

Fractionation Effect on In-homogeneous Dose Distributed Treatments using the Red Shell Concept and Linear Quadratic Modelling

Introduction

In the conventional external radiation therapy, the tumor and the surrounding normal tissue commonly receive a similar amount of radiation dose because the dose distribution is planned to be homogeneous. The same dose is applied to analyze the Biologically Effective Dose (BED) on the tumor and on the normal tissues, using the different α/β ratios (typically 10 for malignant tumor and 3 for normal tissue). Based on this usual difference of the α/β ratios between the tumor and normal tissue and the classic linear-quadratic model, it is readily found and widely accepted that more fraction helps to reduce tissue toxicity while it can maintain a given BED to most types of tumor, except prostate tumors (*Proust-Lima C, Taylor JMG, Secher S et al...Scott Williams. Confirmation of a low a/b ratio for prostate cancer treated by external beam radiotherapy alone using a post-treatment repeated-measures model for PSA dynamics. IJROBP. a/b=1.55 Gy. Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation radiosensitivity of prostate cancer deduced from radiotherapy outcome of 5,969 patients in seven international institutional datasets. IJROBP 2010. Submitted July, accepted with minor modifications Oct, a/b = 1.4(0.9-2.2 Gy). Update of IJROBP 2009;75(3S):Abstract 171, p. S81 a/b=1.6(1.3-1.8)) or malignant melanoma. (Bentzen, SM, Overgaard J, Thames HD et al. Clinical radiobiology of malignant melanoma. *Radiother Oncol* 1989; 16: 169-675 The result was $\alpha/\beta = 0.6$ Gy.)*

- This is meant to be inset as a kind of brief 10-line explanation, like a

sidebar

- **The α/β ratio is the ratio of basic unreparable “one-hit” radiosensitivity (alpha \log_e per Gy) to the “multi-hit” and repairable radiosensitivity (beta \log_e per Gy squared). The ratio is therefore in terms of a dose in Gy. (Fowler, 1989, 2010) and different tissues have large or small ratios, depending on their normal rate of cell turnover being fast or slow respectively. If this ratio is large, the effects of fraction size and dose-rate are small. If α/β is small however, the effects of dose-rate and fraction size can be very large. The effects depend mainly on the α/β of the tissue concerned and on the dose per fraction (or per hour) but also on the volume irradiated to high dose, which involves the Red Shell (Yang et al 2010).**

Their effects are different between conventional external radiation therapy and Stereotactic Body Radiation Therapy (SBRT), which delivers a high oligo-fractionation inhomogeneous dose (Ling et al 2010) to the tumor, and the tissue dose quickly falls off outside the PTV (Planning Target Volume) with distance from the tumor. The tissue that is closely surrounding the tumor (a few mm) often receives a dose greater than tissue tolerance and has some risk of permanent radiation damage. This zone of tissue in high risk is defined as the Red Shell (Yang et al 2010) to quantify tissue toxicity caused by the treatments with these very large doses per fraction.

When tumors are treated with SBRT in parallel-type organs with serial critical organs in proximity, it is important in planning to minimize the volume of the Red Shell and to avoid its overlapping with critical organs and structures such as major blood vessels and airways. In order to achieve that, the dose gradient certainly and probably the conformal index need to be high. (Yang et al 2010). If the best planning effort with

existing fractionation has been utilized to achieve a high dose gradient and good conformality, what else can we do to minimize the tissue toxicity without compromising tumor dose? Can we change the fractionation scheme based on the Linear-Quadratic model in order to reduce the volume of the Red Shell and so to spare more serial critical structures in proximity, and at the same time maintain the same BED to the tumor? It might not be “safer” to the normal tissues, in all circumstances when more biologically tumor-equivalent fractions are adopted? This paper analyzes the changes of the volume of the Red Shell in a parallel-type organ, and the change of the BED of the serial-type organs in different locations in the heterogeneous dose distribution, when different SBRT fractionation schemes are adopted. It shows among many other factors that a few large fractions are best for prostate tumors, and that more and smaller fractions should be avoided for them.

Method

Calculation of the Volume of Red Shell

In a simplified situation for the purpose of mathematical analysis, if we assume a hypothetical spherical CTV with an isotropic PTV margin, receiving a hypothetical spherical dose cloud, then the Volume of the Red Shell (V_{RS}) and the Thickness of the Red Shell (T_{RS}) can be related as:

$$\begin{aligned} V_{RS} &= 4/3 \cdot \pi \cdot (R + T_{RS})^3 - 4/3 \cdot \pi \cdot (R)^3 \\ &= 4/3 \cdot \pi \cdot (3R^2 \cdot T_{RS} + 3R \cdot T_{RS}^2 + T_{RS}^3) \end{aligned} \quad (5)$$

And

$$T_{RS} = \text{PTV margin} + (\text{Prescription Dose} - \text{Tissue Tolerance}) / \text{Dose Gradient} \quad (6)$$

An example calculation of the Red Shell volume and thickness around a hypothetical spherical tumor receiving a hypothetical spherical dose cloud is performed using Equation 5. Suppose we have a spherical CTV that is 2 cm in diameter, a PTV with 5 mm margin, a prescription dose of 20 Gy x 3Fx at the PTV, a dose gradient with a 10% prescription dose decline every 2 mm beyond the PTV radius, and a tissue tolerance (In this paper, commonly use BED 100 Gy³ or EQD2 60 Gy “equivalent total dose which, when delivered in 2 Gy fractions of photon irradiation, produces the same biological effect”). The thickness of the Inner Red Shell (from CTV to PTV) is 5 mm. Using Equation 5 the Inner Red Shell volume is calculated as: $\frac{4}{3} \cdot \pi \cdot (1 + 0.5)^3 - \frac{4}{3} \cdot \pi \cdot (1)^3 = 9.95 \text{ cc}$.

The dose at the inner surface of Outer Red Shell is, as prescribed, 20 Gy x 3Fx. The Outer Red Shell surface constraint dose is 8.61 Gy x 3 Fx (An EQD assumed to be 60 Gy in 2 Gy fractions for Late Complications). The dose fall-off is calculated as: $(20 \times 3 - 8.61 \times 3) / (20 \times 3) = 56.95\%$; so the thickness of the Outer Red Shell is calculated as: $56.95\% / 10\% \times 2 \text{ mm} = 11.4 \text{ mm} = 1.14 \text{ cm}$; and the volume of the Outer Red Shell is calculated as: $\frac{4}{3} \cdot \pi \cdot (1 + 0.5 + 1.14)^3 - \frac{4}{3} \cdot \pi \cdot (1 + 0.5)^3 = 62.85 \text{ cc}$. Thus, the total Red Shell thickness is calculated as: $1.14 + 0.5 = 1.64 \text{ cm}$. The total Red Shell volume can either be obtained by summing the volumes of the Inner and Outer Red Shells ($9.95 + 62.85 = 72.80 \text{ cc}$) or it can be calculated using Equation 3 ($\frac{4}{3} \cdot \pi \cdot (1 + 1.64)^3 - \frac{4}{3} \cdot \pi \cdot (1)^3 = 72.80 \text{ cc}$).

The hypothetical spherical tumor and spherical dose cloud are used to calculate the change of the volume of the Red Shell with the different fractionation schemes (from single fraction to 10 fractions), which have the same biological equivalent dose to the tumor. Using different assumed levels of tumor dose, a/b ratios of target (Tumor) and normal tissue (NT), the equivalent dose is recalculated respectively. We assume to deliver one fraction a day from Monday to Friday, so that 1-10 fractions can all be delivered within two weeks, less than any commonly used tumor T_k of 14 days. As such, the tumor re-population is not considered a factor in the BED calculation in this paper.

Result

For A Parallel Organ – Evaluation using the Red Shell Concept

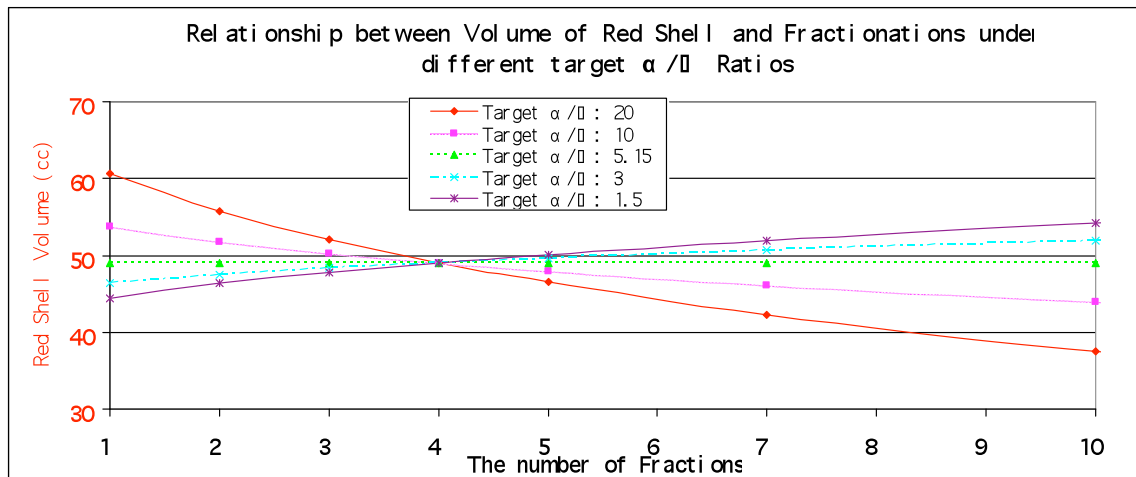
The fractionation would not affect the thickness and volume of the Inner Red shell, but will influence that of the Outer Red Shell, since the BED of tumor and normal tissue will change differently under different fractionation schemes when the tumor and normal tissue have different α/β ratios. The following section reports the change of the volume of Red Shells of a hypothetical tumor with the different fractionation schemes that maintain the same BED to the target (tumor), and the different tumor α/β ratios, prescription doses and normal-tissue tolerances (for late complications assuming $a.b = 3$ Gy) respectively.

Diminishing Return

~~The decrement is the biggest between single fraction schemes and two fraction schemes, and the decrement from further fractions continues but gradually diminishes. As the result, the curve flat~~

Different target α/β Ratios

Assuming the α/β Ratio of a tumor is 20, 10, 5.15, 3 and 1.5 respectively, the volume of the Red Shell using 12.5 Gy x 4 fractions (BED 112.5 Gy₁₀, or EQD2 94 Gy) prescribed to the PTV and its **tumor-equivalent** hypo-fraction tumor dose, based on the different α/β ratios of the tumor, are shown as the series of five curves, one for each α/β ratio listed above, in figure xx.



When the tumor with α/β ratio 20 was treated at the dosage of 12.5Gy x 4 fraction or its tumor-equivalent hypo-fractionation schemes, but with more and smaller fractions as shown along the X-axis, the volume of the Red Shell decreases from 60.64 cc in the single fraction to 37.55 cc in the tumor-equivalent 10-fraction schemes, a 23.09 cc or 38% reduction of Red Shell volume occurs. If the tumor's α/β ratio is however 10, the volume decreases from 53.77 cc in the tumor-equivalent single fraction to 43.96 cc for the tumor-equivalent 10 fractions, a smaller reduction of 9.81 cc or 18.2 %. The reduction is less in volume and by percentage, compared with that of a tumor with the α/β ratio of 20. The trend is clearly that the smaller the α/β ratio of tumor, the slower the volume of Red Shell decreases with more fractions. This is still in the “conventional” direction but

notably more slowly.

When the α/β ratio of the hypothetical tumor is around 5.15 Gy, named the ***Balance Ratio*** in this paper, note that this is no longer at the traditional level of $a/b = 2$ or 3 Gy as may have been expected by the reader -- the volume of Red Shell **does not change with fractionation**. The balance ratio is irrelevant to tumor size, PTV margin, dose gradient or fractionation, but is directly determined by the prescribed dose.

When the tumor's α/β ratio is lower than the balance ratio of 5.15Gy, (as it will be at or below 3Gy, the most commonly assumed ratio for late-complications in normal tissue), more fractions would actually cause a bigger volume of the Red Shell, in other words, potentially worse tissue toxicity. ***This is the same statement as saying that for such tumors (notably prostate tumors) the total dose should be reduced in Hypofractionated treatments, to obtain a constant tumor effect.*** In this example, the volume of the Red Shell – as defined by the volume of tissue receiving any dose between 60 Gy EQD (= 100 Gy₃ BED) and the Prescription dose - increases by 5.44 cc (11.6%) from 46.47 cc in a single-fraction scheme to 51.91 cc in 10 equivalent fractions, not large but a significant trend. This trend shows that the smaller the α/β ratio of the tumor is, the faster the volume of Red Shell increases with fractionation, when the α/β ratio is below the Balance Ratio for the relevant treatment plan. If a tumor's α/β ratio is as low as 1.5Gy, as for prostate tumors (as recently confirmed by the 6,000-patient meta-analyses of Proust-Lima et al 2010 and Miralbell et al 2011), the volume of the Red Shell increases 9.79cc (or 22%) from 44.44 cc in a single fraction to 54.23 cc in 10 tumor-equivalent fractions. The

increment is higher than that of a tumor with an α/β ratio of 3 or 5 Gy, which are closer to the Balance Ratio of 5.15 Gy described above, in both volume and percentage. It is a clear and logical message that more and smaller fractions are **not the best way to go for treatment of prostate tumors**, or for malignant melanoma with its even lower α/β ratio of 0.6 Gy (Bentzen et al 1989). Fewer and larger fractions will be best for treating prostate cancer, exactly as has been said for prostate tumors (Brenner & Hall 1999, Fowler, Chappell & Ritter 2001, Brenner, Martinez et al, 2002); there is no conflict for such tumors; we simply have to avoid using the “more-fractions is safer concept” for those types of tumor..

Prescription Dose

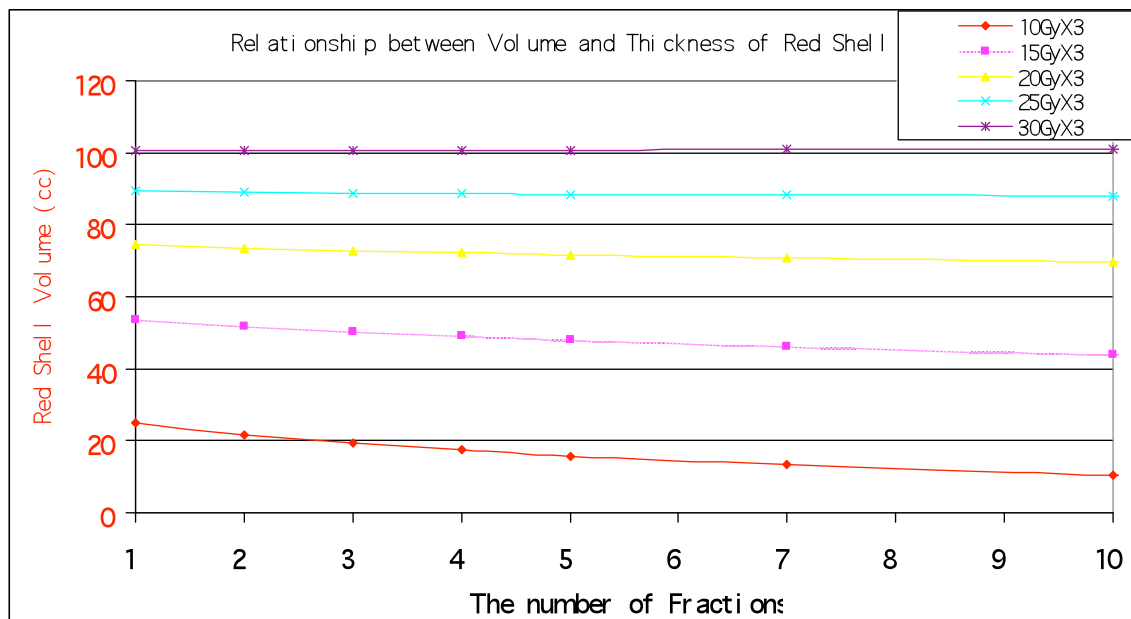
(There is however another factor to consider in relation to Red Shells, and that is the degree of risk, dependent on the local and average dose and log cell kill within the thickness of the Red Shell. This where the level of prescribed dose comes into consideration: smaller prescribed doses might be still above the risk level at the inner border of a Red Shell, at say 60 Gy EQD (100 Gy₃ BED), but for a higher prescribed dose per fraction they will be relatively more risky, that is, causing more total cell kill than the lower prescribed doses. This is logically obvious, but quantifying the cell kill by EUD might become a useful measure of how much risk instead or in addition to NTCP.

The level of risk can be quantified by the EUD of the Red Shell integrated over its volume. It is an independent measure which requires judgement to say just how bad its effect might be, concerning BOTH volume and EUD.

For example I would not expect an EUD of 82 GyEQD to be tolerated if it is as large as 5 cc, but Alan Pollack may have some data recent data about that from his reported use of that dose to some part of rectum in treating Ca prostate. Even if the incidence of complications is less than 5%, it might be worth looking at it. If it is significantly less with Cyberknife, in any tumor site, it might be some evidence about the half-time of repair that we need to find out whether a long fraction

duration loses any effectiveness compared to a shorter one. It would be a stronger effect in Late Complications than in acute ones.) Note: leave to discussion or next project. J Yang.

Assuming the α/β ratio of a hypothetical tumor is 10 Gy and the surrounding normal tissue late-complication ratio is 3 Gy, the different treatment dose levels ranging from 10Gy x 3Fr (60Gy₁₀), 15Gy x 3Fr (111.25Gy₁₀), 20Gy x 3Fr (180Gy₁₀), 25Gy x3 Fr (262.5Gy₁₀) to 30Gy x 3 Fr (360Gy₁₀) and their tumor-equivalent hypo-fractionation dose are used to calculate the volume of Red Shell and shown in figure x.x.



In the successively “low-to-high” dose hypofractionation levels of 10 Gy, 15 Gy, 20Gy and 25Gy x 3 fractions prescribed, (implying more resistant or larger tumors as we go up this graph), the volume of Red Shell (tissue toxicity) decreases when the equivalent effective dose is delivered in more fractions (horizontally in the graph). However, when the prescribed dose level is higher, the volume reduces much less than when lower dose levels are prescribed, and there is no worthwhile gain in terms of reduced volume of

the Red Shell by using more and smaller fractions. However, there is a different effect occurring, that of average or total cell kill because of the rapid fall-off of dose across the thickness of the Red Shell and this “total cell kill” can be quantified by calculating the EUD (the Equivalent Uniform Dose - What’s the ref to it? Niemierko about 1990?). The thickness and the size (volume) of the Red Shell are parameters designed to avoid overlapping with sensitive structures during planning in any given plane; especially “Serial Structure” organs that would be vulnerable to the highest dose anywhere in the organ, rather than to any average dose.

The actual biological danger to a patient will depend on which type of structure is present at the various high doses in the particular Red Shell being considered. Doses within the Red Shell are all potentially dangerous to some degree, but higher EUDs will indicate more risk in general in any organ; Serial Structures are more vulnerable to even a small volume at a higher dose. For this reason we shall learn by experience whether the relative frequency of a high dose in 10 cubic millimeter of spinal cord applies to such tubular organs as esophagus or trachea too. (Ref: Sahgal et al 546. [Sahgal A](#), Gibbs I, Ryu S, Ma L, Gertzten P, Soltys S, Weinburg V, Wong S, Chang E, **Fowler J**, Larson D. Preliminary guidelines for avoidance of radiation-induced myelopathy following spine stereotactic body radiotherapy. ASTRO Abstract 2113. IJROBP 2008; 72(1 Supple): p. S220.)

[Sahgal A](#), Larson D, **Fowler J**, Gibbs I, Ryu S, Soltys S, Weinberg V, Wong S, Gerzten P, Chang E, Ma, L. Myelopathy and tolerance of the spinal cord to hypofractionated radiotherapy Part 2: Modeling inhomogeneous dose distributions. Drafts 30 Nov 07 & 16

Jan 08

MUST CHECK UP ON THIS PAPER – IT IS NOW OUT

At the dose level of 10Gy x 3fx, the lowest in this sample, the volume of Red Shell decreases appreciably 14.54 cc (or 58 %) from 25.03 cc in a single fraction to 10.49 cc in 10 equivalent fraction, the biggest in the group, by both absolute volume and by percentage. At the dose level of 20Gy x 3, however, a commonly used SBRT dose scheme, the Red Shell of the hypothetical tumor decreases only 1.57 cc (or 1.8 %) from 89.36 cc in single fraction to 87.79 cc in 10 equivalent fraction schemes. The Red Shell has almost the same volume, no matter what fractionation schemes are used in the 20 or 25Gy x 3fx dose levels. When the prescription dose is high (such as > 20Gy x 3), fractionation has less or almost no effect in reducing the volume of Red Shell.

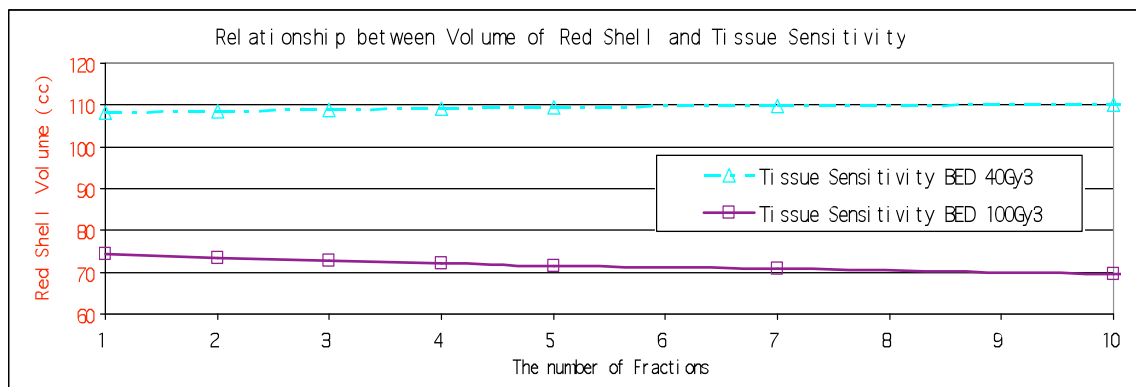
IT'S NOT JUST THE VOL OF THE RED SHELL THAT MATTERS – THE MAX DOSE AT ANY POINT IS IMPORTANT IF THE SENSITIVE STRUCTURE IS “SERIAL”; BUT THE AVERAGE DOSE- OR MUCH BETTER, THE EUD – MATTERS IF THE SENSITIVE ORGAN IS “PARALLEL”. PERHAPS THAT’S ALL WE NEED TO SAY NEAR THIS POINT - JACK NOW GETTING BACK TO REDRAFTING – THURS 21ST OCT.

When the prescribed dose escalates to the level of 28.7Gyx3, named *balance dose*, the volumes of the Red Shell in any fractionation schemes reported are the same of 97.89 cc. If a tumor is to be treated with this balance dose, fine calculation finds no change of the volume of Red Shell no matter what equivalent fractionation scheme adopted. Depending on the local rate of dose fall-off at edge of PTV, they will be a little bit different in volume, but as you say, not very much. How is the Balance Dose related to the peak dose near the middle of the PTV? Is that what causes the Balance Dose to be what and where it is?

When the dose level is higher than the balance dose, 28.7Gyx3 in this case, such as 30Gy x 3 fraction, an uncommon and unlikely clinically used dosage, the volume of Red Shell actually increases slightly with more fractions. When the prescribed dose is higher than the balance dose, hypo-fractionation or fewer fractions is recommended since it has less tissue damage than regular fraction.

Surrounding tissue Sensitivity

We performed following calculation to determine how the tissue sensitivity influences the fraction effect on Red Shell. Assuming the α/β ratio of the hypothetical tumor is 10, the surrounding tissue 3 and prescribed dose 20Gyx3, two different tissue tolerance of BED 40Gy3 (= EQD of 24 Gy) for the sensitive parallel type organ, such as lung or liver) and 100Gy3 (= 60 Gy EQD most of normal tissues) are used to calculate the volume of Red Shell under multiple fractions and shown in figure x.x.



When tissue tolerance is at level of BED 40Gy3, in this sample, the volume of Red Shell slightly increases with fractionation. With higher tissue tolerance of BED 100Gy3 applied in the same situation, the volume decreases with fractions. **I suggest some tables of what are the iso-BED schedules for the various values of a/b or whatever is used to keep a tumor BED constant for different fraction numbers, for any tables after**

the first Table xx - Jack END of P 10 Thurs14th.

Discussion

When evaluates fractionation effect on the volume of Red Shell in SBRT, there are two factors combined to decide whether more fractions will increase or decrease the volume of Red Shell. The two factors are (1) the α/β factor (of the tumor when the α/β ratio for the normal-tissues is 3), and (2) the *RE factor* where $RE = 1 + d/[\alpha/\beta]$. RE is important because it is the factor by which we multiply the physical dose to determine how *biologically effective* the tissue with this α/β and this local dose-per-fraction d will be.

α/β factor: From experience of conventional homogeneous radiation therapy, it has been widely acknowledged that, when the α/β ratio of a tumor is higher than the α/β ratio of late-responding normal tissue, more fractionation helps to spare tissue, and vice versa. This biology effect still exists in the SBRT type of heterogeneous focal dosimetry distribution. The volume of the Red Shell tends to decrease with fractionation when the α/β ratio of the tumor is higher than that of surrounding tissue. On the contrary, naturally the volume tends to increase with fractionation when the α/β ratio of the tumor is lower instead. ~~At a certain α/β ratio value, the volume of Red Shell will not change with fractionation, and we named this the "Balance Ratio of α/β , whether tumor or normal tissue."~~

~~In the a homogeneous dose distribution, the α/β ratio of the normal tissues for late complications is the same with as the a/b ratio of normal tissue, 3 in the most cases,~~

~~however, in the in homogeneous dose distribution, the particular α/β ratio is also determined by the prescribed dose, normally higher than that of normal tissue. I DON'T UNDERSTAND THIS POINT Jack Are you saying just that we will next look at the tumor tissue only for the next sentence?~~

RE factor:

In the linear-quadratic model, the BED is the summation of two contributing parts, the linear part and quadratic part. When very high dose per fraction is used in SBRT, SRS or HDR etc, the quadratic part, which is in the second power of the dose per fraction, as part of RE, is highly significant. The higher dose per fraction used, the more significant the quadratic part becomes and the higher is the RE generated. Since, in SBRT type of focal dosimetry distribution, the inner surface of Red Shell receives higher dose than the tissue at outer surface, the RE at inner surface is higher than that at outer surface. When fractionation applies, the dose per fraction used is less, and RE in the inner surface is reduced more than that of outer surface. Jack – **Where is the prescribed Dose given ?** The total treatment dose in inner surface is higher [[? to compensate the loss of RE, WHAT LOSS?]] and the old external boundary of Outer Red Shell will receive a higher of BED of 100 Gy³ and new external boundary is defined outside of old external boundary at where BED is 100 Gy³. So, the fractionation will increase the volume of Red Shell. This is named as RE factor here. This effect is observed easily in the Table 3 when α/β ratio of tumor is 3, in which α/β factor is not working. [[HERE IS A DISCUSSION POINT !]]

The change of volume of Red Shell under different prescribed dose, fractionation scheme, surrounding tissue sensitivity and α/β ratio is combined effect of the two factors.

MUST SAY “TUMOR- α/β ” OR “NORMAL-TISSUE- α/β ” EVERY TIME, NEVER JUST “ α/β ” ALONE.

When α/β of tumor is higher than 3, the α/β factor and RE factor fight with each other. When α/β of tumor is 10, α/β factor overweight the RE factor and the volume of Red Shell decreases with fractionations. In this specific case, the two factor counterweight at $\alpha/\beta = 7.56$, where the volume does not change much with fractionations. When α/β of tumor is between 3 and 7.56, RE factor overweight the α/β factor and the volume of Red Shell increase with fractionations. When the α/β of tumor is 3, the volume of Red Shell does not change under α/β factor, but increases with fractionation. When the α/β of tumor is less than 3, both of two factors will increase the volume of Red Shell. As long as the BED model is super-linear, the effect should be observed in the treatment with focal dosimetry distribution. Whether fractionation will increase or decrease the volume of Red Shell of a tumor is decided by the two factors, the other factors, like volume of PTV, dose gradient and prescribed dose will not change the trends, but will influence the percentage of change.

Balance Ratio

Balance Ratio is the α/β ratio of tumor with which the volume of Red Shell will not change with fractionation. In this ratio, the α/β factor, in favor of more fraction to decrease the volume of Red Shell, counterweights with the RE factor, which is in favor of

less fraction. << THE α/β RATIO AND THE DOSE PER FRACTION d ARE IN THE SAME TERM OF THE RE, but there are two different RE's involved here . THERE IS A DEPENDENCE ON THE VOLUME OF PTV AND ALSO ON GRADIENT OD DOSE OUTSIDE PT, ALL OF WHIVH NEED TESTING FOR THEIR EFFECT ON VOLUME OF RED SHELL; BUT WHICH OF THE CONDITIONS TO KEEP AS STANDARD NEED CAREFUL CONSIDERATION>>

The balance ratio is decided by the prescribed tumor treatment dose. The lower prescribed tumor is, the weaker RE factor would be, and the lower balance ratio needed for α/β factor to counterweight. ,,

A sample of single fraction equivalent dose is reported in the Table 11:

Single fraction	1Fr x 40 Gy	1 Fx x 35 Gy	1 Fx x 30 Gy	1 Fx x 25 Gy	1 Fx x 20 Gy
Five fraction	5 Fr x 16.08 Gy	5 Fr x 14.08 Gy	5 Fr x 12.07 Gy	5 Fx x 10.055 Gy	5 Gy x 8.0447 Gy
Balance Ratio	7.56 Gy	6.6 Gy	5.65Gy	4.73 Gy	3.78 Gy

Table 11: the Balance Ratio under different dose scheme

tumor α/β ratio	3	4	5	6	7	8	9	10	15
Balance BED	100Gy ³	133.36 Gy ⁴	166.71 Gy ⁵	200 Gy ⁶	233.38 Gy ⁷	266.72 Gy ⁸	300 Gy ⁹	333 Gy ¹⁰	500 Gy ¹⁵
Balance dose (1 Fx)	15.88 x1	21.18 x1	26.48 x1	31.77 x1	37.07 x1	42.37 x1	47.66 x1	52.96 x1	79.43 x1
Balance dose (3 Fx)	8.61 x3	11.48 x3	14.36 x3	17.23 x3	20.1 x3	22.97 x3	25.84 x3	28.71 x3	43.06 x3
Balance dose (5 Fx)	6.39 x5	8.52 x5	10.65 x5	12.78 x5	14.91 x5	17.04 x5	19.17 x5	21.3 x5	31.95 x5

Rx dose (Gy x Fx)	20x1	25x1	30x1	10x3	12x3	14x3	15x3	16x3	18x3	20x3	12.5x4
Balance α/β ratio	3.777	4.472	5.665	3.484	4.18	4.877	5.225	5.574	6.27	6.97	5.15

Conclusions

From the above discussion, we reached the following suggestions for SBRT/SRS/HDR...

Because of the nature of high dose gradient and high treatment dose per fraction used,

1. Higher dose gradient always helps to reduce the volume of Red Shell, <<and any doses outside the PTV.>>

2. Fractionation will only do so for tumors with a/B ratios significantly above the Late-complications a/B ratio of 3 Gy. **OR EVEN YOUR BALANCE RATIO OF**

5.15 Gy - Jack Indeed, for any tumors with a/B ratios below 3 Gy (for example low-risk prostate tumors), more fractions will both increase the Red Shell volume slightly, and will also yield lower (less desirable) Therapeutic Ratios as frequently discussed in the literature, both effects leading to a preference for the Hypofractionated and HDR treatments but only for tumors with very low a/B ratios. **CAN QUOTE 2 META-ANALYSES OF > 6000 patients now.** There are no conflicts. **AGREED - YOU ARE RIGHT- Jack**

2. When tumor control at a high dose level (BED ~ 80 – 200 Gy¹⁰ for example) is required, the key factor is to maximize the dose gradient. Fractionation will certainly give a better ratio of tumor cell kill to late complications, provided tumors have high a/B

ratios, (and the opposite for tumors with low a/B ratios, as is well known), but the quantitative reduction in volume of Red Shell is rather small with increased fraction numbers, and progressively decreases with more fractions. **YES - YOUR GRAPH xx is GREAT AT SHOWING ALL THAT - Jack** When tumor control dose at the level of (120~60 Gy₁₀) is used for rapidly repopulating tumors, (with high a/B ratios), fractionation may help to reduce the volume of Red Shell.

3. The benefit of a reduction in Red Shell Volume, for tumors of high a/B ratio, is most obvious from 1 to 3 fractions, each extra fraction giving diminishing returns.

YES – Jack Fig xx is very good at showing all of this! – Jack

4. For tumors with very low a/B ratios there is no benefit from using larger numbers of fractions, either from Red Shell Volume reduction or from average doses to any surrounding normal tissues. **YES - Jack** Hypofractionation is good for eliminating these tumors, but the limiting normal tissue constraints of Gy₃ BEDs and their associated limited volumes must be studied in detail and respected. **YES - Jack**

The volume reduction from addition of each fraction diminishes with more fractions adopted. **YES - Jack**

When slow growing tumor is treated, the fractionation needs to be analyzed carefully. If the prescribed dose is higher than surrounding tissue tolerance, the fractionation will cause higher volume of Red Shell. **YES - Jack**

The volume of Red Shell is irrelevant to the α/β ratio of tumor in the single fraction scheme **What about the Level of Prescribed Dose Effect? - Jack**

