target. TFRT plans can be easily implemented in present day clinics given our current treatment planning algorithms. Efforts will be directed towards creating more streamlined approaches to plan generation.

## Acknowledgements

J. C. L. Alfonso gratefully acknowledges the funding support of the German Federal Ministry of Education and Research (BMBF) for the eMED project SYSIMIT (01ZX1308D). J. G. Scott thanks the NIH Loan repayment program for their generous support of his research.

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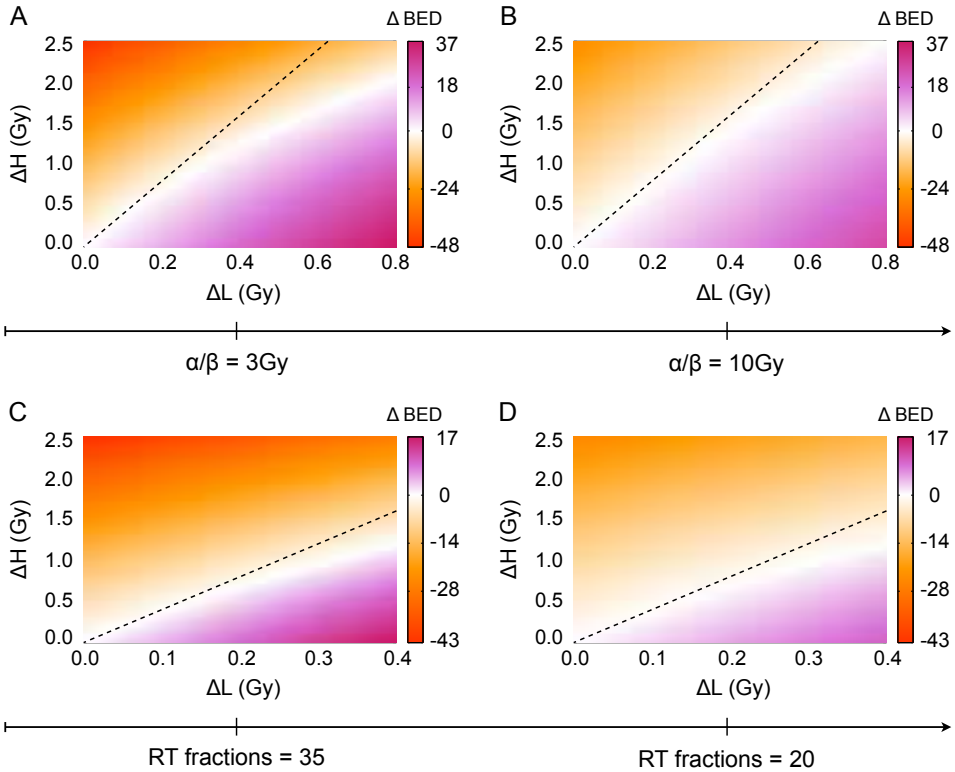
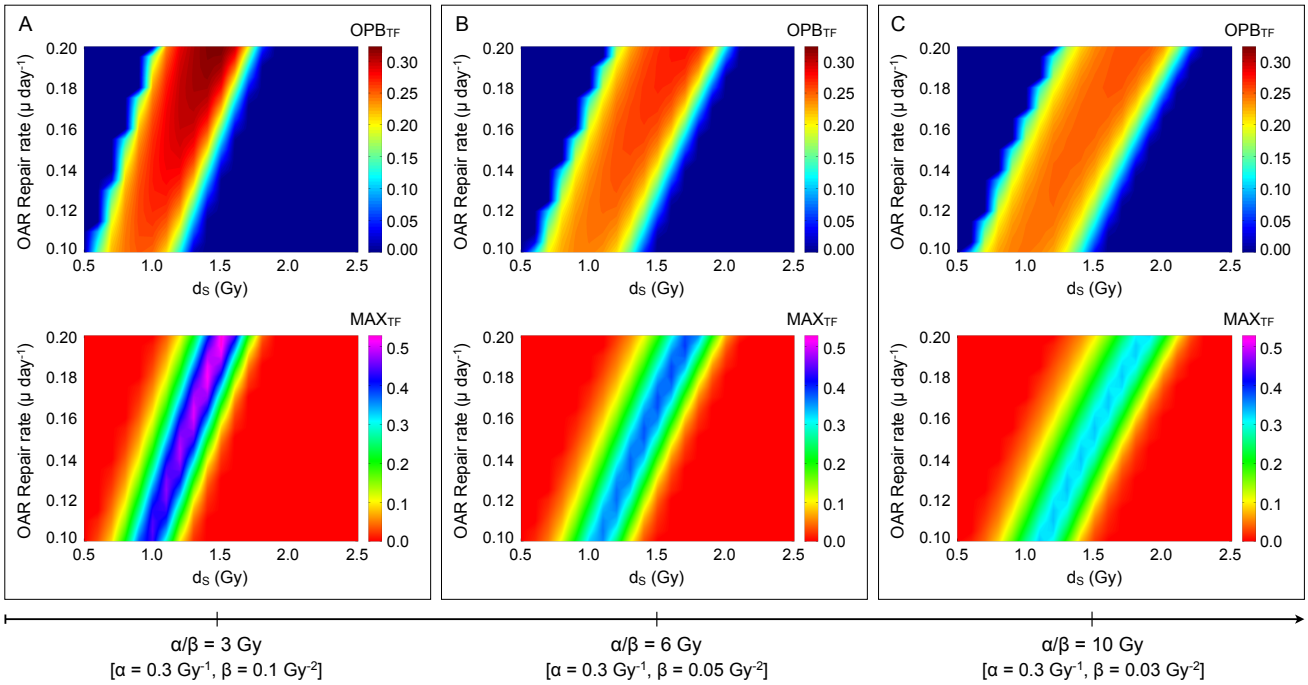
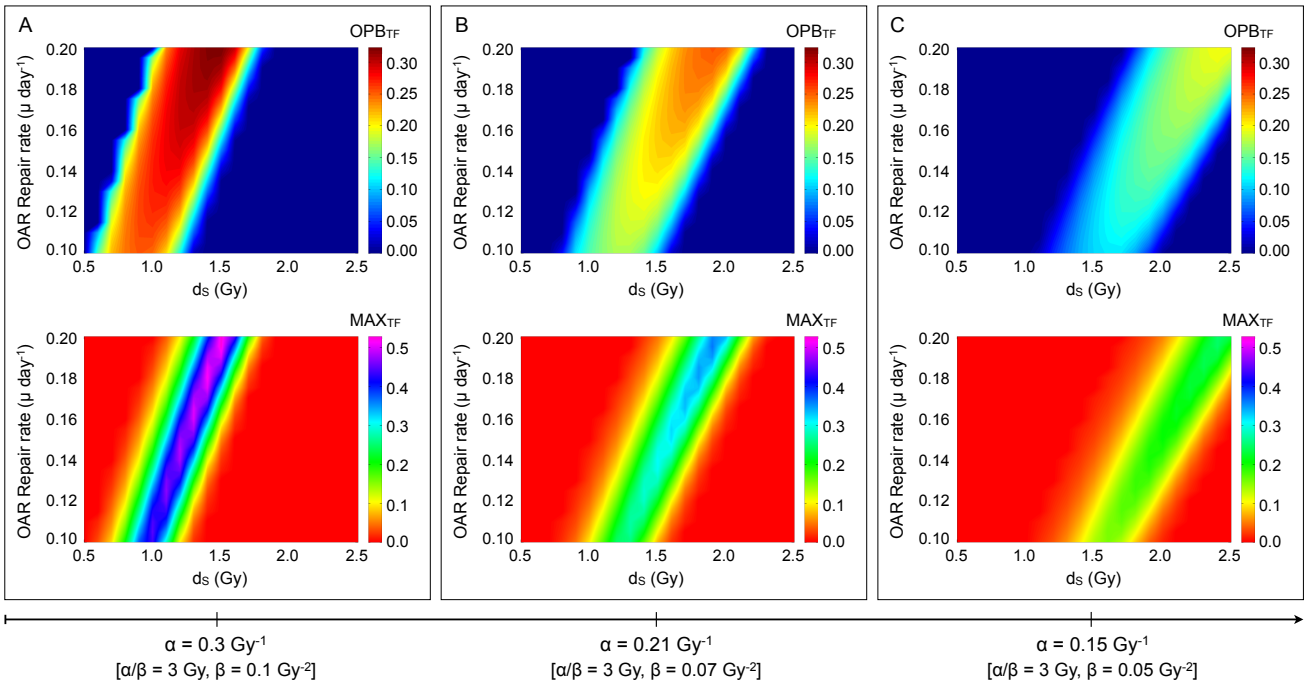
## Supporting Material




**Supporting Figure 1. BED model simulations with comparison of conventional and temporally feathered treatment plans.** Change in the BED is determined by $\Delta\,\mathrm{BED} = (\mathrm{BED_S} - \mathrm{BED_{TF}})$. **(A,B)** representations of BED delivered to OAR depending on various $\alpha/\beta$ rations. In this case, a standard fractionation protocol delivering a dose $d_S = 1.4$ Gy in 35 fractions (28 fractions of $d_L < d_S$ and 7 fractions of $d_H > d_S$ in TF plans). **(C,D)** representations of BED delivered to OAR with $\alpha/\beta = 3$ Gy for different standard fractionation protocols delivering a dose $d_S = 1.0$ Gy in 20 fractions (16 fractions of $d_L < d_S$ and 4 fractions of $d_H > d_S$ in TF plans) and 35 fractions (28 fractions of $d_L < d_S$ and 7 fractions of $d_H > d_S$ in TF plans). The x- and y-axis represent $\Delta L = d_S - d_L$ and $\Delta H = d_H - d_S$ respectively. The dashed line shows the plot at which the total dose of the temporally feathered and conventional plans are equal. The region below (above) the dashed line represents combinations of $d_L$ and $d_H$ in which TF plans deliver lower (higher) total doses compared to a conventional plan, keeping $d_S$ constant.




**Supporting Figure 2. Overall potential benefit of TF plans over conventional fractionated radiotherapy for different $\alpha/\beta$ ratios obtained by varying $\beta$ with respect to the standard fractional dose $d_S$ and OAR repair rate $\mu$.** Parameters $n_L = 28$ and $n_H = 7$ were considered. For each combination of $\mu$ and $d_S$, $\Delta$NTCP values are obtained as a result of comparing a standard plan delivering $d_S$ per fraction, and TF plans with $(d_S - 0.5) \leq d_L \leq d_S$ and $d_S \leq d_H \leq (d_S + 2.5)$. **(A)** $\mathrm{OPB_{TF}}$ is defined as the ratio of TF plans resulting in $\Delta\,\mathrm{NTCP} > 0$ and delivering higher total doses than the corresponding standard plan to all simulated plans. **(B)** Maximum benefit ($\mathrm{MAX_{TF}}$) that can be achieved from the TF plans resulting in $\Delta\,\mathrm{NTCP} > 0$ and delivering higher total doses than the corresponding standard plan.




**Supporting Figure 3. Overall potential benefit of TF plans over conventional fractionated radiotherapy for a $\alpha/\beta = 3$ Gy obtained by varying $\alpha$ and $\beta$ with respect to the standard fractional dose $d_S$ and OAR repair rate $\mu$.** Parameters $n_L = 28$ and $n_H = 7$ were considered. For each combination of $\mu$ and $d_S$, $\Delta$NTCP values are obtained as a result of comparing a standard plan delivering $d_S$ per fraction, and TF plans with $(d_S - 0.5) \leq d_L \leq d_S$ and $d_S \leq d_H \leq (d_S + 2.5)$. **(A)** $\mathrm{OPB_{TF}}$ is defined as the ratio of TF plans resulting in $\Delta\,\mathrm{NTCP} > 0$ and delivering higher total doses than the corresponding standard plan to all simulated plans. **(B)** Maximum benefit ($\mathrm{MAX_{TF}}$) that can be achieved from the TF plans resulting in $\Delta\,\mathrm{NTCP} > 0$ and delivering higher total doses than the corresponding standard plan.