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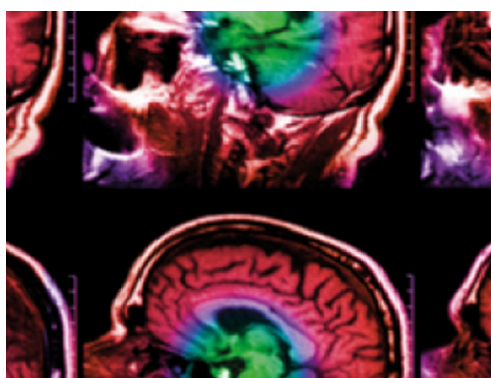
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## PAPER

## Derivation of mean dose tolerances for new fractionation schemes and treatment modalities

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5 February 2018**Abstract**

Avoiding toxicities in radiotherapy requires the knowledge of tolerable organ doses. For new, experimental fractionation schemes (e.g. hypofractionation) these are typically derived from traditional schedules using the biologically effective dose (BED) model. In this report we investigate the difficulties of establishing mean dose tolerances that arise since the mean BED depends on the entire spatial dose distribution, rather than on the dose level alone.

A formula has been derived to establish mean physical dose constraints such that they are mean BED equivalent to a reference treatment scheme. This formula constitutes a modified BED equation where the influence of the spatial dose distribution is summarized in a single parameter, the dose shape factor. To quantify effects we analyzed 24 liver cancer patients for whom both proton and photon IMRT treatment plans were available.

The results show that the standard BED equation—neglecting the spatial dose distribution—can overestimate mean dose tolerances for hypofractionated treatments by up to 20%. The shape difference between photon and proton dose distributions can cause 30–40% differences in mean physical dose for plans having identical mean BEDs. Converting hypofractionated, 5/15-fraction proton doses to mean BED equivalent photon doses in traditional 35-fraction regimens resulted in up to 10 Gy higher doses than applying the standard BED formula.

The dose shape effect should be accounted for to avoid overestimation of mean dose tolerances, particularly when estimating constraints for hypofractionated regimens. Additionally, tolerances established for one treatment modality cannot necessarily be applied to other modalities with drastically different dose distributions, such as proton therapy. Last, protons may only allow marginal (5–10%) dose escalation if a fraction-size adjusted organ mean dose is constraining instead of a physical dose.

**1. Introduction**

The safe use of radiotherapy requires the knowledge of radiation doses that healthy tissues can tolerate. These dose tolerances are typically obtained from clinical data by correlating dose metrics with the occurrence rates of radiation toxicities. Subsequently, they guide the selection of dose constraints in treatment planning to limit the risk of radiation induced side effects. The most common constraints are maximum dose, mean dose, dose volume histogram (DVH) and generalized equivalent uniform dose (gEUD) constraints (Niemierko 1997, 1999, Choi and Deasy 2002, Bentzen *et al* 2010, Emami 2013).

Since the beneficial effects of fractionated radiotherapy have been discovered early on (Coutard (1934), Douglas and Fowler (1976), Fowler (1984), Withers (1985) Moonen and Bartelink (1994) and Bernier *et al* (2004)), the vast majority of treatments have applied 25–35 fractions with 2 Gy dose per fraction, leading to total target doses of 50 Gy to 70 Gy. This is referred to as the standard fractionation. Consequently, most dose tolerances

have been determined for these conventional fractionation schedules. Current trends towards hypofractionation (Beli *et al* 2010, Armpilia *et al* 2011, Rusthoven *et al* 2014, Koontz *et al* 2015) (i.e. the use of fewer fractions with higher dose per fraction) require dose tolerances for such experimental regimens, too. Additionally, the spread of charged particle therapy necessitates establishing dose tolerances for new treatment modalities as well.

Before routine clinical use, dose constraints for a new fractionation scheme (or modality) always have to be validated by outcome data. However, in the initial design of clinical trials testing an experimental treatment schedule, the biologically effective dose (BED) (Douglas and Fowler 1976, Barendsen 1982, Fowler 1984, 2010) model is often used to derive dose tolerances from established fractionation schemes. The procedure for establishing maximum dose constraints—where only a single dose level is considered—is familiar to practitioners (Barendsen 1982, Withers *et al* 1983, Fowler 1984, Newcomb *et al* 1993, Board of the Faculty 2008, Emami 2013, Hoffmann and Nahum 2013). Our paper focuses on the derivation of mean dose tolerances, where additional difficulties arise. Specifically, we address three questions:

- How can mean dose constraints be established for new fractionation schemes using the BED model? Mean organ doses are used to estimate normal tissue complications for several major treatment sites (e.g. liver, lung (Tai *et al* 2009, Pan *et al* 2010, Marks *et al* 2010a, Darby *et al* 2013)). Therefore, the derivation of mean dose tolerances in new (hypofractionated) treatment schedules directly affects their safety. Since the mean BED in an organ depends not only on the mean physical dose, but also on the entire, typically inhomogeneous dose distribution, this should be accounted for (section 3.2).
- Can mean dose constraints established for one modality (e.g. 3DCRT or IMRT) be applied one-to-one to other modalities (e.g. VMAT, protons)? In clinical trials investigating the efficacy of proton treatments (versus photons), dose escalation is often done based on the mean physical dose of adjacent healthy organs (Hong 2016). However, proton dose distributions are significantly different from photon distributions: for the same mean dose, protons typically emphasize the high dose region and reduce the low dose bath. Consequently, proton plans usually have higher mean BED for the same mean dose, making it important to study the potential effects of the spatial differences (section 3.3).
- What is the dose escalation potential of proton therapy versus photons for the same normal tissue complication probability (NTCP)? Current proton therapy plans often have larger margins around the target structures than state-of-the-art IMRT plans, mainly due to uncertainties in proton range (e.g. a typical 3.5% range uncertainty can translate to a distal margin up to 1 cm (Paganetti 2012)). At the same time, adjusting for fractionation with the BED model effects high dose values more than low doses. Consequently the dose escalation potential of proton therapy, as assessed from gEUD based NTCP-models, is expected to decrease when the physical dose is adjusted for fractionation. With the spread of particle therapy treatments aimed at increasing target doses these effects should be investigated (section 3.5).

## 2. Methods and materials

### 2.1. Biologically effective dose model

To describe fractionation effects we use the standard BED model (Douglas and Fowler 1976, Barendsen 1982, Fowler 1984, 2010), stating that the biological dose is

$$\text{BED} = Nd \left( 1 + \frac{d}{\alpha/\beta} \right) = D \left( 1 + \frac{D}{N\alpha/\beta} \right), \quad (1)$$

where  $D = Nd$  is the total dose given in  $N$  fractions with dose per fraction  $d$ , and  $\alpha/\beta$  represents the fractionation sensitivity of the tissue. Equation (1) is frequently used to guide the derivation of iso-effective doses in experimental fractionation schemes based on established schemes (Barendsen 1982, Fowler 1984, Newcomb *et al* 1993, Board of the Faculty of Clinical Oncology 2008, Emami 2013). If an organ-at-risk (OAR) can tolerate a dose  $D_{\text{ref}}$  in  $N_{\text{ref}}$  fractions, the tolerance in a new scheme with  $N_{\text{new}}$  fractions can be obtained by equating the BEDs for the two regimens, i.e. solving

$$D_{\text{new}} \left( 1 + \frac{D_{\text{new}}}{N_{\text{new}}\alpha/\beta} \right) = D_{\text{ref}} \left( 1 + \frac{D_{\text{ref}}}{N_{\text{ref}}\alpha/\beta} \right) \quad (2)$$

for the new dose tolerance  $D_{\text{new}}$ . The solution is

$$D_{\text{new}} = \frac{1}{2} \left[ \sqrt{(N_{\text{new}}\alpha/\beta)^2 + 4D_{\text{ref}} \left( N_{\text{new}}\alpha/\beta + D_{\text{ref}} \frac{N_{\text{new}}}{N_{\text{ref}}} \right)} - N_{\text{new}}\alpha/\beta \right]. \quad (3)$$

Equation (3) is equivalent to the well-known Withers iso-effect formula (Withers *et al* 1983), except here we use the total dose and the number of fractions as variables instead of the total dose and the dose per fraction.

Traditionally, the Withers formula has been used to derive maximum dose constraints for serial OARs located within or near the target volume. In this case the reference dose  $D_{\text{ref}}$  is given by the prescription dose and it is assumed that the OAR receives the same dose. Therefore, as also pointed out in Hoffmann and Nahum (2013), this approach implicitly assumes that the iso-effect is calculated for a serial organ receiving the same dose in the same number of fractions as the tumor.

## 2.2. Mean BED versus BED of the mean

Not every OAR can however be considered serial and radiation induced side effects not only depend on the maximum dose: for different organs various dose volume histogram (DVH) metrics were found to be predictive of normal tissue damage (Marks *et al* 2010b, Emami 2013). Consequently, NTCP models typically include DVH reduction methods (e.g. gEUD or effective volume) using a volume parameter  $n$  to describe the ‘volume effect’ of organs (Kutcher and Burman 1989, Niemierko 1997, Marks *et al* 2010c), with  $n$  being close to zero when the effect is small (in serial organs) and around unity when the effect is large (in parallel organs). The exact value of the volume parameter is subject to considerable uncertainty, however, for several OARs it has been found to be sufficiently close to 1 (Dawson *et al* 2002, Marks *et al* 2010a) such that simply the mean dose could be considered predictive of radiation damage.

In clinical radiotherapy practice therefore mean dose tolerances are still commonly employed in treatment planning for organs with parallel structure (e.g. lung, liver (Tai *et al* 2009, Pan *et al* 2010, Marks *et al* 2010a)). Hence it is desirable to be able to use the BED model to derive mean dose tolerances in experimental fractionation schemes from established ones. The difficulty arises from the fact that the true mean BED of an inhomogeneous dose distribution is not the same as the BED corresponding to the mean physical dose of that distribution. Introducing the voxel doses  $D_i$  (and for later use the dose vector  $\mathbf{D} = (D_1, D_2, \dots, D_M)$ , where  $M$  is the number of voxels), the mean BED can be calculated using the mean physical dose  $D_{\text{mean}} = 1/M \sum_{i=1}^M D_i$  as:

$$\begin{aligned} \text{BED}_{\text{mean}} &= \frac{1}{M} \sum_{i=1}^M \text{BED}_i = \frac{1}{M} \sum_{i=1}^M D_i (1 + D_i / (N\alpha/\beta)) = D_{\text{mean}} \left( 1 + \frac{1}{D_{\text{mean}}} \frac{1}{M} \sum_{i=1}^M D_i^2 \right) \\ &= D_{\text{mean}} \left( 1 + \frac{D_{\text{mean}}}{N\alpha/\beta} \frac{\frac{1}{M} \sum_{i=1}^M D_i^2}{\left( \frac{1}{M} \sum_{i=1}^M D_i \right)^2} \right) = D_{\text{mean}} \left( 1 + \frac{D_{\text{mean}}}{N\alpha/\beta} \frac{M \sum_{i=1}^M D_i^2}{\left( \sum_{i=1}^M D_i \right)^2} \right). \end{aligned} \quad (4)$$

Equation (4) reveals that the mean BED is not only defined by the mean physical dose and the fractionation scheme, but also by the spatial distribution of the dose. The effect of the dose distribution can be summarized by a single dimensionless parameter, the dose shape factor

$$\varphi = \frac{M \sum_{i=1}^M D_i^2}{\left( \sum_{i=1}^M D_i \right)^2}. \quad (5)$$

The appendix of Hoffmann and Nahum (2013) gives a practically identical derivation for equation (4), but calls the dose shape factor of equation (5) the ‘dose heterogeneity factor’, and implicitly Nahum (2015) also makes use of this formulation. In essence, the dose shape factor provides a practical, straightforward insight into the effect of the dose distribution on the mean BED (however, it ‘only’ accounts for the shape, and not for example for organ structure or heterogeneities in radiobiological properties, etc).

Using equation (5) allows the mean BED to be calculated as

$$\text{BED}_{\text{mean}} = D_{\text{mean}} \left( 1 + \frac{D_{\text{mean}}}{N\alpha/\beta} \varphi \right).$$

Therefore, to obtain mean dose tolerances  $D_{\text{new}}$  for a treatment modality characterized by  $\varphi_{\text{new}}$ , based on a reference modality with dose shape factor  $\varphi_{\text{ref}}$  and mean dose tolerance  $D_{\text{ref}}$ , one has to solve

$$D_{\text{new}} \left( 1 + \frac{D_{\text{new}}}{N_{\text{new}}\alpha/\beta} \varphi_{\text{new}} \right) = D_{\text{ref}} \left( 1 + \frac{D_{\text{ref}}}{N_{\text{ref}}\alpha/\beta} \varphi_{\text{ref}} \right) \quad (6)$$

for  $D_{\text{new}}$  (instead of equation (2)). The solution is

$$D_{\text{new}} = \frac{1}{2} \left[ \sqrt{\left( \frac{N_{\text{new}}\alpha/\beta}{\varphi_{\text{new}}} \right)^2 + 4D_{\text{ref}} \left( \frac{N_{\text{new}}\alpha/\beta}{\varphi_{\text{new}}} + D_{\text{ref}} \frac{\varphi_{\text{ref}}}{\varphi_{\text{new}}} \frac{N_{\text{new}}}{N_{\text{ref}}} \right)} - \frac{N_{\text{new}}\alpha/\beta}{\varphi_{\text{new}}} \right]. \quad (7)$$

There are three important aspects regarding the impact of the dose shape factor on the mean BED:

- The dose shape factor is never smaller than unity, i.e.  $\varphi \geq 1$ . Therefore the mean BED is always bigger than the simple BED equivalent of the mean physical dose ( $\varphi = 1$  only holds for completely homogeneous distribution).
- The dose shape factor and the mean BED both increase with the variance of the spatial dose distribution<sup>4</sup> (Hoffmann and Nahum (2013)). This can be seen if we use the variance of the dose distribution,  $\text{var}(\mathbf{D}) = 1/M \sum_{i=1}^M (D_i - D_{\text{mean}})^2$ , to rewrite equation (5) as

$$\varphi = \frac{1}{D_{\text{mean}}} \frac{\sum_{i=1}^M D_i^2}{\sum_{i=1}^M D_i} = \frac{1}{D_{\text{mean}}} \left( D_{\text{mean}} + \frac{\text{var}(\mathbf{D})}{D_{\text{mean}}} \right).$$

Higher variance in the dose distribution therefore leads to higher  $\varphi$  and mean BED as well.

- Two treatments with identical mean physical doses  $D_{\text{mean}}^1 = D_{\text{mean}}^2$  and fractionation schemes  $N^1 = N^2$  are not necessarily equivalent in terms of mean BED.  $\text{BED}_{\text{mean}}^1 = \text{BED}_{\text{mean}}^2$  only holds if the spatial distributions are also similar, i.e. if  $\varphi^1 = \varphi^2$ .

### 2.3. Consistency with gEUD based NTCP modelling

Requiring the equivalence of the mean BEDs (equation (6)) is consistent with typical NTCP modelling. This is presented in detail in appendix A. The main result is that for a majority of NTCP models—including the popular Lyman–Kutcher–Burman model (see appendix B)—two dose distributions have the same NTCP if they have identical ‘generalized equivalent uniform biologically effective doses’ (Hoffmann *et al* 2008, Hoffmann and Nahum 2013), i.e. if

$$\text{gEUBED}_n(\mathbf{D}_{\text{new}}, N_{\text{new}}, \alpha/\beta) = \text{gEUBED}_n(\mathbf{D}_{\text{ref}}, N_{\text{ref}}, \alpha/\beta). \quad (8)$$

The ‘generalized equivalent uniform biologically effective dose’, denoted by  $\text{gEUBED}_n(\mathbf{D}, N, \alpha/\beta)$  is simply a generalized equivalent uniform Dose calculation  $\text{gEUD}_n(\text{BED}(\mathbf{D}, N, \alpha/\beta))$  based on the BED distribution  $\text{BED}(\mathbf{D}, N, \alpha/\beta)$  corresponding to the physical dose distribution  $\mathbf{D}$  given in  $N$  fractions, with fractionation sensitivity  $\alpha/\beta$ , using  $n$  as the volume parameter:

$$\text{gEUBED}_n(\mathbf{D}, N, \alpha/\beta) = \left( \frac{1}{M} \sum_{i=1}^M \text{BED}_i^{1/n} \right)^n = \left[ \frac{1}{M} \sum_{i=1}^M \left( D_i \left( 1 + \frac{D_i}{N\alpha/\beta} \right) \right)^{1/n} \right]^n. \quad (9)$$

For  $n = 1$  the gEUD is identical to the arithmetic mean and equation (8) simplifies to equation (6), which can be solved analytically to yield equation (7).

We specifically use equation (8) to study iso-toxic dose escalation. To calculate how a dose distribution  $\mathbf{D}_{\text{new}}$  can be scaled to a distribution  $f \cdot \mathbf{D}_{\text{new}}$  such that it leads to the same NTCP as the reference distribution  $\mathbf{D}_{\text{ref}}$ ,

$$\text{gEUBED}_n(f \cdot \mathbf{D}_{\text{new}}, N_{\text{new}}, \alpha/\beta) = \text{gEUBED}_n(\mathbf{D}_{\text{ref}}, N_{\text{ref}}, \alpha/\beta)$$

has to hold. Filling in the formula for calculating the gEUBEDs (equation (9)) for the two dose distributions leads to

$$\left[ \frac{1}{M} \sum_{i=1}^M \left( f \cdot D_{\text{new},i} \left( 1 + \frac{f \cdot D_{\text{new},i}}{N_{\text{new}}\alpha/\beta} \right) \right)^{1/n} \right]^n = \left[ \frac{1}{M} \sum_{i=1}^M \left( D_{\text{ref},i} \left( 1 + \frac{D_{\text{ref},i}}{N_{\text{ref}}\alpha/\beta} \right) \right)^{1/n} \right]^n. \quad (10)$$

For given dose distributions ( $\mathbf{D}_{\text{new}}, \mathbf{D}_{\text{ref}}$ ), fraction numbers ( $N_{\text{new}}, N_{\text{ref}}$ ) and chosen  $n$  and  $\alpha/\beta$  values, the only unknown is the scaling factor  $f$ . Hence numerically solving equation (10) for  $f$  provides a general method for iso-NTCP based dose escalation.

### 2.4. Using BED formulas

The effects of the dose shape factor on the mean BED—detailed in section 2.2—have important consequences when iso-effective (i.e. iso-toxic) mean doses are calculated between fractionation schemes and between modalities. We consider 3 scenarios corresponding to special cases of equation (6):

- Case 1 demonstrates the effects of the dose shape when doses are calculated between fractionation schemes ( $N_{\text{new}} \neq N_{\text{ref}}$ ) for the same irradiation modality ( $\varphi_{\text{new}} = \varphi_{\text{ref}}$ , section 3.2).
- Case 2 compares different modalities ( $\varphi_{\text{new}} \neq \varphi_{\text{ref}}$ ) for the same fractionation ( $N_{\text{new}} = N_{\text{ref}}$ , section 3.3). We consider photons as the reference (with  $\varphi_{\text{ref}}$  being the photon dose shape factor) and calculate the mean dose

<sup>4</sup> Temporal variance similarly increases the mean BED, see section 1.1 of the supplementary materials (SM) ([stacks.iop.org/PMB/63/035038/mmedia](https://stacks.iop.org/PMB/63/035038/mmedia)).



in photon plans ( $D_{\text{ref}} = D_{\text{new}} + \Delta D$ ) that is mean BED equivalent with proton mean doses  $D_{\text{new}}$  (with  $\varphi_{\text{new}}$  being the proton dose shape factor). The difference  $\Delta D = D_{\text{ref}} - D_{\text{new}}$  represents an effective dose difference resulting from the shape difference  $\Delta\varphi = \varphi_{\text{new}} - \varphi_{\text{ref}}$ .

- Case 3 uses equation (6) to relate one treatment with dose shape  $\varphi_{\text{new}}$ ,  $N_{\text{new}}$  fractions, and mean dose  $D_{\text{new}}$  to another treatment characterized by  $\varphi_{\text{ref}}$ ,  $N_{\text{ref}}$  fractions, and  $D_{\text{ref}}$  (section 3.4). Specifically, for a hypofractionated proton treatment with mean dose  $D_{\text{new}}$  and dose shape factor  $\varphi_{\text{new}}$  ( $N_{\text{new}} = 5$  or  $15$ ), we calculate the mean dose  $D_{\text{ref}}$  in a conventionally fractionated ( $N_{\text{ref}} = 35$ ) photon plan with dose shape factor  $\varphi_{\text{ref}}$ , that would be mean BED equivalent.

Additionally, we study the dose escalation potential of proton therapy versus photon therapy as assessed by iso-NTCP based dose escalation:

- Case 4 compares the given proton plans  $\mathbf{D}_{\text{proton}}$  (which were delivered to the patients in  $N = 5$  or  $15$  fractions) to the planned photon plans  $\mathbf{D}_{\text{photon}}$ , when the photon plans are scaled such that they lead to the same NTCP as their proton counterpart. We use equation (10) to search for a scale factor  $f$ , such that the scaled photon dose distribution  $f\mathbf{D}_{\text{photon}}$  in  $N$  fractions gives the same gEUBED<sub>n</sub> as protons. The dose escalation potential of protons is  $\frac{D_{\text{proton}}^{\text{GTV}}}{fD_{\text{photon}}^{\text{GTV}}}$ , which is the ratio of the average GTV doses in the (delivered) proton dose distribution and the scaled (planned) photon dose distribution. The ratio will clearly depend on the chosen volume parameter  $n$  and the fractionation sensitivity  $\alpha/\beta$ , however, not on the fraction size  $fs$  used to adjust for fractionation (see appendix A). For  $\alpha/\beta = \infty$  the ratio signals the dose escalation potential based purely on physical dose, whereas for  $\alpha/\beta < \infty$  the dose escalation also takes into account the effects of fractionation. In order to estimate the dose escalation potential for standard fractionation as well, we perform the same calculations by considering scaled proton plans delivering 70 Gy to the GTV in  $N = 35$  fractions as the reference. Therefore, we also determine the scale factors  $f$  such that the scaled photon dose distributions  $f\mathbf{D}_{\text{photon}}$  in  $N = 35$  fractions give the same gEUBED<sub>n</sub> values as the scaled proton dose distributions  $70 \text{ Gy}/D_{\text{proton}}^{\text{GTV}} \cdot \mathbf{D}_{\text{proton}}$  in  $N = 35$  fractions, yielding the dose escalation potential of protons for standard fractionation as  $\frac{70 \text{ Gy}}{fD_{\text{photon}}^{\text{GTV}}}$ .

Throughout the paper relative biological effectiveness (RBE) is taken into account by adjusting proton doses with  $\text{RBE}_{\text{proton}} = 1.1$ . BED calculations are done subsequent to the RBE adjustment using equation (1) and all presented proton dose values are the RBE corrected doses  $D_{\text{proton}} = \text{RBE}_{\text{proton}} \cdot \tilde{D}_{\text{proton}}$ . Dale and Jones (1999) introduced a modified BED formulation that allows the direct incorporation of RBE effects. Our theoretical models can be generalized accordingly, and the differences between the two approaches are relatively small (for a detailed discussion and a comparison of the results see appendix C).

## 2.5. Patient data

We analyzed 24 liver cancer patients with varying tumor size, location and recurrence status. Patients underwent a 2 day CT simulation to assess internal motion and reproducibility. Plans were created using mid-ventilation CT (30% phase) where the tumor volume was derived from arterial/venous phase contrast CT scan fused to the planning CT.

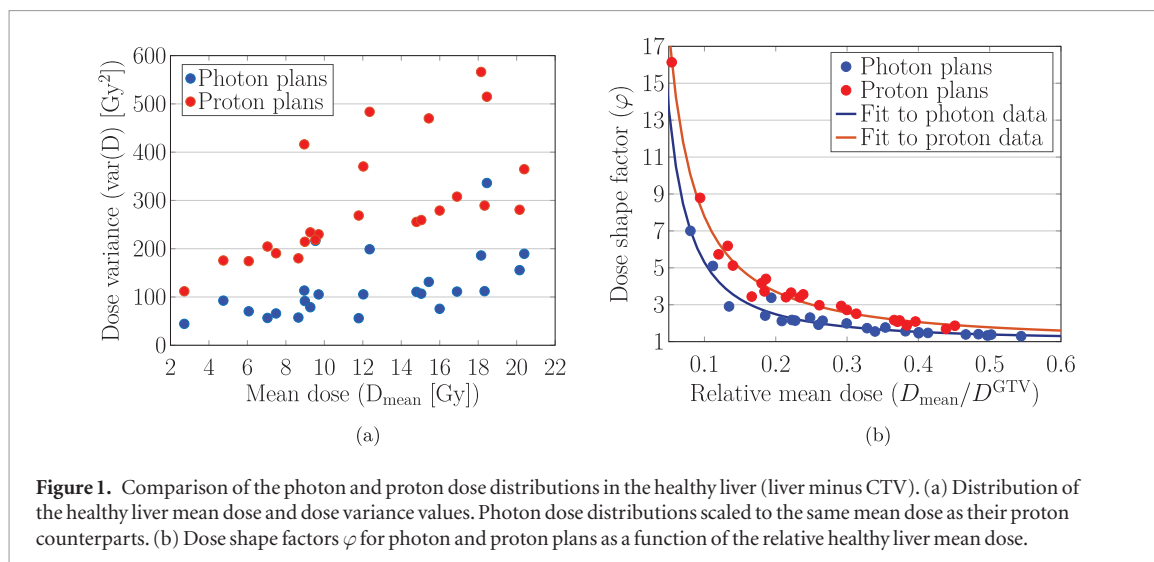
All patients were treated with passively scattered protons in 5 or 15 fractions, with prescription doses of 40 Gy or 50 Gy for the former; and between 45 Gy to 67.5 Gy for the latter schedule. Proton plans incorporated aperture expansion and compensator smearing based on measured internal organ motion, utilizing 2–3 fields per plan. For research purposes, IMRT plans were also made for the patients, using the same target volumes, 7–10 treatment fields, and standard clinical planning procedures. Since the passively scattered protons were used for treatment and liver motion was considerable, proton plans typically employed larger margins than their photon counterparts to avoid potential loss of target coverage. For all proton and photon plans the mean dose and the dose variance were calculated for the healthy liver (liver minus the clinical target volume), and subsequently the dose shape factors were determined. For analysing the dose variance in section 3.1 and the example patient in section 3.3.1, the IMRT plans were scaled such that the healthy liver mean physical dose matched that of their proton counterpart. For the calculations of case 4 (section 3.5) IMRT plans were scaled according to equation (10), such that the healthy liver gEUBEDs were identical to those of the proton plans for a range of volume parameters  $n \in [0, 1.2]$  and three different fractionation sensitivity values of  $\alpha/\beta \in \{2, 4, \infty\}$  Gy.

## 3. Results

### 3.1. Dose variance and dose shape factor of proton and photon plans

Figure 1 gives an overview of the dose differences between proton and photon plans. There is a clear distinction in terms of the dose variance (figure 1(a)): proton plans have higher dose variance for the same mean healthy liver





dose. The distinction in terms of dose shape factor  $\varphi$  becomes apparent in figure 1(b) showing the dose shape factor as a function of the relative liver dose (i.e. the fraction of the mean dose in the healthy liver and the GTV). Photon plans have smaller dose shape factors than proton plans. The average dose shape factor across all photon plans is 2.2, whereas the average dose shape factor for proton plans is 4.0. Furthermore, as shown in figure 1(b), there is a decreasing trend of  $\varphi$  with the relative mean dose (for the fit results see section 2 of the supplementary materials (SM)). This is intuitive: lower relative mean dose signals better dose sparing, which inevitably leads to more dose variation in the organ.

### 3.2. Calculating iso-effective mean doses in new fractionation schemes (case 1)

#### 3.2.1. Analysis of proton and photon plans

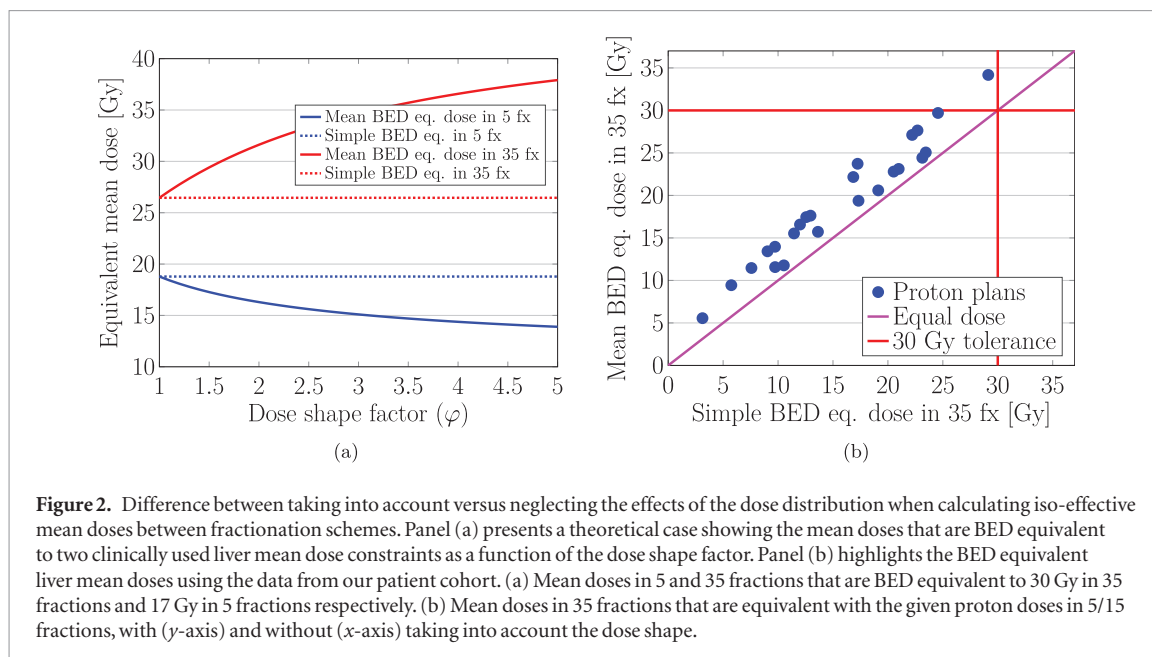
Figure 2 demonstrates the effects of the dose shape factor when iso-effective mean doses in new fractionation schemes are calculated for commonly used liver mean dose tolerances (Dawson *et al* 2002, Pan *et al* 2010, Emami 2013) and  $\alpha/\beta^{\text{Liver}} = 4$  Gy. First, we calculate the dose to be delivered in 5 fractions that is equivalent with 30 Gy in 35 fractions, a widely applied mean dose constraint in standard fractionation (blue lines, figure 2(a)). The traditional BED formulation (equation (3)) yields an equivalent 5-fraction dose of 18.8 Gy (dashed line). In contrast, when the calculation is done employing equation (7) (using  $\varphi_{\text{ref}} = \varphi_{\text{new}} \geq 1$ ), the 5-fraction doses are systematically lower (solid line). E.g. for a commonplace value of  $\varphi = 3$  the equivalent dose is 15 Gy, 20% lower than 18.8 Gy. Second, we calculate the dose in 35 fractions that is equivalent to 17 Gy in 5 fractions (red lines). The standard BED formulation yields 26.5 Gy, whereas the mean BED equivalent doses are up to 40% higher for realistic  $\varphi$  values.

Figure 2(b) quantifies this effect for clinical treatment plans. The healthy liver mean doses  $D_{\text{ref}}$  in the proton plans—delivered in 5 or 15 fractions—were converted to equivalent 35-fraction doses  $D_{\text{new}}$  ( $N_{\text{ref}} = 5$  or 15,  $N_{\text{new}} = 35$ ,  $\varphi_{\text{ref}} = \varphi_{\text{new}}$  corresponding to the proton dose shape factors), in order to compare them to proton treatments with standard fractionation. The truly mean BED equivalent 35-fraction doses are systematically and significantly higher than what the traditional BED formulation (equation (3)) suggests. Differences up to 8 Gy (+40%) can be observed. Moreover, while all plans seem safe according to the simple BED model having 35-fraction mean doses below 30 Gy, for 1 patient the mean BED equivalent mean dose is 5 Gy higher than the tolerance.

#### 3.2.2. Analysis of the protocol of a phase II randomized trial for hepatocellular carcinoma

In the NRG-GI003 cooperative group clinical trial protocol (Hong 2016) (clinicaltrials.gov identifier NCT03186898, currently recruiting patients) liver tolerances are given as prescription dose dependent values, separately for 5- and 15-fraction treatments (shown in black in table 1). Assuming  $\alpha/\beta^{\text{Tumor}} = 10$  Gy, the prescription dose levels in the 2 fractionation schemes (columns 1 and 2) are approximately iso-effective: e.g. 50 Gy in 5 fractions and 67.5 Gy in 15 fractions both represent  $\approx 100$  Gy<sub>10</sub> BED. The corresponding tumor BED values (shown in blue, column 3) are monotonically decreasing with decreasing prescription dose.

Columns 4 and 5 show the mean dose constraints for the healthy liver for 5 and 15 fractions, respectively. Making the 4 dose tolerance pairs belonging to the same tumor BED levels BED equivalent requires unrealistically low  $\alpha/\beta_{\text{eq}} \in [0.17, 1.14]$  Gy values (shown in red table 1) if the simple BED formula equation (2) is used. Furthermore, the resulting equivalent liver BED levels BED<sub>eq</sub> vary non-monotonically. Using a realistic  $\alpha/\beta^{\text{Liver}} = 4$  Gy value in equation (3) to calculate the 15-fraction equivalent of 5-fraction tolerances yields doses



**Figure 2.** Difference between taking into account versus neglecting the effects of the dose distribution when calculating iso-effective mean doses between fractionation schemes. Panel (a) presents a theoretical case showing the mean doses that are BED equivalent to two clinically used liver mean dose constraints as a function of the dose shape factor. Panel (b) highlights the BED equivalent liver mean doses using the data from our patient cohort. (a) Mean doses in 5 and 35 fractions that are BED equivalent to 30 Gy in 35 fractions and 17 Gy in 5 fractions respectively. (b) Mean doses in 35 fractions that are equivalent with the given proton doses in 5/15 fractions, with ( $y$ -axis) and without ( $x$ -axis) taking into account the dose shape.

**Table 1.** Mean liver tolerances for 5 and 15 fractions in the NRG-GI003 cooperative group clinical trial protocol. Calculated tumor BEDs are shown in blue (column 3). The  $\alpha/\beta_{eq}$  values making the liver dose constraints (columns 4 and 5) corresponding to the same tumor BED level equivalent and the equivalent liver  $BED_{eq}$  values are displayed in red (columns 6 and 7). 15-fraction liver mean dose tolerances calculated from the 5-fraction values using  $\alpha/\beta = 4$  Gy and the traditional BED formulation are in yellow (column 8), whereas the values calculated by taking into account the dose shape differences are in cyan (last column).

Prescription dose <sup>a</sup>		Tumor BED <sup>b</sup>	Used constraints <sup>a</sup>		$\alpha/\beta_{eq}$ <sup>c</sup>	$BED_{eq}$ <sup>d</sup>	Calculated 15 fx constraints <sup>a</sup>	
$N = 5$	$N = 15$		$N = 5$	$N = 15$			W/o shape	With shape
50	67.5	100/97.88	13	22	0.17	211.4	16.77	20.91
45	58.05	85.5/80.52	15	24	0.74	76.36	19.75	24.70
40	N/A	72/N/A	15	N/A	N/A	N/A	19.75	24.70
35	45	59.5/58.5	15.5	24	1.14	57.82	20.51	25.65
30	37.5	48/46.88	16	27	0.24	232.6	21.26	26.61
27.5	N/A	42.63/N/A	17	N/A	N/A	N/A	22.79	28.53

<sup>a</sup> Physical dose values are in units of Gy.

<sup>b</sup> BED values are calculated using  $\alpha/\beta^T = 10$  Gy, and are displayed as 5 fraction BED/15 fraction BEDs in  $Gy_{10}$  units.

<sup>c</sup>  $\alpha/\beta$  values displayed in units of Gy.

<sup>d</sup> Equivalent BED values displayed in units of  $\alpha/\beta_{eq}$ , i.e. the  $\alpha/\beta$  that makes the liver mean dose constraints BED equivalent using the simple BED formula (equation (2)).

(shown in yellow) 4 Gy to 6 Gy (more than 20%) below the actual values. Consequently, the used liver tolerance values are not consistent with the traditional BED formalism.

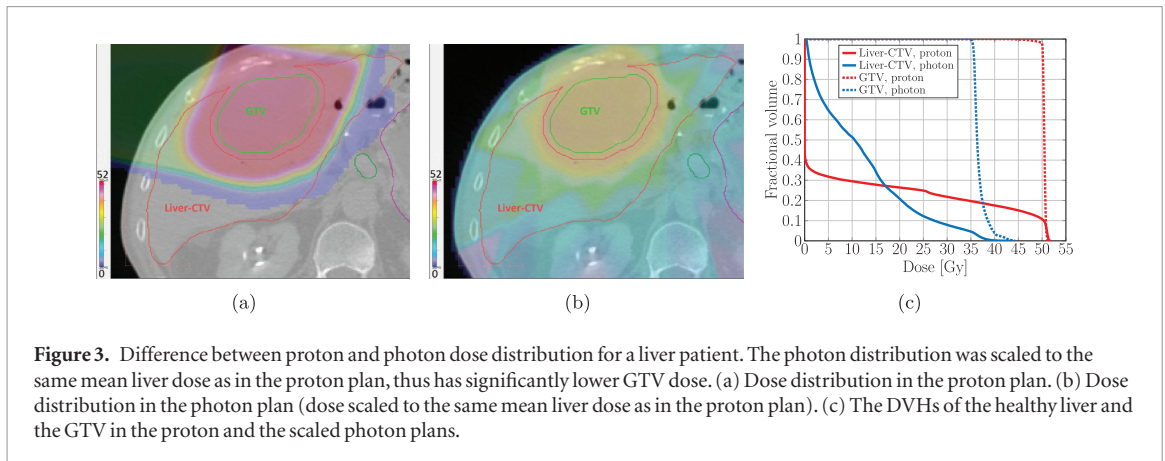
The average dose shape factor of the photon plans for the patients treated with 15 and 5 fractions is  $\varphi_{photon}^{15} = 1.80$  and  $\varphi_{photon}^5 = 2.49$ , respectively. Using these values in equation (7) to extrapolate the 5-fraction doses to 15 fractions (i.e.  $\varphi_{ref} = \varphi_{photon}^5$ ,  $\varphi_{new} = \varphi_{photon}^{15}$ ,  $N_{ref} = 5$  and  $N_{new} = 15$ ) results in the doses shown in cyan in table 1, corresponding far better to the actual mean dose tolerances (within 0.3 Gy to 1.6 Gy).

### 3.3. Calculating iso-effective mean doses in new modalities (case 2)

#### 3.3.1. Detailed analysis of a selected patient

We present a detailed analysis of a patient where the difference between the proton and photon plans was significant. The patient received proton treatment delivering  $D_{new}^{GTV} = 50.4$  Gy in 5 fractions to the target volume, and  $D_{new} = 12$  Gy mean dose to the healthy liver. The corresponding dose distribution is plotted in figure 3(a), the DVHs in figure 3(c). 60% of the liver was completely spared, whereas the part close to the target received the full prescription dose. The relative liver dose is therefore low,  $D_{new}/D_{new}^{GTV} = 0.239$ , while the dose variance is high,  $var(D_{new}) = 370$  Gy<sup>2</sup>. Consequently the dose shape factor is relatively large,  $\varphi_{new} = 3.561$ .

The dose distribution in the (9 field) photon plan—that is scaled to the same mean liver dose as the proton plan—is shown in figure 3(b), with the corresponding DVHs in figure 3(c). No part of the healthy liver is com-



**Figure 3.** Difference between proton and photon dose distribution for a liver patient. The photon distribution was scaled to the same mean liver dose as in the proton plan, thus has significantly lower GTV dose. (a) Dose distribution in the proton plan. (b) Dose distribution in the photon plan (dose scaled to the same mean liver dose as in the proton plan). (c) The DVHs of the healthy liver and the GTV in the proton and the scaled photon plans.

pletely spared, hence the relative dose is higher than in the proton plan,  $D_{\text{ref}}/D_{\text{ref}}^{\text{GTV}} = 0.328$ , but the dose variance is smaller,  $\text{var}(\mathbf{D}_{\text{ref}}) = 105.4 \text{ Gy}^2$ . Consequently, the dose shape factor is smaller,  $\varphi_{\text{ref}} = 1.730$  (for details on why proton plans generally have higher  $\varphi$ , see section 1.2 of the SM).

Due to the shape difference, the same 12 Gy mean liver dose leads to significantly different mean BEDs of 37.64  $\text{Gy}_4$  for protons and 24.46  $\text{Gy}_4$  for photons ( $\alpha/\beta^{\text{Liver}} = 4\text{Gy}$ ). Equation (6) reveals that the proton plan is mean BED equivalent to a photon plan with a mean dose of 15.87 Gy, more than 30% higher than 12 Gy. Conversely, if the proton plan was scaled to have identical mean BED to its photon counterpart, the proton mean dose would be 9.24 Gy, 23% lower than 12 Gy. Hence, while protons allow a dose escalation of 35% (i.e. a target mean dose of 50.4 Gy versus 36.9 Gy with photons, see figure 3(c)) by matching the liver mean physical dose levels in the 2 modalities, this reduces to only 5% (proton target dose of 38.6 Gy) when matching the mean BEDs.

### 3.3.2. Quantifying the effects of shape difference

Figure 4 highlights the effects of the dose shape factor when iso-effective mean doses are calculated in different modalities. Figure 4(a) shows the additional dose  $\Delta D = D_{\text{ref}} - D_{\text{new}}$  in a reference modality (with  $\varphi_{\text{ref}} = 2$ , typical for IMRT) as a function of the shape difference  $\Delta\varphi = \varphi_{\text{new}} - \varphi_{\text{ref}}$  between two modalities for  $N_{\text{ref}} = N_{\text{new}} = 5$  and different  $D_{\text{new}}$  values. The additional dose increases both with the difference in the spatial distribution  $\Delta\varphi$  and with the mean dose  $D_{\text{new}}$  in the new modality, whereas it decreases with the reference dose shape factor  $\varphi_{\text{ref}}$ . The dose difference can get substantial for large shape differences: e.g. for a shape difference of  $\Delta\varphi = 3$ , a 5-fraction mean dose of 17 Gy in the new modality is equivalent to a mean dose of 25 Gy in the reference modality, representing a +50% increase.

To quantify effects for clinical treatment plans, proton mean liver doses  $D_{\text{new}}$  (with dose shape factor  $\varphi_{\text{new}}$ ) were converted to mean BED equivalent photon mean doses  $D_{\text{ref}} = D_{\text{new}} + \Delta D$  (with dose shape factor  $\varphi_{\text{ref}}$ ) for all 24 patients, using the clinically delivered number of fractions for  $N_{\text{new}} = N_{\text{ref}}$ . Figure 4(b) displays the resulting additional mean dose  $\Delta D$  relative to the proton dose as a function of the shape difference  $\Delta\varphi = \varphi_{\text{new}} - \varphi_{\text{ref}}$ . Generally, higher dose shape differences lead to higher relative dose differences, reaching 30–40% (in agreement with the theoretical results shown in figure 4(a)). In absolute terms, the mean BED equivalent photon doses are 1 Gy–4 Gy higher than the proton doses (figure 4(c)).

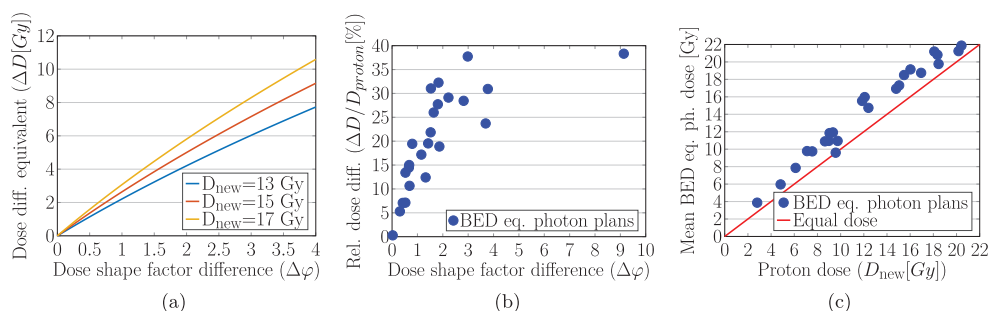
### 3.4. Potential dangers of neglecting the shape effect (case 3)

To study whether the additional dose due to shape differences can be potentially unsafe, figure 5 displays the mean BED equivalent 35-fraction photon mean doses (i.e. the results of equation (6)) versus the simple BED equivalent mean doses (i.e. the results of equation (3)). When the traditional BED formula is used (equation (2)), all 35-fraction doses are below the 30 Gy liver tolerance (Dawson *et al* 2002, Emami 2013). When the proton-photon shape differences are accounted for (equation (6)) the mean dose is above 30 Gy in two cases (for a discussion of the 30 Gy tolerance see section 3 of the SM.).

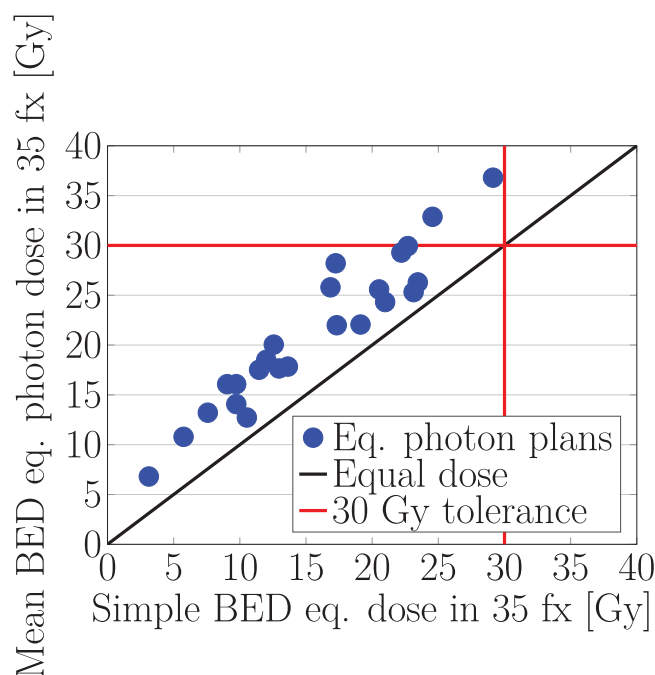
### 3.5. Dose escalation potential of proton therapy (case 4)

The ratio of the proton/scaled photon GTV doses—having identical gEUBED values for the healthy liver according to equation (10)—averaged over the 24 patients can be seen in figure 6 for three different  $\alpha/\beta$  ratios and a range of volume parameters  $n \in [0, 1.2]$ . There are three findings:

- When  $0 < n < 0.6$ , photon plans are generally better based on the physical dose, which is a result of penalizing the larger high dose region of proton plans in the gEUD calculations. The only exception is  $n = 0$



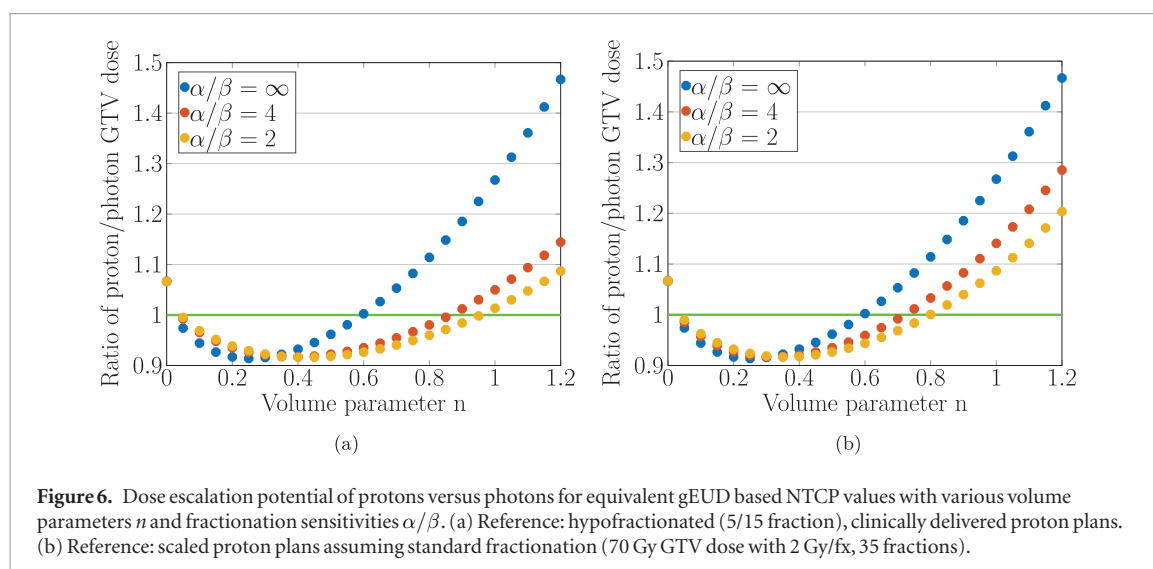
**Figure 4.** Dose effects of shape differences. (a) Additional dose in a 5-fraction plan with a dose shape factor of  $\varphi_{\text{ref}} = 2$  due to higher dose inhomogeneity ( $\Delta\varphi$ ). (b) Relative dose difference resulting from the dose shape difference between proton and photon plans. (c) Mean BED equivalent photon mean dose as a function of proton mean dose.



**Figure 5.** Mean BED equivalent 35-fraction photon mean doses versus simple BED equivalent 35-fraction mean doses.

(when only the maximum point dose in the healthy liver matters), primarily caused by the slightly better homogeneity of proton plans in the GTV (see figure 3(c)), typically leading to higher average GTV doses for the same maximum point dose.

- For  $n > 0.6$ , protons are clearly better in terms of physical dose, as the low dose bath of photon treatments starts to limit the GTV dose for a given gEUD value. For  $n = 1$  on average a 25% dose escalation potential can be observed for the same liver mean physical dose, well corresponding to the 35% dose escalation found for the patient in section 3.3.1 (case 2).
- Most importantly, adjusting for fractionation ( $\alpha/\beta < \infty$ ) significantly influences the achievable benefit of protons. Except for small volume parameters ( $n \approx 0$ ), photons remain generally better till around  $n \approx 0.6$  (also see figure C2 in appendix C). For higher volume parameters ( $n > 0.6$ ) proton plans become better, but the BED adjustment increasingly penalizes them—mainly due to their high dose region—decreasing their benefits. For the hypofractionated, clinical proton plans (figure 6(a)) we only see a 5% average dose escalation potential for  $n = 1$  with  $\alpha/\beta = 4$  Gy (versus 25% based on physical dose), increasing to 10% (versus 35%) for  $n = 1.1$  (the value previously found for liver in Dawson and Balter (2004)). For standard fractionation (figure 6(b)) the degradation is less substantial, but is still significant, only allowing for 15%/20% higher target doses with protons for  $n = 1/1.1$  (instead of 25%/35%). For a more detailed discussion of how the method of incorporating RBE affects the dose escalation potential, see appendix C.



## 4. Discussion

### 4.1. Regarding the dose shape effects

The dose shape factor has an opposite effect when deriving doses for less and more fractions (figure 2(a)). The truly mean BED equivalent doses are always lower than what the traditional BED formalism (equation (2)) suggests when deriving doses for more hypofractionated schedules. Hence the standard BED equation leads to potentially unsafe, higher dose tolerances than intended. Conversely, neglecting the dose shape factor when calculating the equivalent of hypofractionated mean doses in traditional fractionation schemes results in lower values than what is mean BED equivalent. Therefore the simple BED formalism underestimates the effects of mean doses in hypofractionated schedules (section 1.3 of the SM provides a mathematical proof of this duality).

Mean doses in plans with high dose variance could be mean BED equivalent to vastly (50%) higher mean doses in less inhomogeneous plans (figure 4(a)). Clinical treatment plans indeed exhibit such sizable dose differences (figures 4(b) and (c)). Therefore, applying mean dose tolerances established for one modality on-to-one to another with significantly more inhomogeneous dose distribution should be done with caution, as this may lead to dose constraints that are too high. Instead, it is better to establish dose tolerances according to equation (7) by taking into account the (typical) differences between the dose distributions of the two modalities.

The shape effect is especially important when the organ in question is the dose limiting structure, so that its mean dose is close to its tolerance. For example, this is the case for liver tumors treated in a dose escalation protocol where the liver mean dose meets the constraint in order to maximize the prescription dose (Hong 2016). If a mean dose constraint was derived from patients treated with photon beams, and the patient is treated with proton beams to the maximally allowed mean dose, the proton treatment will typically violate the constraint in terms of mean BED. In our patient cohort on average protons allowed for 25% dose escalation compared to photons for the same physical liver mean dose (as shown in figure 6). When dose escalation is instead performed based on mean liver BED, protons allowed for only marginally ( $\approx 5\%$ ) higher prescription doses. Although this degradation of proton dose escalation potential is less severe if standard fractionation is assumed for the plans ( $N = 35$  fractions, 70 Gy proton target dose with 2 Gy/fx), it was still significant, only allowing for  $\approx 15\%$  higher proton doses.

#### 4.1.1. Regarding mean BED tolerances

Our results are not specific for mean doses. As figure 6 (and C2) highlight the dose escalation potential of proton therapy is significantly decreased for a wide range of volume parameters ( $n > 0.6$ ) when using a gEUD based NTCP model taking into account fractionation. Hence while there is considerable uncertainty regarding the dose-volume effects in the liver (and in other OARs in general), regardless of what the exact value of volume parameter is, the dose shape, and specifically the larger margins of proton dose distributions compared to photon dose distributions have an important effect on tolerances. These larger high dose areas get emphasized when adjusting for fractionation, and consequently result in higher NTCP values in general. Therefore, within the validity of gEUD based NTCP models including fractionation effects, proton plans are indicated to result in higher normal tissue complications than what could be expected purely from the physical dose distribution.

As a result, the dose escalation potential of protons is substantially reduced if mean BED (or in general gEUBED) rather than mean physical dose (or gEUD) is the relevant metric to limit toxicity. Based on the outcome data from photon treatments, this may indeed be the case e.g. for the liver and the lung (Dawson *et al* 2002, Seppenwoolde *et al* 2003). These works conclude that the volume parameter is close to  $n = 1$  in these organs and the



mean of the fraction-size adjusted dose distribution—which is only different from the mean BED up to patient-independent constant factor, see equation (A.1) in appendix A—correlates with organ damage. In fact, the liver SBRT protocol of Dawson (2006) already describes the clinical use of such a mean BED constraint, since the authors employ an LKB model based dose escalation scheme with a volume parameter of  $n = 0.97$  to determine individualized prescription doses for given NTCP values (5%, 10% or 20%).

In general, hepatotoxicity data from the published literature is always difficult to compare, mainly due to considerable variation across studies in patient population, treatment regimens, exact definition of radiation induced liver disease (RILD), etc. Moreover, research specifically focusing on analysing the outcomes from proton versus photon radiation therapy for RILD is rare (Qi 2015). Thus, in the context of comparing protons and photons for liver SBRT in particular, it is not clear whether mean physical dose, mean BED, or some other metric is the most relevant for tissue damage. Preliminary data from our own institution suggests that liver function is better preserved in proton therapy than in photon therapy. A mean dose/BED constraint may therefore underestimate proton's advantage of avoiding the low dose bath in a significant portion of the liver. If instead a DVH point for the low dose bath is the relevant metric for example, the dose escalation potential of protons is substantially higher. A commonly used constraint for the liver in SBRT protocols, the sparing of at least 700 cm<sup>3</sup> of the healthy liver to less than 15 Gy in 3–6 fractions (Timmerman 2008, Pan *et al* 2010) indeed suggests that this may be the case. Based on this metric, should a proton plan deliver virtually no dose to at least 700 cm<sup>3</sup> of the liver, its dose escalation potential would be infinite.

#### 4.1.2. Regarding relative biological effectiveness and margins

Throughout the paper RBE effects were taken into account by adjusting proton doses with  $RBE_{\text{proton}} = 1.1$ . Therefore all presented and plotted proton doses were the RBE adjusted doses  $D_{\text{proton}} = RBE_{\text{proton}} \tilde{D}_{\text{proton}}$  and all BED calculations were done subsequent to the RBE adjustment. This can be considered a simplified approach, but is consistent with current clinical practice, where the proton RBE is assumed to be fraction-size independent. Dale and Jones (1999) introduced a modified BED formulation that allows for the incorporation of RBE effects. The differences between the two formulations are discussed in detail in appendix C. The main conclusion is that the presented theory can easily be generalized according to Dale and Jones (1999), and for protons—having an RBE relatively close to unity—the exact method of accounting for RBE is only of minor importance, with the Dale–Jones RBE methodology predicting 5–10% smaller effects than our constant RBE model.

A central focus of the paper is to study the effects of the dose shape. Clearly, the shape of the dose distribution is closely connected to the employed margins in the proton (and photon) plans. Margins in turn strongly depend on the considered organ motion, motion mitigation techniques as well as the choice of proton delivery method (passive scattering or pencil beam scanning). Since our patient cohort focused on liver cases (having relatively large motion uncertainties) treated with passively scattered protons, and these proton plans were compared to state-of-the-art IMRT, our results likely represent a worst case scenario for protons. For treatment sites with less motion, where better immobilization and motion mitigation methods can be applied (e.g. brain), effects will be smaller. Additionally, advances in on-line proton range verification methods are expected to decrease proton planning margins, which will further reduce the current disadvantage of protons, i.e. the irradiation of larger areas around target structures with the prescription dose compared to photons.

#### 4.1.3. Regarding the context of our work

The main novelty of our work is a practical, but consistent methodology that allows the establishment of (primarily) mean dose tolerances in new fractionation schemes and new treatment modalities, such that they are iso-toxic as assessed from NTCP models. Essentially, we achieve this by building on established radiobiological models (BED, DVHs and gEUD) to arrive to the formulation of the gEUBED. These concepts are all well known and have been validated in clinical practice. However, they mainly represent phenomenological descriptions reflecting the experience with fractionation (for BED) and volume effects (for DVH and gEUD), rather than a detailed understanding of the exact radiobiological mechanisms underlying organ damage. As any model, they unavoidably have their limitations. For example, the accuracy of the BED model to high dose per fraction values has been debated excessively for decades, without final resolution (Brenner *et al* 2008, Kirkpatrick *et al* 2008). Summarizing three-dimensional dose distributions by DVHs disregards where the dose is deposited exactly, therefore cannot account for varying radiation sensitivity within the organ or the relative importance of some functional sub-units over others for overall organ function. gEUD is a completely empirical concept: the volume parameter is derived purely from experience and there is no known radiobiological justification behind its mathematical form. Since our work builds on these concepts instead of using first principles, it necessarily inherits all their shortcomings as well. Simply put, our message is that—regardless of the actual underlying radiobiology—the presented approach is useful for its intended purpose: to establish mean dose tolerances in a more meaningful way than currently possible, taking into account fractionation, dose shape and possibly RBE (see appendix C) effects.

Despite these limitations of our study (and the fact that it is an in-silico comparison for patients for whom outcome data is not yet available), it well justifies a warning and discussion regarding the use of mean dose—and in general gEUD—constraints for proton therapy that were derived for photon therapy. As first reported by Blanchard *et al* (2016), photon-derived normal tissue complication models may indeed be relatively well applicable to proton therapy treatments as well. Though the derivation of proton specific NTCP models is naturally expected to remain an active research area, until such models are obtained and validated, only the currently available ones can be used (e.g. to guide patient selection eligible for proton treatments (Langendijk *et al* 2013)). These (fraction-size adjusted) gEUD based NTCP models indicate that proton therapy's dose escalation potential may be reduced for a wide range of volume parameters, especially for treatment sites with significant organ motion requiring large margins, warranting caution when using a physical dose based escalation strategy. Similar care should be taken when applying photon therapy based physical dose constraints to proton treatments, as they may overestimate tolerable doses due to the significantly different dose distributions.

## 5. Conclusions

When mean dose tolerances are chosen for new fractionation schemes or irradiation modalities the shape of the dose distribution should be accounted for. The traditional BED formalism tends to overestimate tolerances when they are calculated for more hypofractionated regimes. In addition, mean tolerance values—and gEUD tolerances in general—established for one modality cannot necessarily be applied to other modalities having drastically different dose distributions. The formalism introduced in this paper allows the incorporation of the spatial dose distribution into BED based estimation of mean dose constraints, which can help alleviating these issues.

## Appendix A. Compatibility of mean BED equivalent and Iso-NTCP based derivation of mean dose constraints

Let us suppose we have an organ that receives a dose distribution  $\mathbf{D} = (D_1, \dots, D_M)$  in  $N$  fractions ( $M$  is the number of voxels). To calculate the associated NTCP value, most models rely on using the generalized Equivalent Uniform Dose (the popular Lyman–Kutcher–Burman (LKB) approach also belongs to this category, see appendix B). When using any gEUD based NTCP model with a fractionation component (as in Kwa *et al* (1998), Dawson *et al* (2002), Seppenwoolde *et al* (2003), Rancati *et al* (2004), Belderbos *et al* (2005) and Chapet *et al* (2005)) the following three steps are made (Gay and Niemierko 2007, Hoffmann and Nahum 2013):

- First, the doses are adjusted for fraction size, i.e. a dose distribution is calculated which—if given in uniform fractional doses  $f_s$  in each voxel—is BED equivalent to the original dose. This dose in voxel  $i$  is

$$D_{\text{adj},i} = D_i \frac{1 + \frac{D_i}{N\alpha/\beta}}{1 + \frac{f_s}{\alpha/\beta}} = \frac{\text{BED}_i}{1 + \frac{f_s}{\alpha/\beta}}. \quad (\text{A.1})$$

Tomé and Fenwick (2004) appropriately calls equation (A.1) the ‘fraction-size equivalent dose’ and Bentzen *et al* (2012) refers to it as ‘equieffective dose’. If the fraction size is  $f_s = 2$  Gy/fraction equation (A.1) is the well-known normalized total dose (NTD) (Withers *et al* 1983, Flickinger and Kalend 1990, Lebesque and Keus 1991) or equivalent dose delivered in 2 Gy fractions (EQD2).

- Next, using the fraction size adjusted dose distribution, the generalized Equivalent Uniform Dose is calculated for a chosen volume parameter  $n$  (Niemierko 1999) as

$$\begin{aligned} \text{gEUD}_n(\mathbf{D}_{\text{adj}}) &= \left( \frac{1}{M} \sum_{i=1}^M D_{\text{adj},i}^{1/n} \right)^n = \left( \frac{1}{M} \sum_{i=1}^M \left( \frac{\text{BED}_i}{1 + \frac{f_s}{\alpha/\beta}} \right)^{1/n} \right)^n \\ &= \frac{\left( \frac{1}{M} \sum_{i=1}^M (\text{BED}_i)^{1/n} \right)^n}{1 + \frac{f_s}{\alpha/\beta}} = \frac{\text{gEUD}_n(\text{BED}(\mathbf{D}, N, \alpha/\beta))}{1 + \frac{f_s}{\alpha/\beta}} = \frac{\text{gEUBED}_n(\mathbf{D}, N, \alpha/\beta)}{1 + \frac{f_s}{\alpha/\beta}}. \end{aligned} \quad (\text{A.2})$$

We used the notation  $\text{gEUBED}_n(\mathbf{D}, N, \alpha/\beta)$  to signal a  $\text{gEUD}_n(\text{BED}(\mathbf{D}, N, \alpha/\beta))$  calculation based on the BED distribution  $\text{BED}(\mathbf{D}, N, \alpha/\beta) = (\text{BED}_1, \text{BED}_2, \dots, \text{BED}_M)$ , corresponding to giving a dose distribution  $\mathbf{D}$  in  $N$  fractions to an organ with fractionation sensitivity  $\alpha/\beta$  (as opposed to a  $\text{gEUD}_n(\mathbf{D})$  calculation based on the physical dose distribution  $\mathbf{D}$  directly). Simply stated, equation (A.2) means that if we adjust for fractionation, the gEUD in an organ is a constant factor times the ‘generalized Equivalent Uniform BED’



(Hoffmann *et al* 2008). This constant factor is  $1/(1 + fs/\alpha/\beta)$ , only depending on the chosen fraction size  $fs$  and the  $\alpha/\beta$  ratio. In the literature equation (A.2) has also been called the ‘modified equivalent uniform dose’ (Park *et al* 2005) and the ‘radiobiologically corrected gEUD’ (Hoffmann and Nahum 2013).

- Last, normal tissue complication probability is calculated as

$$NTCP = h(\text{gEUD}_n(\mathbf{D}_{\text{adj}})) = \frac{1}{1 + \left( \frac{TD_{50}}{\text{gEUD}_n(\mathbf{D}_{\text{adj}})} \right)^{\gamma_{50}}} \quad (\text{A.3})$$

where the given logistic function in equation (A.3) is only one possibility, in general there are several possible forms for  $h(\text{gEUD}_n(\mathbf{D}_{\text{adj}}))$ .

Under this approximation two dose distributions  $\mathbf{D}_{\text{ref}}$  in  $N_{\text{ref}}$  fractions and  $\mathbf{D}_{\text{new}}$  in  $N_{\text{new}}$  fractions will be iso-effective if they lead to the same NTCP given by equation (A.3). However, for a chosen NTCP model (e.g. for fixed  $TD_{50}$  and  $\gamma_{50}$  parameters in a logistic model) this equivalence simply requires that after adjusting for fractionation the two dose distributions give identical gEUDs according to equation (A.2). Consequently, if the same fraction size  $fs$  is used to adjust doses for fraction size, the equivalence further simplifies to the equivalence of the ‘generalized Equivalent Uniform BEDs’, i.e. to

$$\text{gEUBED}_n(\mathbf{D}_{\text{ref}}, N_{\text{ref}}, \alpha/\beta) = \text{gEUBED}_n(\mathbf{D}_{\text{new}}, N_{\text{new}}, \alpha/\beta),$$

which for a parallel structure ( $n = 1$ ) leads to equation (6). Hence our mean BED equivalent derivation for a mean dose tolerance  $D_{\text{mean}}$  in a new fractionation scheme with  $N_{\text{new}}$  number of fractions is simply a special case of requiring the generalized EUD based NTCP values of the new and the reference dose distributions to be identical for a parallel structure.

## Appendix B. The dependence of the Lyman–Kutcher–Burman (LKB) NTCP model on the gEUD

In Luxton *et al* (2008) it is proven that ‘the EUD for an OAR calculated by the generalized Niemierko formula yields a dose which, if applied uniformly to the entire volume of the OAR, would result in the same NCTP as the effective volume Kytcher-Burman DVH reduction algorithm, calculated for any reference dose’. Essentially the authors of Luxton *et al* (2008) have already shown that the classic LKB model of NTCP can be reformulated to depend on the  $\text{gEUD}_n$ , furthermore (Therapy Physics Committee 2012) also highlights it, but for clarity this is explicitly pointed out here.

In the Lyman model (Lyman 1985) the NTCP for a uniform irradiation of a fraction  $v = V/V_{\text{ref}}$  of an organ to dose  $D$  depends on a parameter

$$u = \frac{D - TD_{50}(v)}{m \cdot TD_{50}(v)},$$

where  $TD_{50}(v) = TD_{50}(1) \cdot v^{-n}$  and  $TD_{50}(1)$  are the partial-volume-dependent and whole organ doses for 50% complication probability and  $m$  characterizes the steepness of the dose response. For inhomogeneous organ irradiation the Kutcher-Burman volume reduction is used (Kutcher and Burman 1989), resulting in the effective volume

$$v_{\text{eff}} = \sum_{j=1}^M v_j \left( \frac{D_j}{D_{\text{ref}}} \right)^{\frac{1}{n}},$$

where  $v_j$  is the relative volume of element  $j$  ( $\sum_{j=1}^M v_j = 1$ ) receiving a normalized dose  $D_j/D_{\text{ref}}$  for a reference dose  $D_{\text{ref}}$ . The assumption is that irradiation a  $v_{\text{eff}}$  fractional volume of the organ with dose  $D_{\text{ref}}$  would result in the same complication probability as the inhomogeneous irradiation. Correspondingly, the final NTCP value in the LKB model depends on

$$u = \frac{D_{\text{ref}} - TD_{50}(v_{\text{eff}})}{m \cdot TD_{50}(v_{\text{eff}})}.$$

However, this dependence can be reformulated as

$$\begin{aligned}
u &= \frac{D_{\text{ref}} - \frac{TD_{50}(1)}{v_{\text{eff}}^n}}{m \cdot \frac{TD_{50}(1)}{v_{\text{eff}}^n}} = \frac{D_{\text{ref}} - \frac{TD_{50}(1)}{\left(\sum_{j=1}^M v_j \left(\frac{D_j}{D_{\text{ref}}}\right)^{\frac{1}{n}}\right)^n}}{m \cdot \frac{TD_{50}(1)}{\left(\sum_{j=1}^M v_j \left(\frac{D_j}{D_{\text{ref}}}\right)^{\frac{1}{n}}\right)^n}} = \frac{1 - \frac{TD_{50}(1)}{\left(\sum_{j=1}^M v_j D_j^{\frac{1}{n}}\right)^n}}{m \cdot \frac{TD_{50}(1)}{\left(\sum_{j=1}^M v_j D_j^{\frac{1}{n}}\right)^n}} \\
&= \frac{1 - \frac{TD_{50}(1)}{\text{gEUD}_n(\mathbf{D})}}{m \cdot \frac{TD_{50}(1)}{\text{gEUD}_n(\mathbf{D})}} = \frac{\text{gEUD}_n(\mathbf{D}) - TD_{50}(1)}{m \cdot TD_{50}(1)},
\end{aligned}$$

which concludes our proof that the LKB model is an NTCP model directly depending on the generalized equivalent uniform dose as defined by Niemierko (1999).

## Appendix C. Inclusion of relative biological effectiveness

Throughout the paper we included RBE effects by using  $\text{RBE}_{\text{proton}} = 1.1$  and consequently presenting all proton physical doses as the RBE corrected doses  $D_{\text{proton}} = \text{RBE}_{\text{proton}} \tilde{D}_{\text{proton}}$ . All BED calculations were done subsequent to taking into account the RBE effect, thus the derived proton doses for new fractionation regimens and new dose shape factors were directly the RBE corrected doses. This is consistent with current clinical practice, where the proton RBE is assumed to be fraction-size independent. In Dale and Jones (1999) a modified BED formulation is presented that directly incorporates RBE effects into the BED model. This modified BED formulation reads

$$\text{BED} = D \left( \text{RBE} + \frac{D}{N\alpha/\beta_L} \right),$$

where  $\alpha/\beta_L$  is the  $\alpha/\beta$  ratio representative for low Linear Energy Transfer (LET) radiation (practically photons, simply denoted as  $\alpha/\beta$  from this point), and  $D$  and  $\text{RBE}$  are the (non-RBE adjusted) dose and the intrinsic RBE value for the given radiation (which can be both low and high LET). All our results can be generalized according to this Dale-Jones RBE model, and this appendix presents both these general formulas, as well as the sensitivity of our results to this different formulation.

### C.1. Generalized BED formulas

Equating the BEDs for two regimens with different radiations yields the general counterpart of equation (2) as

$$D_{\text{new}} \left( \text{RBE}_{\text{new}} + \frac{D_{\text{new}}}{N_{\text{new}}\alpha/\beta} \right) = D_{\text{ref}} \left( \text{RBE}_{\text{ref}} + \frac{D_{\text{ref}}}{N_{\text{ref}}\alpha/\beta} \right). \quad (\text{C.1})$$

The solution of equation (C.1) for the new dose  $D_{\text{new}}$  (see equation (3)) is

$$D_{\text{new}} = \frac{1}{2} \left[ \sqrt{(N_{\text{new}}\alpha/\beta \text{RBE}_{\text{new}})^2 + 4D_{\text{ref}} \left( N_{\text{new}}\alpha/\beta \text{RBE}_{\text{ref}} + D_{\text{ref}} \frac{N_{\text{new}}}{N_{\text{ref}}} \right)} - N_{\text{new}}\alpha/\beta \text{RBE}_{\text{new}} \right]. \quad (\text{C.2})$$

The mean BED is a straightforward extension of equation (4) with the RBE effect leading to

$$\text{BED}_{\text{mean}} = D_{\text{mean}} \left( \text{RBE} + \frac{D_{\text{mean}}}{N\alpha/\beta} \varphi \right). \quad (\text{C.3})$$

Therefore, a new mean dose tolerance  $D_{\text{mean}}$  can be obtained in a mean BED equivalent manner by solving

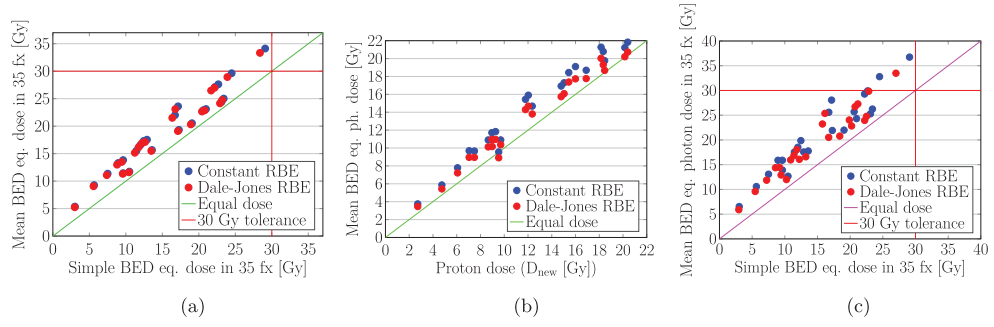
$$D_{\text{new}} \left( \text{RBE}_{\text{new}} + \frac{D_{\text{new}}}{N_{\text{new}}\alpha/\beta} \varphi_{\text{new}} \right) = D_{\text{ref}} \left( \text{RBE}_{\text{ref}} + \frac{D_{\text{ref}}}{N_{\text{ref}}\alpha/\beta} \varphi_{\text{ref}} \right) \quad (\text{C.4})$$

instead of equation (6). The solution (see equation (7)) is

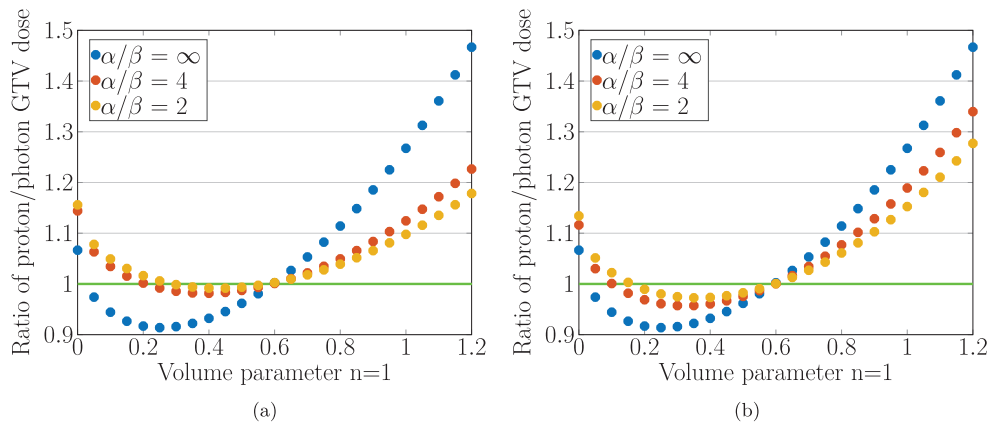
$$D_{\text{new}} = \frac{1}{2} \left[ \sqrt{\left( \frac{N_{\text{new}}\alpha/\beta \text{RBE}_{\text{new}}}{\varphi_{\text{new}}} \right)^2 + 4D_{\text{ref}} \left( \frac{N_{\text{new}}\alpha/\beta \text{RBE}_{\text{ref}}}{\varphi_{\text{new}}} + D_{\text{ref}} \frac{\varphi_{\text{ref}}}{\varphi_{\text{new}}} \frac{N_{\text{new}}}{N_{\text{ref}}} \right)} - \frac{N_{\text{new}}\alpha/\beta \text{RBE}_{\text{new}}}{\varphi_{\text{new}}} \right]. \quad (\text{C.5})$$

Last, the formula for the generalized Equivalent Uniform BED with the RBE being taken into account (see equation (9)) reads

$$\text{gEUBED}_n(\mathbf{D}, N, \alpha/\beta, \text{RBE}) = \frac{1}{M} \left[ \sum_{i=1}^M \left( D_i \left( \text{RBE} + \frac{D_i}{N\alpha/\beta} \right) \right)^{1/n} \right]^n. \quad (\text{C.6})$$



**Figure C1.** The influence of the method of taking into account the RBE of protons. The Dale–Jones RBE model predicts slightly smaller effects than the constant RBE method, however the differences do not alter our main conclusions. (a) Mean doses in 35 fractions that are equivalent with the given proton doses in 5/15 fractions, with ( $y$ -axis) and without ( $x$ -axis) taking into account the dose shape (see figure 2(b)). (b) Mean BED equivalent photon mean dose as a function of proton mean dose (see figure 4(c)). (c) Mean BED equivalent 35-fraction photon mean doses versus simple BED equivalent 35-fraction mean doses (see figure 5).



**Figure C2.** Dose escalation potential of protons versus photons for equivalent gEUD based NTCP values with various volume parameters  $n$  and fractionation sensitivities  $\alpha/\beta$ , with the Dale–Jones method of accounting for RBE based on Dale and Jones (1999). (a) Reference: hypofractionated (5/15 fraction), clinically delivered proton plans (see figure 6(a)). (b) Reference: scaled proton plans assuming standard fractionation (70 Gy GTV dose with 2 Gy/fx, 35 fractions, see figure 6(b)).

Thus, for iso-toxic dose escalation, i.e. to calculate how a dose distribution  $\mathbf{D}_{\text{new}}$  (with a radiation type having an RBE value  $\text{RBE}_{\text{new}}$ ) can be scaled to a distribution  $f \cdot \mathbf{D}_{\text{new}}$  such that it leads to the same NTCP as the reference distribution  $\mathbf{D}_{\text{ref}}$  (with an RBE value of  $\text{RBE}_{\text{ref}}$ ),

$$\text{gEUBED}_n(f \cdot \mathbf{D}_{\text{new}}, N_{\text{new}}, \alpha/\beta, \text{RBE}_{\text{new}}) = \text{gEUBED}_n(\mathbf{D}_{\text{ref}}, N_{\text{ref}}, \alpha/\beta, \text{RBE}_{\text{ref}})$$

has to hold, leading to the general counterpart of equation (10), reading

$$\left[ \frac{1}{M} \sum_{i=1}^M \left( f \cdot D_{\text{new},i} \left( \text{RBE}_{\text{new}} + \frac{f \cdot D_{\text{new},i}}{N_{\text{new}} \alpha/\beta} \right) \right)^{1/n} \right]^n = \left[ \frac{1}{M} \sum_{i=1}^M \left( D_{\text{ref},i} \left( \text{RBE}_{\text{ref}} + \frac{D_{\text{ref},i}}{N_{\text{ref}} \alpha/\beta} \right) \right)^{1/n} \right]^n. \quad (\text{C.7})$$

This more consistent formulation decreases the BED values for all proton plans. In our original formulation, the proton physical doses  $D_{\text{proton}} = \text{RBE}_{\text{proton}} \tilde{D}_{\text{proton}}$  were used directly in the BED equation, leading to  $\text{BED} = D_{\text{proton}} \left( 1 + \frac{D_{\text{proton}}}{N \alpha/\beta} \right)$ . In contrast, the more consistent formulation reads  $\tilde{D}_{\text{proton}} \left( \text{RBE}_{\text{proton}} + \frac{\tilde{D}_{\text{proton}}}{N \alpha/\beta} \right) = D_{\text{proton}} \left( 1 + \frac{D_{\text{proton}}}{N \alpha/\beta \text{RBE}_{\text{proton}}} \right)$ , obviously smaller for RBE values above 1. The relative BED difference (compared to our original formulation) is

$$\frac{\Delta \text{BED}}{\text{BED}} = - \frac{\text{RBE}_{\text{proton}}^2 - 1}{\text{RBE}_{\text{proton}}^2} \frac{1}{1 + \frac{N \alpha/\beta}{D_{\text{proton}}}}. \quad (\text{C.8})$$

For  $\text{RBE}_{\text{proton}} = 1.1$  this translates to a maximum difference of  $-17.3\%$  (for  $D_{\text{proton}}/N = \infty$ ), and it decreases with decreasing dose per fraction size (e.g. for  $D_{\text{proton}}/N = 2$  Gy and  $\alpha/\beta = 3$  Gy we find  $\Delta \text{BED}/\text{BED} = -6.9\%$ ).

## C.2. Sensitivity to accounting for RBE

To test the sensitivity of our results to the different incorporation of the RBE all calculations have been done using both approaches. Figure C1 shows the general counterparts of the most important figures regarding the shape and fractionation effects, displaying both the results of our original formulation (labeled as ‘Constant RBE’ in blue) as well as the formulation of Dale and Jones (1999) (‘Dale–Jones RBE’ in red). As expected, the more consistent methodology decreases effects. Nevertheless, the differences are small (around 5–10%), and our main conclusions remain valid: neglecting the shape effect when calculating iso-effective doses in new fractionation schemes (figure C1(a)) and new modalities (figure C1(b)) underestimates their biological effects, and there are situations where neglecting the dose shape effect leads to significantly lower doses than are iso-effective (figure C1(c)).

The effect of the proton RBE incorporation on the dose escalation potential of protons compared to photons is also relatively small (see figure C2). All physical dose based results ( $\alpha/\beta = \infty$ ) naturally remain unchanged, whereas the BED based calculations ( $\alpha/\beta < \infty$ ) yield around 5–10% higher proton/photon GTV dose ratios than our original formulation (compare with figure 6). This is a straightforward consequence of the different handling of the RBE: since the Dale–Jones method leads to lower BED values for protons, photon doses—for which the two formulations are identical—can be scaled less, leading to higher proton/photon target dose ratios. For a mean BED constraint ( $n = 1$ ) with our hypofractionated (5/15 fraction) treatments adjusting for fractionation decreases protons’ dose escalation potential to only 12% compared to the 25% based on physical dose, and for  $n = 1.1$  (Dawson and Balter 2004) to only 17% compared to 35% (see our 5% and 10% estimates based on figure 6(a)). Just as is the case in section 3.5, the differences somewhat decrease when standard fractionation is assumed (figure C2(b)). Understandably, the biggest contrast between the two formulations is seen for  $n \in [0, 0.6]$ , since for small volume parameters more and more the highest dose values matter (i.e. the voxels having the highest doses and dose per fraction values), and the BED difference is increasing with the dose per fraction (in accordance with equation (C.8)). In this region the BED adjustment including RBE predicts higher dose escalation potential than based on physical dose, as the degradation due to accounting for fractionation is counterbalanced by the more beneficial RBE effect. For  $n > 0.6$  the fractionation effect becomes dominant (as all voxels become increasingly important), and though the Dale–Jones RBE approach does predict a higher dose escalation potential for protons than our constant RBE approach, this potential is still substantially lower than is expected based on physical dose.

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