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SCIENTIFIC PAPER

Use of 3D biological effective dose (BED) for optimizing multi-target liver cancer treatments

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Abstract

The purpose is to calculate the composite 3D biological effective dose (BED) distribution in healthy liver, when multiple lesions are treated concurrently with different hypo-fractionated schemes and stereotactic body radiation therapy, and to investigate the potential of biological based plan optimization. Two patients, each having two tumors that were treated sequentially with different treatment plans, were selected. The treatment information of both treatment plans of the patients was used and their dose matrices were exported to an in-house MATLAB software, which was used to calculate the composite BED distribution. The composite BED distributions were used to determine if the healthy liver received BED beyond tolerance. When the dose to the minimum critical volume was less than tolerance, an optimization code was used to derive the scaling factors (ScF) that should be applied to the dose matrix of each plan until the minimum critical volume of healthy liver reaches a BED close to tolerance. It was shown that for each patient, there is a margin for dose escalation regarding the doses to the individual targets. More specifically, the ScFs of the doses range between 5.6 and 99 in the first patient, whereas for the second patient, the ScFs of the optimal doses range between 12.7 and 35.6. The present study indicates that there is a significant margin for dose escalation without increasing the radiation toxicity to the healthy liver. Also, the calculation of the composite BED distribution can provide additional information that may lead to a better assessment of the liver's tolerance to different fractionation schemes and prescribed doses as well as more clinically relevant treatment plan optimization.

Keywords BED · Biological · Optimization · Liver cancer radiotherapy · Multi-phase treatment protocols

Introduction

Stereotactic body radiotherapy (SBRT) is known to be a hypo-fractionated radiation treatment that accurately delivers dose to a small, focused region in the body employing coplanar and non-coplanar beams. This treatment has been shown to improve tumor control probability (TCP) while maintaining or even decreasing the conventional normal tissue complication probability (NTCP). However, there is still a significant uncertainty in predicting the side effects of hypo-fractionated SBRT treatments and accurately assessing the effects of the different fractionation schemes and dose prescriptions used. This is due to the lack of solid clinical data to provide adequate validation of the parameters that describe the response of a tissue to radiation. Presently, there are mainly dosimetric dose limits for SBRT, which have been recommended by the American Association of Medical Physics (AAPM) or related reports [1–3]. Regarding standard fractionation schemes, such data and dose limits have been collected over a much longer period of time [4].

Due to the dependence of Cellular Surviving Fraction (CSF) on fractionation scheme, the biological effective dose (BED) concept was introduced and studied in order to identify its correlation with clinical results and its impact on different fractionation schemes [5–10]. Despite the long history of BED and its broad acceptance, its clinical use is still limited, especially in the treatment plan evaluation and analysis of intensity modulated radiation therapy (IMRT) and SBRT. Regarding IMRT treatments, Barton created tables of dose limits, which are based on

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the conversion of the Emami et al. limits to equivalent fractionation schemes of 2 Gy/fraction (fx) [4, 5]. It was noted that there are still uncertainties in the correlation of BED with the clinical outcomes but this correlation is much better relative to the correlations provided by the physical dose (PD).

Regarding hypo-fractionated SBRT, there are studies indicating that the linear-quadratic (LQ) model, which is the basis of the BED function, is not accurate at larger dose per fractions [6]. Kirkpatrick et al. specifically showed how the simple BED function at large dose per fractions would underestimate the fraction of surviving cells [6]. Due to these findings, many groups have studied the survival curve at large doses to try and modify the LQ model in order to take into account the linearity at larger doses [7–12].

The liver is considered to be a late-responding tissue and several research groups have assumed that its α/β value is 3 Gy [13–16]. There have been other studies that have reported a higher α/β value for healthy liver, such as the work done by Son et al. [17]. They used clinical data from patients with hepatocellular carcinoma and concluded that α/β in this case was 8 Gy. Garcia et al. concluded that depending on the methodology in deriving the value for α/β (especially the dose range), a significant variation in the determined values could be observed [18].

Presently, the liver SBRT dose limits that are used in clinical practice are mainly based on research data, which, however, assume that only one fractionation scheme is used. Furthermore, there are treatment protocols that involve multi-prescription SBRT liver treatments, which makes the accurate determination of the composite BED more complicated due to the fact that the healthy liver is exposed to different fractionation schemes and dose distributions by the different phases of the treatment.

Based on the mathematical formalism of BED, different fractionation schemes can be isoeffective (e.g., $BED_1 = BED_2$ or $BED_1 + BED_2 = BED_3$). Consequently, if there is a BED limit that is associated with a given clinical endpoint in liver, then the BED limit for liver hypo-fractionated SBRT should be the same for any fractionation scheme applied. This would simplify the physician's task of delivering a given dose prescription to the tumor (or even escalating it), while keeping the dose to the healthy liver below tolerance limits.

This work aims at investigating a proposed method of optimizing multi-prescription, hypo-fractionated SBRT liver treatment plans using the currently applied dose limits in conjunction with the BED formalisms for both low- and high-dose regions. This work also studies the magnitudes by which the prescribed doses for each prescription can be increased when the cumulative BED distribution is significantly below the BED limit.

Material and methods

In this study, the equations that were used to calculate BED are shown below:

$$BED_{LQ} = nd\left(1 + \frac{d}{\alpha/\beta}\right) \text{ for } d < d_T \tag{1}$$

$$BED_{LQL} = nd_T\left(1 + \frac{d_T}{\alpha/\beta}\right) + \left[n\left(\gamma/\alpha\right)\left(d - d_T\right)\right] \text{ for } d \geq d_T \tag{2}$$

where

$$\gamma/\alpha = 1 + \left[\frac{2d_T}{\alpha/\beta}\right] \tag{3}$$

γ is the slope of the survival curve at d_T which is the "threshold dose", n is the number of fractions, d is the dose per fraction, and α and β are the coefficients within the LQ-model that fit the equation to the survival curve. d_T is the point at which the survival curve responds linearly rather than quadratically. So, when the fractionated dose is less than d_T, the BED is derived from the LQ-model, whereas when the fractionated dose is greater than d_T, then the BED is calculated by the linear-quadratic-linear (LQL) model (Eqs. 1–3) [7]. In this study, the α/β value of 3 Gy is used. Based on reports, which state that d_T approximately equals 2α/β [7], the threshold dose for the liver should be 6 Gy.

Using Eqs. 1–3 to calculate the BED delivered to the liver in both the low- and high-dose ranges, the cumulative dose to the healthy liver in multi-prescription hypo-fractionated SBRT treatment plans could be calculated. The cumulative BED is calculated by simply calculating the 3D-BED distribution of each treatment plan separately, and subsequently summing them on a voxel-to-voxel basis.

MATLAB 2010 (MathWorks, Natick, MA) was used to three-dimensionally analyze the PD matrices of two patients receiving multi-prescription hypo-fractionated SBRT treatment plans [19]. The PD matrices of the two patients were created and exported using the treatment planning system (TPS) Pinnacle^3 (Philips Medical, Fitchburg, WI). Table 1 lists the specific prescriptions for each patient along with the PD statistics of the GTVs involved in each case. In Table 1, the three common fractionation schemes of 15 Gy/fx in 3 fxs (fractions), 10 Gy/fx in 5 fxs, and 3 Gy/fx in 10 fxs are also shown.

In the present study, the BED limits corresponding to 17.1 Gy (5.7 Gy/fx) and 21 (4.2 Gy/fx) covering the volume of 700 cm^3, which have been clinically implemented for liver SBRT treatments, were used [20]. When converting the physical dose limit to BED in both the three and five fraction

Table 1 Physical dose prescriptions of the studied patients for the GTV in the liver (Px: prescribed fractionation; $^{Max}D_{GTV}$: maximum prescribed dose to the GTV; V_{GTV}: volume of the GTV)

Patient	Px1 (Gy/fx)	Px2 (Gy/fx)	$^{Max}D_{GTV1}$ (Gy)	$^{Max}D_{GTV2}$ (Gy)	V_{GTV1} (cm^3)	V_{GTV2} (cm^3)
1	50/5	30/10	61.6	33.8	7.07	1.51
2	45/3	30/10	58.4	37.8	3.40	8.54

schemes, the BEDs were 49.6 Gy_3 and 50.4 Gy_3. Based on this finding, the value of 50 Gy_3 was set to be the BED limit, which should not exceed the minimum critical volume of 700 cm^3 to avoid liver failure. 50 Gy_3 will also be applied to hypo-fraction (e.g., 30 Gy in 10 fxs) since BED produces a quantitative value independent of the fractionation scheme used. From the dose distributions in each of the patients in Table 1, the BED distributions were calculated in order to associate them with the BED limit.

Due to the fact that multi-prescription plans were applied in the examined patients, the composite BED volume histograms (BEDVH) had to be calculated first in order to determine whether the planned BED exceeded the BED limit that was derived from the clinically accepted PD limits. In all the cases, the planned dose distributions were further optimized in term of increasing the BED-coverage of the targets while BED-sparing the healthy liver. Dose heterogeneity is included in the analysis by performing all calculations on a voxel by voxel basis.

Treatment plan optimization

After initially calculating the composite BED dose distribution and comparing it against the established critical volume and BED limits, it can be determined how much the dose in each voxel can escalate. This can be done by applying voxel-based scaling factors (ScF), which correspond to a percentage increase of the initial prescribed dose to the target while maintaining the dose delivered to the healthy liver below the relevant tolerance limits.

More specifically, after the calculation of the initial and final composite 3D-BED distribution matrices (BED_i, and BED_f, respectively), the difference between them can be found. The two equations that were used to calculate the difference are:

$$BED_{1i}(\vec{r}) + BED_{2i}(\vec{r}) = BED_i(\vec{r}) \tag{4}$$

and

$$BED_{1f}(\vec{r}) + BED_{2f}(\vec{r}) = BED_f(\vec{r}) \tag{5}$$

where $BED_{1i}(\vec{r})$ and $BED_{2i}(\vec{r})$ are the initial BED values in a voxel due to prescriptions 1 and 2, respectively, and $BED_{1f}(\vec{r})$ and $BED_{2f}(\vec{r})$ are the final BED values in the same voxel following an increase in the dose of each prescription by the respective scaling factor, ScF_1 and ScF_2.

The two variables (e.g. $BED_{1f}(\vec{r})$ and $BED_{2f}(\vec{r})$), that are unknown and need to be determined in order to calculate the ScFs for each prescription, can now be solved by first subtracting Eq. 5 from Eq. 4, which leads to the following expression:

$$\begin{aligned}&\left(BED_{1f}(\vec{r}) - BED_{1i}(\vec{r})\right) + \left(BED_{2f}(\vec{r}) - BED_{2i}(\vec{r})\right)\\ &\quad = \left(BED_f(\vec{r}) - BED_i(\vec{r})\right)\end{aligned} \tag{6}$$

with

$$\Delta = BED_f(\vec{r}) - BED_i(\vec{r}) \tag{7}$$

Δ is already known since $BED_f(\vec{r})$ is assumed to be the BED limit of 50 Gy_3 and $BED_i(\vec{r})$ is calculated based on the PD distributions of the initial plan. Equation 7 can be rewritten as follows:

$$\frac{\left(BED_{1f}(\vec{r}) - BED_{1i}(\vec{r})\right)}{\Delta} + \frac{\left(BED_{2f}(\vec{r}) - BED_{2i}(\vec{r})\right)}{\Delta} = 1 \tag{8}$$

where each summation component is expressed as

$$\tau = \frac{\left(BED_{1f}(\vec{r}) - BED_{1i}(\vec{r})\right)}{\Delta} \tag{9}$$

and

$$\delta = \frac{\left(BED_{2f}(\vec{r}) - BED_{2i}(\vec{r})\right)}{\Delta} \tag{10}$$

τ and δ will be considered the percentages of Δ that will be contributed by each prescription. For example, if prescription 1 (Px1) could not be increased, then τ will be set to 0 and δ would be set to 1. On the other hand, if both prescriptions (Px1 and Px2) could be increased and the treatment planner wants both to equally contribute to the dose increase, then τ and δ would be set to 0.5. The ScFs for each prescription depends on what τ and δ are set to. As seen in Eqs. 8–10, the sum of τ and δ will always be 1.

Based on Eqs. 8–10, $BED_{1f}(\vec{r})$ and $BED_{2f}(\vec{r})$ can now be solved as follows:

$$BED_{1f}(\vec{r}) = \tau\Delta + BED_{1i}(\vec{r}) \tag{11}$$

and

$$BED_{2f}(\vec{r}) = \delta\Delta + BED_{2i}(\vec{r}) \tag{12}$$

The values of τ and δ depend on the initial dose distributions since for example Px1 may need to remain unchanged due to limitations imposed by other healthy organs such as spinal cord. $BED_{1i}(\vec{r})$ and $BED_{2i}(\vec{r})$ are already determined from the initial plan and Δ is determined from Eq. 7.

Once $BED_{1f}(\vec{r})$ and $BED_{2f}(\vec{r})$ have been calculated, Eqs. 1 and 2 can be used to determine the new ds of the two phases in order to render the voxel's BED 50 Gy_3. As mentioned earlier, some voxels may receive a d greater than d_T, while others lower than that. Hence the two equations used are the following:

$$d_f(\vec{r}) = \frac{-\alpha/\beta + \sqrt{\left(\alpha/\beta\right)^2 + \frac{4\alpha/\beta}{n} BED_f(\vec{r})}}{2}, \quad \text{for } d_i < d_T \tag{13}$$

and

$$d_f(\vec{r}) = \frac{\alpha}{\gamma n}\left(BED_f(\vec{r}) - nd_T\left(1 + \frac{d_T}{\alpha/\beta}\right) + \frac{\gamma n}{\alpha} d_T\right) \quad \text{for } d_i \geq d_T \tag{14}$$

where BED_f will be set to either BED_{1f} or BED_{2f} in order to calculate ScF_1 or ScF_2, respectively. Once d_f is determined, the corresponding ScF can also be determined by finding the ratio between the final and initial dose per fraction.

$$ScF(\vec{r}) = d_f/d_i \tag{15}$$

The ScF value of each voxel is the factor by which its physical dose should increase in order to produce a BED of 50 Gy_3. The ScF of a given voxel in each prescription may not be the same for other voxels within the same prescription (if applied to other voxels, BED might result being greater than or less than 50 Gy_3). Consequently, the ScF is found for each voxel within the healthy liver's dose distribution matrices and then the average will be calculated. To ensure that the average ScF will not lead to a dose distribution exceeding the BED dose constraint, the average ScF will be applied and if the dose constraint is exceeded, ScF will be reduced until the dose constraint is satisfied.

Results

Table 2 shows both the physical and biological effective dose statistics for the normal liver (e.g., liver minus GTV) of each patient. The minimum critical volume that cannot receive more than 50 Gy_3 is 700 cm^3. The volume that can receive at least 50 Gy_3 is the total normal liver volume minus the minimum critical volume (e.g., $\Delta V = V_{total} - 700\ cm^3$). For patients 1 and 2, the volume that can receive 50 Gy_3 or more is 872 cm^3 and 1614 cm^3, respectively. Table 2 also displays the dose that the ΔV volume receives, and as it is shown, in each patient the ΔV volume receives less than 50 Gy_3, which means that there is a significant margin for increasing in prescribed dose to the targets. Figure 1 displays the

Table 2 Statistical indices based on the composite PD and BED distributions including the volume of the normal liver (V_{NL}) and the dose that volume ΔV receives ($D_{\Delta V}$)

Patient	Physical dose (Gy)					Biological effective dose (Gy_3)				
	D_{mean}	D_{SD}	D_{min}	D_{max}	V_{NL} (cm^3)	BED_{mean}	BED_{SD}	BED_{min}	BED_{max}	$D_{\Delta V}$
1	9.96	12.1	0.33	59.4	1572	23.7	44.5	0.33	237	6.09
2	11.5	11.3	0.24	59.0	2314	30.0	45.1	0.25	256	5.04

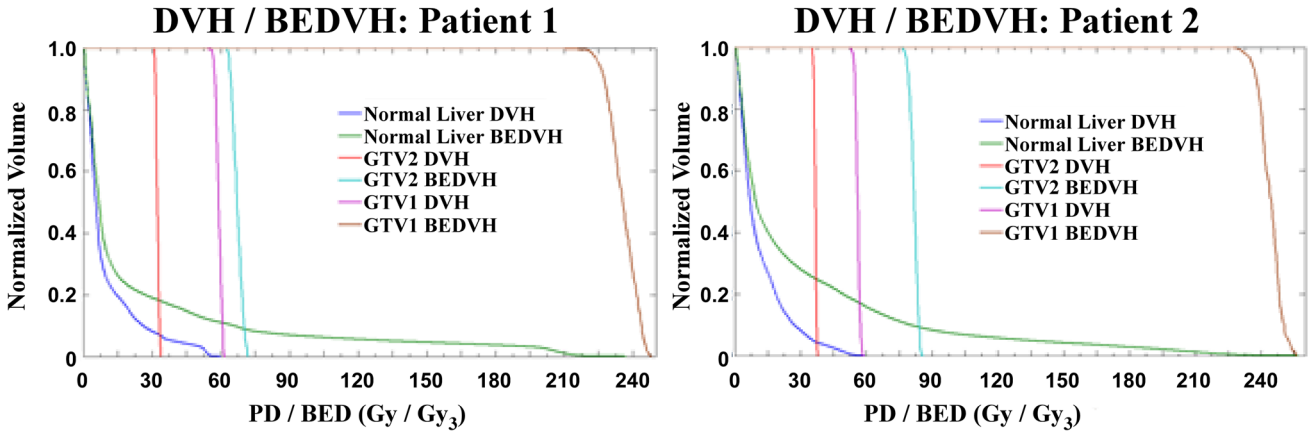

Fig. 1 The DVHs and BEDVHs of the targets and normal liver of the patients

Table 3 The extreme fractional contributions to the scaling factors (ScFs) leading to 50 Gy_3 to the minimum critical volume for the individual patients

Patient	τ (Plan 1)	δ (Plan 2)	ScF (Plan 1, Plan 2)	d_f (Plan 1, Plan 2) (Gy/fx)
1	0.0	1.0	(1.0, 99.0)	(10.0, 297.0)
	1.0	0.0	(5.6, 1.0)	(56.1, 3.0)
2	0.0	1.0	(1.0, 35.6)	(15.0, 106.0)
	1.0	0.0	(12.7, 1.0)	(191.0, 3.0)

DVHs and BEDVHs representing the data in Tables 1 and 2 for the two patients.

Treatment plan optimization

As shown in Table 2, all the patients receive significantly less dose than 50 Gy_3 to the minimum critical volume of 700 cm^3 of their healthy liver. This indicates that there is a good margin for an increase in each of the applied dose prescriptions.

Table 3 shows the increase in the dose prescriptions for each of the examined patients so that the dose to the critical 700 cm^3 of the normal liver will not exceed the limit of 50 Gy_3. As seen in Figs. 2 and 3, both patients can have their doses increased by a relatively large amount. Both patients can have relatively large dose increases because the initial BED to the minimum critical volume was much less than 50 Gy_3.

Discussion

A common source of uncertainty in treatments involving multi-lesion irradiation with different fractionation schemes for each target is the determination of the appropriate tolerance dose constraint in the involved OARs. In liver hypofractionated SBRT, this uncertainty has led to the clinical implementation of more conservative treatment protocols in

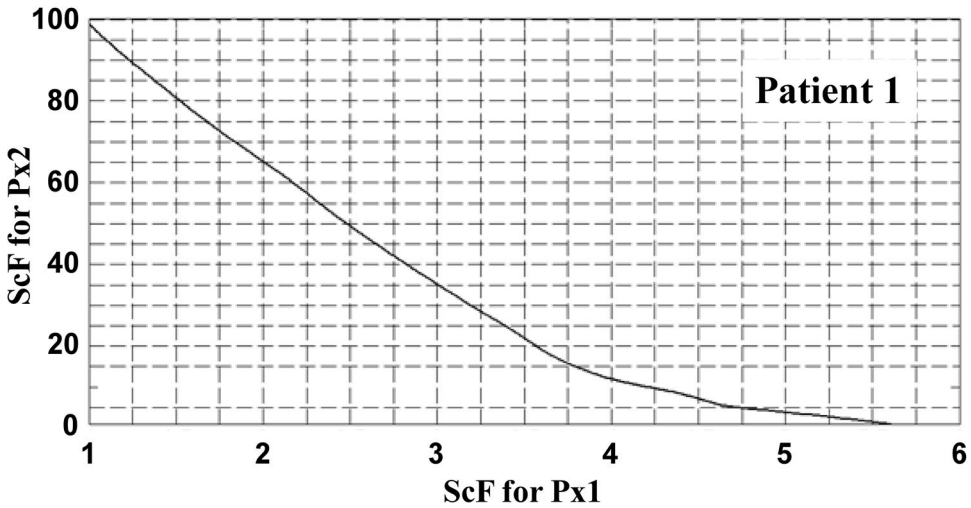

Fig. 2 Illustration of the relation of ScF_1 and ScF_2 for values between the maximums revealed in Table 3. Depending on the value of ScF_1, which ranges between 1 and 5.6, this plot displays the value of ScF_2 so that the tolerance limit to the healthy liver will not be exceeded

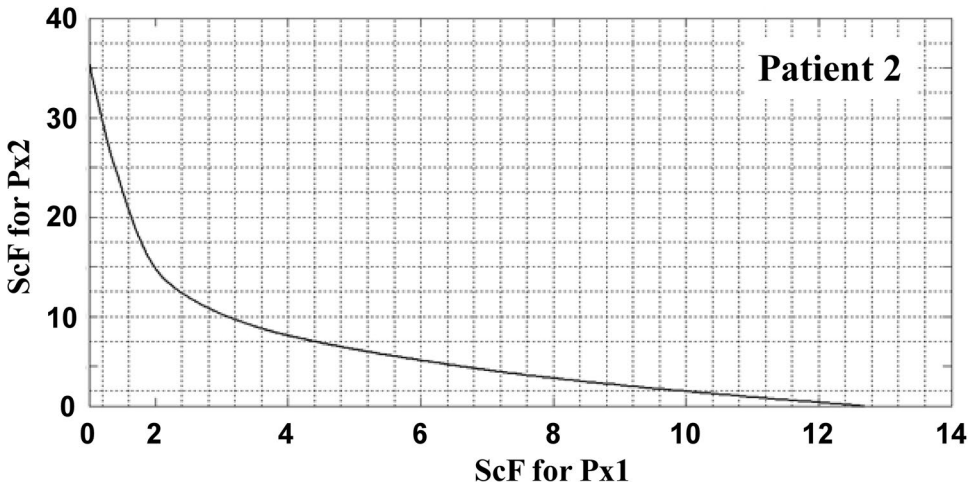

Fig. 3 Illustration of the relation of ScF_1 and ScF_2 for values between the maximums revealed in Table 3. Depending on the value of ScF_1, which ranges between 1 and 12.7, this plot displays the value of ScF_2 so that the tolerance limit to the healthy liver will not be exceeded

an effort to avoid increased rates of normal tissue toxicity. A potential problem of this approach is that it may lead to reduced tumor control rates in order to prevent damage to the healthy liver. Dose delivery in excess of the BED limit of 50 Gy_3 has been reported to lead to liver failure. More specifically, Timmerman et al. showed that the dose limits for the healthy liver in three and five fraction schemes of hypofractionated SBRT was 17.1 Gy (5.7 Gy/fx) and 21 (4.2 Gy/fx) covering, in both cases, the minimum critical volume of 700 cm^3 [20].

The present study showed that the two patients had fractionation schemes and dose prescriptions that resulted in significantly lower doses than the BED limit of 50 Gy_3 to the critical 700 cm^3 of the healthy liver. This observation indicates that there is a good margin for increasing the dose to the tumors while preventing liver failure. More specifically, the optimization algorithm showed in each patient that the ScFs of the separate dose prescriptions were always large, which indicates that there is possibility for dose escalation and tumor control improvement without exceeding the point of liver failure.

Astrahan had shown through *in-vitro* and *in-vivo* cellular survival curves that Eqs. 1 and 2 nicely fit many of those survival curves while the equation of Park et al. fits only one [7, 10]. It has been reported that the accuracy of the traditional BED equation is compromised at large doses. An important aspect of Astrahan's work was his observation that late-responding tissues displayed a threshold dose d_T approximately equal to $2\alpha/\beta$ [7]. Fisher et al. showed that the value of α/β for the hepatocytes of mice ranged between ~ 1–2 Gy hence concluding that they were late-responding tissues [21]. Since for most of the tissues the α/β is known with some uncertainty, this means that the knowledge of the exact value of d_T is subject to the same uncertainty, which however does not change the fact that survival curves respond linearly at higher doses. For this work, it is assumed that the calculated d_T is the true value. As for the linearity component added to the BED equations derived through the LQ-model, it is independent of α/β, as seen in Eq. 2. γ/α will always be equal to 5 Gy.

Regarding the present optimization approach there a few points that need additional analysis. The first point is that despite the margin of the prescribed total dose and d to increase to larger values, neighboring OARs may become the dose limiting tissues. For example, in patient 1, d could be as high as 297 Gy/fx for $\tau = 0$ and $\delta = 1$, which however would definitely lead to increased complications such as skin erythema or over-dosage to another nearby healthy organ. The maximum doses per fraction that are shown on Table 2 (56.1 Gy and 297 Gy for patient 1, 106 Gy and 191 Gy for patient 2), are extremely high and stem from the fact that the physical doses to the healthy liver are very low for the corresponding plan. So, by escalating the whole dose distribution to the point that those doses will reach the BED limit of the healthy liver, the nominal dose per fraction to the tumor will be very high. Of course, one does not need to reach those extreme values but to escalate up to a point that will ensure a high local control rate.

The second point is that this optimization approach assumes that only the prescribed total doses and ds are changed versus being able to simultaneously change the complete beam configuration and consequently the composite dose distribution. There could be a possibility of increasing the prescribed d of the treatment plans and preventing the first restriction previously mentioned by rearranging the beam setup or adding more beams.

Another point deals with the clinical validity of the linear-quadratic-linear (LQL) model. Brown et al. worked on the analysis of the LQ-model and its accuracy at larger fractional doses [22]. The LQ-model has been studied by many research groups, specifically trying to specify its accuracy in predicting cell survival and determine other parameters that could be added in order to increase its predictive ability. There are new expanded LQ-based models with additional parameters, which better fit the cellular survival curve at higher ds (based on in-vitro studies). However, for both the LQ and LQL models newer and clinically validated α/β values are published for different organs, which makes the presented work more clinically relevant.

A recent review study showed that the 1-, 2-, and 3-year actuarial local control rates after SBRT for primary liver tumors ($n = 431$) were 93%, 89%, and 86%, respectively. For liver metastases, outcomes were significantly better for lesions treated with BEDs exceeding 100 Gy_{10} (3-year local control 93%) than for those treated with BEDs of ≤ 100 Gy_{10} (3-year local control 65% [23]. Another study showed that a mean BED_2 of 73 and 16 Gy for the whole liver appeared appropriate to prevent RILD in patients with Child–Pugh classes A and B, respectively [24]. So, the fact that a dose escalation may lead to an increase in the local control rates by almost 30% is a very good reason for trying to escalate the dose in the way it is shown in the present study trying however not to exceed the BED limits to the healthy liver. In line with those studies, a different group examined simultaneously the BEDs of tumors and healthy liver and showed that spatiotemporal fractionation presents a method of increasing the ratio of prescribed tumor BED to mean BED in the noninvolved liver by approximately 10–20%, compared to conventional SBRT using identical fractions [25]. Their conclusions agree with the results of this work.

It is known that all the existing radiobiological models (including the LQ and LQL) have been built on some assumptions and they do not account for all the biological mechanisms. This has an impact on the determination of the model parameters of the different tissues. Additionally, the values of those model parameters are characterized by

uncertainties, which do not step only the imperfection of the models but are imposed by inaccuracies in the patient setup and treatment delivery during radiotherapy and the lack of knowledge of the inter-patient radiosensitivity. Consequently, the determined model parameters and the corresponding dose–response curves are characterized by confidence intervals. So, the dose escalation that is indicated by this study should be done conservatively by taking into account those confidence intervals and in this way reduce the risk for observing detrimental effects after radiotherapy. The results of this study depend on the accuracy of the radiobiological models and the parameters that describe the dose–response relations of the examined normal tissue.

Although the presented methodology was implemented on liver SBRT, it can be used for other tumor sites (e.g. brain), which involve multiple lesions, which are treated with different fractionation schemes. However, due to the fact that the presented method is ideal for tissues with parallel structure, in order to generalize it for other sites it would be better to calculate the corresponding normal tissue complication probabilities (NTCP) of the tissues involved. The use of NTCP concept allows the consideration of the parallel or serial organ architecture of the normal tissues at hand.

The present work is a conceptual study based on two patients to indicate the potential of dose escalation in multi-target liver SBRT and a method to achieve it. Due to this fact and the considerable variation of tumor lesions' size and shape and patients' geometry, a larger patient cohort should be employed to more closely identify the range of dose escalation and how this may change between different patients.

Consequently, further study needs to be done to address the previously mentioned issues. The incorporation of the presented evaluation and optimization method to the optimization algorithm of the treatment planning system could significantly increase the quality of the treatment plans. This approach would not only optimize the dose distribution regarding the liver tumors and healthy liver but also with respect to the proximal OARs.

Conclusion

Utilizing a BED limit of 50 Gy_3, as well as the optimization algorithm, has shown that many multi-prescription liver SBRT patients are treated with fairly conservative treatment plans and that the margin for dose escalation is significant. Many patients can receive a greater dose within each prescription plan increasing the control of the tumor while remaining within tolerance regarding liver failure. This optimization algorithm can be applied after the development of the initial treatment plans in order to increase the prescribed dose to the limit of 50 Gy_3 for the critical healthy liver volume of 700 cm^3. The optimization algorithm will can also guide a beam rearrangement in order to more optimally accommodate the increase in the dose prescription. This BED limit as well as the optimization algorithm has the potential to greatly improve multi-prescription liver SBRT treatments in addition to simplifying the analysis of the treatment plan.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Medical University of Warsaw and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants.

References

1. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B et al (2010) Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 37:4078–4101
2. Lo SS, Sahgal A, Chang EL, Mayr NA, Teh BS, Huang Z et al (2013) Serious complications associated with stereotactic ablative radiotherapy and strategies to mitigate the risk. Clin Oncol 25:378–387
3. Grimm J, LaCouture T, Croce R, Yeo I, Zhu Y, Xue J (2011) Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy. J Appl Clin Med Phys 12:267–292
4. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE et al (1991) Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21:109–122
5. Barton M (1995) Tables of equivalent dose in 2 Gy fractions: A simple application of the linear quadratic formula. Int J Radiat Oncol Biol Phys 31:371–378
6. Kirkpatrick JP, Meyer JJ, Marks JB (2008) The Linear-Quadratic Model Is Inappropriate to Model High Dose per Fraction Effects in Radiosurgery. Semin Radiat Oncol 18:240–243
7. Astrahan M (2008) Some implications of linear-quadratic-linear radiation dose-response with regard to hypofractionation. Med Phys 35:4161–4172
8. Guerrero M, Li X (2004) Extending the linear-quadratic model for large fraction doses pertinent to stereotactic radiotherapy. Phys Med Biol 49:4825–4835
9. Wang JZ, Mayr NA, Yu WTC (2007) A generalized linear-quadratic formula for high-dose-rate brachytherapy and radiosurgery. Int J Radiat Oncol Biol Phys 69:S619–S620
10. Park C, Papiez L, Zhang S, Story M, Timmerman R (2008) Universal survival curve and single fraction equivalent dose: Useful tools in understanding the potency of ablative radiation therapy. Int J Radiat Oncol Biol Phys 70:847–852
11. Atwood K, Norman A (1949) On the interpretation of multi-hit survival curves. Proc Natl Acad Sci USA 35:696–709
12. Carlone M, Wilkins D, Raaphorst G (2005) The modified linear quadratic model of Guerrero and Li can be derived from

mechanistic basis and exhibits linear-quadratic-linear behavior. Phys Med Biol 50:L9–L15
13. Hall E (2011) Time, Dose, and Fractionation in Radiotherapy in Radiobiology for the Radiologist, 7th edn. Lippincott Williams & Wilkins, Philadelphia, pp 391–411
14. Sawrie MS, Fiveash JB, Caudell JJ (2010) Stereotactic body radiation therapy for liver metastases and primary hepatocellular carcinoma: Normal tissue tolerances and toxicity. Cancer Control 17:111–119
15. Schefter TE, Kavanagh BD, Timmerman RD, Cardenes HR, Baron A, Gaspar LE (2005) A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases. Int J Radiat Oncol Biol Phys 62:1371–1378
16. Schefter TE, Kavanagh BD, Raben D, Kane M, Chen C, Stuhr K et al (2006) A phase I/II trial of stereotactic body radiation therapy (SBRT) for lung metastases: initial report of dose escalation and early toxcitiy. Int J Radiat Oncol Biol Phys 66:S120–S127
17. Son SH, Jang HS, Lee H, Choi BO, Kang YN, Jang JW (2013) Determination of the α/β ratio for the normal liver on the basis of radiation-induced hepatic toxicities in patients with hepatocellular carcinoma. Radiat Oncol 8:1–8
18. Garcia LM, Wilkins DE, Raaphorst GP (2007) α/β ratio: a dose range dependence study. Int J Radiat Oncol Biol Phys 67:587–593
19. Kauweloa KI, Gutierrez AN, Stathakis S, Papanikolaou N, Mavroidis P (2016) A graphical user interface (GUI) toolkit for the calculation of three-dimensional (3D) multi-phase biological effective dose (BED) distributions including statistical analyses. Comput Methods Progr Biomed 131:1–12
20. Timmerman RD (2008) An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. Semin Radiat Oncol 18:215–222
21. Fisher DR, Hendry JH (1988) Dose fractionation and hepatocyte clonogens: alpha/beta congruent to 1–2 Gy, and beta decreases with increasing delay before assay. Radiat Res 113:51–57
22. Brown JM, Carlson DJ, Brenner DJ (2014) The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? Int J Radiat Biol Phys 88:254–262
23. Ohri N, Tomé WA, Méndez Romero A et al (2018) Local control after stereotactic body radiation therapy for liver tumors. Int J Radiat Oncol Biol Phys. https://doi.org/10.1016/j.ijrobp.2017.12.288
24. Doi H, Masai N, Uemoto K et al (2017) Validation of the liver mean dose in terms of the biological effective dose for the prevention of radiation-induced liver damage. Rep Pract Oncol Radiother 22:303-309
25. Unkelbach J, Papp D, Gaddy MR et al (2017) Spatiotemporal fractionation schemes for liver stereotactic body radiotherapy. Radiother Oncol 125:357–364