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Spatiotemporal fractionation schemes for irradiating large cerebral arteriovenous malformations

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Abstract

Purpose and Objectives—We consider fractionation effects in the context of radiosurgery treatments of large cerebral arteriovenous malformations (AVM). In current practice, fractionated treatments divide the dose evenly into several fractions, which generally leads to low obliteration rates. In this work, we investigate the potential benefit of delivering distinct dose distributions in different fractions.

Methods and Materials—Five patients with large cerebral AVMs were reviewed and were replanned for intensity-modulated arc therapy delivered with conventional photon beams. Treatment plans allowing for different dose distributions in all fractions were obtained by performing treatment plan optimization based on the cumulative biologically effective dose (BED) delivered at the end of treatment.

Results—We show that distinct treatment plans can be designed for different fractions such that high single fraction doses are delivered to complementary parts of the AVM. All plans create a similar dose bath in the surrounding normal brain and thereby exploit the fractionation effect. This partial hypofractionation in the AVM along with fractionation in normal brain achieves a net

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Conflicts of interest:

None

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improvement of the therapeutic ratio. We show that a biological dose reduction of approximately 10% in the healthy brain can be achieved compared to reference treatment schedules that deliver the same dose distribution in all fractions.

Conclusions—Boosting complementary parts of the target volume in different fractions may provide a therapeutic advantage in fractionated radiosurgery treatments of large cerebral AVMs. The strategy allows for a mean dose reduction in normal brain that may be valuable for a patient population with an otherwise normal life expectancy.

1. Introduction

1.1. Treatment approaches for large cerebral AVMs

Small cerebral arteriovenous malformations (AVM) are successfully treated with single fraction radiosurgery with a typical prescription dose between 16 Gy and 24 Gy. Many studies report obliteration rates in the order of 70% to 90% [1,2,3]. Established treatment techniques include the Gamma Knife, linear accelerator and proton therapy. In contrast, the best treatment approach for large cerebral AVMs is controversial. High single fraction doses as used for small AVMs bear the risk of radiation injury and associated neurological side effects due to the larger volume of normal brain exposed to high doses. Besides lowering the prescription dose for single fraction radiosurgery, there have been two main approaches to modifying radiosurgery practice in an attempt to improve safety and efficacy of treating large lesions:

1. Fractionation [4,5,6]: The total dose is equally divided into smaller fractions that are delivered over multiple days. The main rationale for this approach is the fractionation effect in normal brain, i.e. brain tissue adjacent to the target volume can tolerate a higher total dose.
2. Volume-staged radiosurgery [7,8,9]: In this approach, the AVM is divided into several regions (typically 2–4). Each region is treated separately with a high single fraction dose. Between treatments, a rest period of 3–9 months is imposed. The main rationale for the volume-staged approach is that each part of the AVM is treated to an effective single fraction dose, while the normal brain recovers in between treatments.

The main disadvantage of fractionated radiosurgery is that low fractional doses are relatively ineffective at treating AVM. This generally results in poor reported obliteration rates unless the total dose is increased substantially [5,10]. One main concern regarding volume-staged treatments is that partial obliteration of the AVM after the initial stages may change blood flow patterns and increase the risk of hemorrhage [10]. Currently, there is little evidence for the superiority of one approach over the other. In a literature review by Moosa et al. [10], the volume-staged approach was found to yield higher obliteration rates (47%, versus 22% for fractionated treatments), which may be explained by the fact that these treatments generally deliver higher cumulative biologically effective doses than fractionated approaches. On the other hand, this did not result in a lower incidence of hemorrhage (the main rationale for treatment) over the follow-up period reported. The main dose-limiting normal tissue is the brain adjacent to the AVM that is exposed to high doses. However, it is also of utmost

importance to minimize integral dose to the normal brain as these patients are often asymptomatic and have otherwise normal life expectancy.

1.2. Nonuniform spatiotemporal fractionation schemes

In this paper, we consider fractionation effects in more detail. Fractionation decisions face the trade-off between increasing the number of fractions to improve normal tissue tolerance, and increasing the total physical dose in order to maintain the same biological effect in the target volume. In that regard, it would be ideal to simultaneously achieve fractionation in normal tissue and deliver high single fraction doses to the target volume. In this paper, we demonstrate that this is possible to a limited degree in the context of rotational therapy with conventional x-ray beams such as Tomotherapy or volumetric modulated arc therapy (VMAT). An intuitive explanation of this effect is as follows: rotational therapy spreads out the dose in normal tissues surrounding the target volume, creating an even dose bath. Distinct treatment plans for different fractions can be designed such that each fraction boosts a different region of the target volume while creating a similar dose bath in the normal tissue. Thereby, high single fraction doses are delivered to parts of the target volume while simultaneously achieving fractionation in surrounding normal tissues, providing a net improvement of the therapeutic ratio. The use of such nonuniform spatiotemporal fractionation schemes has previously been demonstrated for proton therapy [11,12]. For proton beams, the entrance dose is mostly independent of the proton range, which provides the opportunity to move dose from proximal to distal parts of the target volume without changing the dose in the entrance region.

1.3. Contribution of this paper

In this paper, we demonstrate that not only protons, but also x-ray beams, may give rise to nonuniform spatiotemporal fractionation schemes, even though the mechanism is different. We investigate the benefit of such schemes for treating large cerebral AVMs as a potential application.

2. Methods and Materials

2.1. Patients

We reviewed cerebral AVMs treated at our institution between 2012 and 2014, which were irradiated in a 2-fraction regimen. Patients with AVM volumes larger than 18 cc that did not have prior embolization were selected for further analysis. This resulted in 5 cases, which represent a spectrum of different target locations and shapes. Case 1 is an AVM located in the right frontal lobe with a volume of 30 cc and is used for illustration in the result section. The geometries of cases 2–5 are illustrated in the supplementary material (appendix A.1).

2.2. Fractionation effects

To describe fractionation effects, we assume that the uniform fractionation schemes summarized in Table 1 are iso-effective. These fractionation schemes can be modeled via the biologically effective dose (BED) model [13], assuming an α/β -ratio of 2 Gy in normal brain and an α/β -ratio of 4 Gy in the AVM. For a uniform n -fraction treatment that delivers the same dose d in all fractions, the BED b is given by

$$b=nd \left[1 + \frac{d}{\alpha/\beta} \right] \quad (1)$$

For this work, we consider a generalization of the standard BED model (1) to nonuniform treatments with varying fraction doses. The cumulative BED in voxel i delivered over n treatment fractions is then given by

$$b_i = \sum_{t=1}^n \left[d_{ti} + \frac{d_{ti}^2}{(\alpha/\beta)_i} \right] \quad (2)$$

where d_{ti} is the physical dose delivered to voxel i in fraction t and $(\alpha/\beta)_i$ is the α/β -ratio of the tissue that voxel i belongs to.

Equation (2) extrapolates from uniform fractionation schemes to nonuniform treatments. For example, a two-fraction treatment that delivers 10 Gy plus 4.93 Gy to the AVM yields the same BED as 16 Gy in two 8 Gy fractions. For more intuitive quantitative interpretation, the cumulative BED distribution of a treatment plan can be rescaled by a factor $1/[1 + X/(\alpha/\beta)]$ where X is a reference dose level. This yields the equieffective dose *EQDX* [14], which is interpreted as the total physical dose that needs to be delivered in a uniform treatment with a dose per fraction of X Gy to achieve the same BED.

$$EQDX_i = \frac{b_i}{\left[1 + \frac{X}{(\alpha/\beta)_i} \right]}$$

Note that *EQDX* is simply the BED multiplied by a factor that is constant within one tissue. Hence, relative improvements in biological dose between two plans are the same independent of whether the difference is measured in BED or *EQDX*.

2.3. Treatment planning

We consider IMRT plans with 6 MV photon beams and a 5 mm beamlet size. We use 36 coplanar beam directions at 10° separation, which represents the best possible coplanar IMRT plan that can be delivered with Tomotherapy or VMAT. Treatment planning is performed by simultaneously optimizing n possibly distinct treatment plans for n fractions, based on objective and constraint functions evaluated for the cumulative BED similar to the work in [12]. We consider the following IMRT planning problem:

Constraints

1. Limit the maximum dose to normal brain outside of the target volume to a BED of 80 Gy (16 Gy in 2 fractions).
2. Constrain the maximum BED in the AVM to 160 Gy (32 Gy in 2 fractions).

Objectives

1. Deliver a BED of at least 48 Gy to the AVM (16 Gy in 2 fractions) (quadratic underdose objective).
2. Achieve conformity (implemented via a quadratic overdose objective with a voxel-dependent maximum dose that linearly depends on the distance of the voxel from the AVM contour. Between the AVM contour and 1 cm distance a BED fall-off from 80 Gy to 24 Gy is requested; between 1 cm and 2 cm distance from 24 Gy to 8 Gy.)
3. Maximize the mean BED to the AVM.
4. Minimize the mean BED to the normal brain.

We first optimize a reference treatment plan that delivers the same dose in all fractions. To determine the nonuniform spatiotemporal plan, we minimize the mean normal tissue BED and maximize the mean AVM BED, subject to the constraint that the values of the conformity and AVM underdose objectives are no worse than in the reference plan. Hence, reference and spatiotemporal plans are optimized for identical objective and constraint functions. A full description of the treatment plan optimization methods, together with a discussion of the rationale behind the above formulation, can be found in the supplementary material (appendix A.2). In this paper we consider treatments using 4 fractions (see the supplementary material, appendix B.3 for discussion on this choice).

3. Results

We first consider a reference treatment for case 1 using 4 identical fractions. The resulting dose distribution is illustrated in figure 1a. The dose at the edge of the target volume is close to 21 Gy due to the normal brain maximum BED constraint; close to 43 Gy are delivered to the center of the AVM nidus, which corresponds to the maximum BED constraint.

Figure 2 shows a nonuniform spatiotemporal treatment plan that delivers a different dose distribution in all fractions. The four dose distributions deliver high single fraction doses to different parts of the AVM nidus. Maximum single fraction doses are approximately 20 Gy (note that 23.38 Gy in a single fraction corresponds to the maximum BED constraint of 160 Gy). Figure 3 illustrates the deviation from uniform fractionation. The figure shows, voxel-by-voxel, the fraction of the total physical dose that is delivered by the fraction that contributes the highest dose among all 4 fractions. A value of 25% corresponds to uniform fractionation. A single fraction dose of 20 Gy corresponds to approximately 50%–60% of the total dose.

Figure 1c shows the cumulative physical dose of the spatiotemporal treatment plan, and figure 1e shows the difference in total physical dose between the reference plan in figure 1a and the spatiotemporal plan. Due to partial hypofractionation in the AVM, a higher BED can be achieved with a lower physical dose. In this case, the mean physical dose in the AVM is reduced from 31.3 Gy to 29.0 Gy (7.3% reduction). The largest physical dose reduction is observed in regions that receive the highest single fraction doses.

Because some degree of fractionation is achieved in the normal brain, the reduction in physical dose leads to a net reduction in BED in the normal brain. Figures 1b and 1d show the equieffective dose *EQDX* for the reference plan and the spatiotemporal plan, respectively. Here, $X = 5.21$ Gy was chosen as the reference dose value, which is the prescribed dose per fraction in the 4-fraction reference plan. Figure 1f shows the difference in *EQDX*. Within the target volume, a higher BED is achieved in spite of the reduction in total physical dose. Figure 4 compares the dose-volume histograms (DVH) of the reference plan and the spatiotemporal plan (evaluated for *EQDX*). This confirms that a reduction in the mean BED in the normal brain is achieved along with an increase in BED in the target volume. For this plan, the mean BED is increased by 5.5% in the AVM and decreased by 5.4% in a 1 cm rim of normal brain around the target volume. In all normal tissues combined the mean BED is lowered by 15.8%.

Similar results were obtained for the other four cases studied. Table 2 summarizes the improvement of spatiotemporal treatments plans over a 4-fraction reference plan. Above, we analyzed a spatiotemporal treatment plan that both increases the AVM mean BED and decreases the normal tissue BED. In Table 2, we consider treatment plans that focus on normal tissue dose reduction, subject to the constraint that the mean AVM BED is the same as in the reference plan.

For all cases, a mean physical dose reduction of approximately 10% was observed in the AVM while maintaining the same mean BED. In the normal brain, the mean physical dose reduction is larger than in the target volume (approximately 20%). This is a result of minimizing normal brain BED alone while constraining the conformity, underdose, and AVM mean objectives to their values in the reference plan. Hence, the entire improvement of the spatiotemporal plan over the reference plan is directed into the mean normal tissue BED objective - rather than distributing the improvement evenly over the multiple treatment goals.

Comparing the physical dose reduction in normal brain (column 2) to the reduction in BED (column 3) indicates to what degree physical dose reduction translates into biological dose reduction. The BED reduction is smaller than the physical dose reduction, mostly because of a deviation from ideal uniform fractionation. In a 1 cm rim of normal tissue surrounding the AVM, where substantial deviation from uniform fractionation is expected due to the proximity to the AVM, approximately half of the physical dose reduction translates into BED reduction. In all normal tissues combined, the BED reduction is approximately three quarters of the physical dose reduction.

The benefit of spatiotemporal fractionation depends on size and shape of the target volume. For very small AVM size, the benefit of spatiotemporal fractionation is expected to drop because the ability to hypofractionate distinct parts of the target in different fractions disappears. Larger AVM size increases the benefit within limits. To confirm this trend, we considered two modified versions of case 1 where the AVM was isotropically expanded and contracted by 5 mm, resulting in altered target size without changing shape and location. The resulting normal tissue dose reductions are shown in Table 2, confirming the anticipated trend. Further considerations regarding the benefit of spatiotemporal fractionation are discussed in the supplementary materials (appendix B.1).

4. Discussion

To our knowledge, this is the first work to demonstrate that, using rotational therapy with conventional x-ray beams, partial hypofractionation of the target volume can be achieved along with near uniform fractionation in healthy tissues. Thereby, it is demonstrated that the therapeutic ratio can potentially be improved by delivering distinct dose distributions in different fractions, purely motivated by fractionation effects rather than geometric changes of the patient over the course of treatment. This represents a novel concept considering that current radiotherapy treatments aim for the same target dose in each fraction.

In our work, we use the BED model to describe fractionation effects. Although it is difficult to determine from clinical outcome data which fractionation schemes are truly iso-effective, leading to uncertainty in the α/β -ratio, it is generally assumed that AVMs have a fractionation sensitivity that is similar to normal tissues. Our choice of α/β -ratios reflects this and the iso-effective fractionation schemes assumed in Table 1 are consistent with schemes in use [10]. In addition to Table 1, the main assumption made in this paper is that the BED model can be generalized to non-uniform fractionation schemes with varying doses per fraction, and that it is valid over a large range of dose levels. For example, 16 Gy delivered as one 10 Gy fraction plus one 6 Gy fraction is assumed to be an intermediate biological dose that is less effective than a single 16 Gy fraction but more effective than two 8 Gy fractions. Since virtually all clinical experience is based on stationary fractionation schemes that deliver the same dose every day, there is no direct clinical evidence for the validity of this assumption. However, it is a plausible working hypothesis for exploring new treatment approaches. Nevertheless, an eventual clinical application of spatiotemporal fractionation schemes should be done cautiously and under a protocol. Additional discussion on the validity of the BED model is provided in the supplementary materials (appendix B.2).

The spatiotemporal treatment plans discussed in this work have similarities to volume-staged treatments in the sense that a different part of the AVM is irradiated to high single fraction doses on different days. However, it should be noted that the motivation is different. Spatiotemporal fractionation schemes are motivated purely by fractionation effects, i.e. repair processes that occur within hours after irradiation, and are meant to be delivered on consecutive days so that the entire AVM is irradiated within one treatment cycle. Thus, the goal is to improve on fractionated radiosurgery that delivers the same dose in each fraction. In contrast, volume-staged treatments are motivated by normal brain recovery over the period of several months. It is assumed that in each stage a limited volume of normal brain can tolerate a high single fraction dose. After a rest period of several months, it is assumed that the brain recovers and can tolerate the same dose again. Such long-term recovery effects are not considered in this paper.

AVMs have multiple features in favor of spatiotemporal fractionation schemes: 1) reduction of integral dose to the brain is a relevant objective for otherwise healthy patients with long life expectancy; 2) the patient can be well immobilized so that dose distributions from different treatment days achieve a summation as intended; 3) a low α/β -ratio. Nevertheless, the concept of spatiotemporal fractionation schemes could also be evaluated for tumors embedded in a dose limiting normal tissue such as brain tumors or liver tumors. For

example, dose prescription for liver stereotactic body radiotherapy (SBRT) treatments is often based on the mean liver dose. Hence, a reduction in mean liver dose through spatiotemporal fractionations schemes could facilitate further dose escalation.

5. Conclusion

We demonstrate that the standard BED model gives rise to nonuniform spatiotemporal fractionation schemes, i.e. a projected benefit of delivering different dose distributions in different fractions. Using rotational therapy techniques and conventional photon beams, distinct dose distributions can be designed such that partial hypofractionation in the target volume can be achieved along with near uniform fractionation in normal tissues -- resulting in a net improvement of the therapeutic ratio. We investigate this approach for the irradiation of large cerebral AVMs, which respond poorly to fractionated radiosurgery and present a management challenge. It is shown that through this approach, a reduction of the mean BED of approximately 10% can be achieved in normal brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) cumulative physical dose of a 4-fraction reference plan that delivers the same dose distribution in all fractions; (b) equieffective dose EQDX for the reference plan; (c) cumulative physical dose of the spatiotemporal plan; (d) equieffective dose EQDX for the spatiotemporal plan; (e) difference in physical dose; (f) difference in EQDX. In (e) and (f) the reference plan is subtracted from the spatiotemporal plan, i.e. negative values indicate a higher dose in the reference plan. A reference dose value of $X = 5.21$ Gy is used for EQDX distributions.

Figure 2. Dose distributions in 4 fractions of a nonuniform spatiotemporal treatment plan. The inner contour represents the target volume, the outer contour represents a 1 cm rim of normal brain surrounding the target.

Figure 3. Fraction of the total physical dose that is delivered by the hottest fraction in the spatiotemporal plan. A value of 0.25 corresponds to uniform fractionation.

Figure 4.

DVH comparison of reference plan (solid line) and spatiotemporal plan (dashed line), evaluated for EQDX (using the reference dose level $X = 5.21$ Gy). The healthy tissue DVH refers to all non-target tissues in the irradiated region (i.e. voxels receiving zero dose in both plans are removed).

Fractionation schemes, specified by the total physical dose in 1–4 fractions, that are assumed to be iso-effective regarding obliteration of the AVM and damage to normal brain. We assume that all end points relevant for normal brain such as radiation necrosis or brain atrophy have the same fractionation sensitivity as described by $\alpha/\beta=2$. The dose levels are motivated by the objective and constraint functions used for plan optimization (section 2.2). The equieffective dose EQDX is calculated for $X = 5.21$ Gy.

Table 1

# fractions	1	2	3	4	BED	EQDX
AVM dose [Gy]	12	16	18.74	20.84	48	20.84
($\alpha/\beta = 4$)	17.7	24	28.47	32	96	41.69
	23.38	32	38.23	43.23	160	69.48
Brain dose [Gy]	11.69	16	19.11	21.61	80	22.18
($\alpha/\beta = 2$)	6	8	9.37	10.42	24	6.66
	3.12	4	4.55	4.94	8	2.22

Table 2

Mean physical dose and BED reductions in the spatiotemporal plan compared to the uniform 4-fraction reference plan. The first column states the mean physical dose in the reference plan. The mean dose in the normal tissue refers to all non-target tissues in the irradiated region (i.e. voxels receiving zero dose in both plans are removed). Note that relative reductions in equieffective dose EQDX are identical to BED reductions. The bottom row states the dose and BED reductions averaged over the 5 cases together with the standard deviation.

Case	Structure	ref. dose [Gy]	dose red. [%]	BED red. [%]
1	AVM	31.3	10.2	0
(30 cc)	1 cm rim	11.5	11.5	7.0
	normal tissue	4.0	20.3	17.5
2	AVM	30.4	11.0	0
(53 cc)	1 cm rim	12.5	13.0	7.3
	normal tissue	5.4	16.3	12.9
3	AVM	31.0	12.6	0
(21 cc)	1 cm rim	11.0	16.5	10.1
	normal tissue	2.9	23.7	19.3
4	AVM	31.3	13.0	0
(19 cc)	1 cm rim	11.2	14.9	7.7
	normal tissue	3.5	20.6	15.6
5	AVM	30.3	15.5	0
(32 cc)	1 cm rim	11.8	17.8	8.8
	normal tissue	3.9	24.5	19.2
1 + 5 mm	AVM	29.3	13.7	0
(62 cc)	1 cm rim	12.1	15.0	7.8
	normal tissue	4.7	23.9	20.3
1 – 5 mm	AVM	30.7	8.0	0
(13 cc)	1 cm rim	12.2	11.4	6.3
	normal tissue	3.0	17.9	14.2
Average	AVM		12.5 (± 1.8)	0
(case 1–5)	1 cm rim		14.7 (± 2.3)	8.2 (± 1.1)
	normal tissue		21.1 (± 2.9)	16.9(± 2.4)