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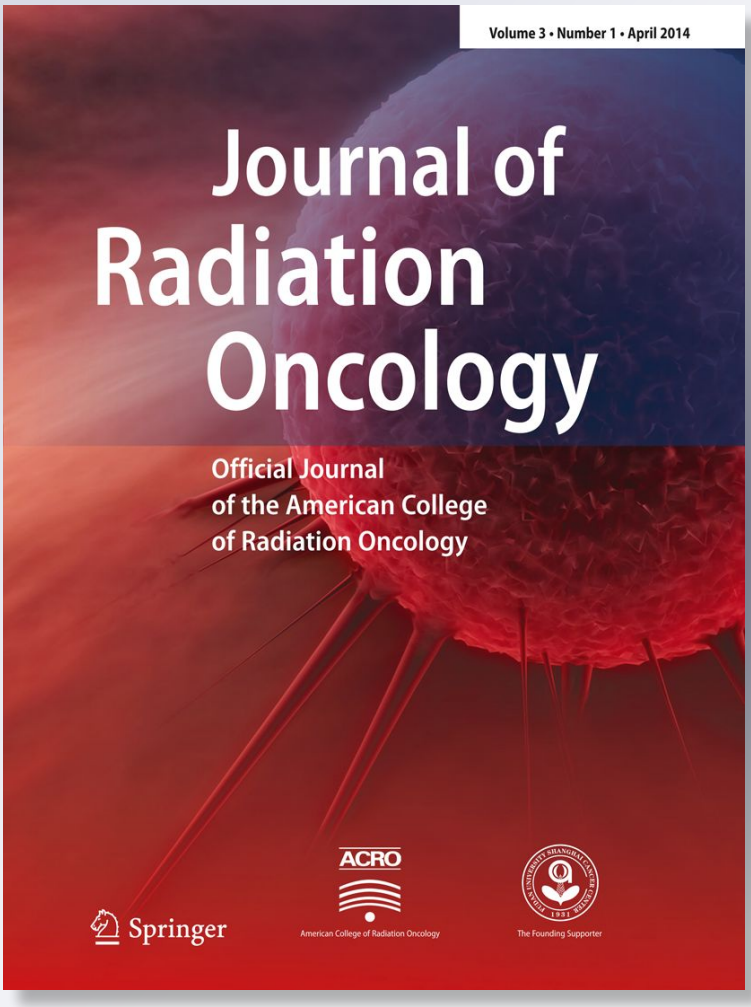

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ORIGINAL RESEARCH

Assessment of the alpha/beta ratio of the optic pathway to adjust hypofractionated stereotactic radiosurgery regimens for perioptic lesions

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Abstract

Background Hypofractionation has been recently considered as an alternative to improve stereotactic radiosurgery treatments of lesions close to the optic pathways. To estimate the intrinsic benefit from fractionation versus single-dose radiosurgery for perioptic lesions, the value of the alpha/beta ratio of the optic pathways needs to be known. Based on the linear quadratic (LQ) model, hypofractionation versus single-fraction SRS can be justified in cases where parts of the optic apparatus necessarily receive the full therapeutic peripheral dose, if there is a positive difference between α/β of the lesion and the α/β of the surrounding organs at risk. Furthermore, the knowledge of α/β ratios is required to calculate radiobiological dose parameters, such as the biologically effective dose (BED) and single fraction equivalent dose (SFED), and helps estimate normal tissue complication probability (NTCP), dose constraints, and retreatment doses. Only 3 alpha/beta ratios for the visual system have been published so far, varying between -0.6 and 3.06 Gy.

Material and methods The alpha/beta ratio of the optic pathways was estimated from a fraction equivalent plot based on a meta-analysis of 429 studies published between 2000 and June 2018. We included 15 studies with fraction sizes between 1 and 31, considering the following inclusion criteria: at least one well-documented RION case with detailed dosimetric analysis for the visual system, follow-up period (FUP) of at least 24 months, no tumor progression, no prior radiation. Additionally, we included results from our center on 68 hypofractionated treatments and 161 single-fraction SRS treatments for perioptic lesions.

Results The fraction equivalent (FE) plot method revealed an alpha/beta ratio of the optic pathway of 1.03 Gy, confidence interval [-0.38–1.60]. Well-documented RION cases are rare in the literature; there is still not enough data to distinguish between alpha/beta ratios of the optic chiasm, the nerves, and the tracts. Optimized hypofractionation schedules were calculated for the treatment of meningiomas, chordomas, and brain metastases.

Conclusion Compared to single-fraction SRS, a significant intrinsic benefit from hypofractionation can be achieved, not only for perioptic malignant tumors, but for benign lesions as well, because of the very low alpha/beta ratio of the optic system of 1.03 Gy. An increased single fraction equivalent dose of up to 10% for perioptic meningiomas and of more than 25% for malignant tumors can be reached with optimized hypofractionated stereotactic radiosurgery schedules.

Keywords Radiosurgery · Hypofractionation · Alpha/beta ratio · Anterior visual pathway · Single fraction equivalent dose

Introduction

Historically, radiosurgical targets have been treated with the total radiation dose given in one fraction under stereotactic conditions defined as stereotactic radiosurgery (SRS) [1]. Recently, treatment schedules consisting of more than one fraction have been applied either when (i) the target volume is relatively large and/or when (ii) critical structures are close to the target volume. Hypofractionated stereotactic radiosurgery (HFSRS) is by definition limited to 2–5 fractions; if more

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fractions are applied, this is defined as fractionated stereotactic radiotherapy (FSRT).

Knowledge of both the α/β ratio of tumors and as well of surrounding organs at risk (OAR) helps to ascertain if HFSRS would be of intrinsic benefit resulting in a therapeutic gain versus single-fraction SRS. Considering the LQ model with its known limitations, and excluding technology-related aspects, only in the case that the α/β ratio of the target tissue is significantly larger than that of the OAR, a therapeutic gain can be expected from HFSRS. Otherwise single-fraction SRS is indicated. Therefore, not only the α/β of a tumor needs to be known, but as well the α/β of surrounding OARs.

The optic apparatus is one of the important OARs to spare in cerebral SRS. While initial studies indicate positive outcomes for several HFSRS schedules for different intracranial pathologies [2, 3], both clinical and theoretical data on hypofractionation of perioptic lesions are still limited [4, 5]. Radiation-induced optic neuropathy (RION) is a major late complication in radiosurgery of perioptic lesions, caused by irradiation of the anterior visual pathway (AVP). RION results in acute and irreversible visual loss. The onset of RION occurs within an average of 18 months after treatment; the period may range from 3 months to 10 years [6, 7]. Single doses to parts of the anterior visual pathway larger than 10–12 Gy are usually required for RION to develop [4, 8, 9]. Deng et al. [10] found that compressed optic nerves in cats are more sensitive to Gamma Knife radiosurgery than normal optic nerves, and described 12 Gy as minimum dose causing RION in normal, while 11 Gy in compressed optic nerves, respectively. Vascular injury from radiation has been suggested as a significant contributor to RION [11, 12]. Optic nerve injury characteristically causes monocular visual loss, while injury to the entire chiasm can result in bilateral vision loss. An injury limited to the inferior central optic chiasm typically damages the bilateral upper outer quadrant visual field, whereas RION of an optic tract causes loss of the same half of the visual field in each eye. RION is diagnosed by exclusion of other conditions that might affect vision. Acuity problems can result from cataracts, dry eye, or radiation retinopathy, usually distinguishable from RION [4].

When judging single session SRS versus HFSRS, questions may arise: Even applying larger total doses, is HFSRS just the same as SRS, but with reduced effects to both lesion and OAR? How close to OAR can one treat safely with HFSRS? Which are the optimal doses and HFSRS courses? What are the corresponding SRS equivalent doses?

The goal of this study was (i) to estimate the alpha/beta ratio of the optic apparatus and based on this ratio (ii) evaluate if SRS of perioptic lesions may benefit from hypofractionation and (iii) quantify benefits from optimal fractionation schedules.

Material and methods

Linear quadratic model

Within the linear quadratic (LQ) model, α/β ratios are required to estimate the efficiency of different fractionation schedules. Dose fractionation causes a lower biological effect from multiple fractions compared to the effects of a single dose of the same amount. As the number (n) of fractions increases, the total dose (nd) required to achieve a specific biological effect increases, weighted by the α/β ratio. The biologically effective dose (BED) is defined as the total dose delivered in an infinite number of infinitesimally small dose fractions that has the same biologic effect as the dose-fractionation regimen in question and is expressed by

$$\mathrm{BED} = \mathrm{nd}\,(1 + d/(\alpha/\beta))$$

The concept of a single fraction equivalent dose (SFED) has been developed to serve as a more intuitive approach to compare different dose-fractionation courses. SFED is defined as the dose delivered in a single fraction that would have the same biologic effect as the dose-fractionation scheme in question. The calculation of the SFED of a fractionated course makes it possible to easily apply the extensive clinical experience accumulated with single-fraction radiosurgery in determining fractionated courses that should be safe and effective [13–15]. Single fraction equivalent doses can be directly derived from the LQ model [16].

$$\mathrm{SFED} = \mathrm{sqrt}\left[(\alpha/\beta)^2/4 + (\alpha/\beta)\mathrm{BED}\right] - (\alpha/\beta)/2$$

Assessment of α/ß ratios

Historically, α/β ratios have been derived from in vitro studies, by irradiating cell lines with different fraction schedules. In vitro studies can determine α/β ratios for specific cells, but radiosurgical targets usually consist of different cell types, and the interactions between cells in the target in vivo cannot be simulated by in vitro studies [17]. Another limitation of in vitro studies is the absence of normal tumor environment, particularly the lacking vascularization. SRS applies large dose doses above 10 Gy, which are assumed to cause vascular damage resulting in decreased blood perfusion and leading to indirect tumor cell death [18, 19]. This limitation not only affects the accuracy of the α/β estimation but as well the basic theory of the LQ model [20].

Using clinical data, it is possible to estimate the α/β ratio, based on iso-effective fractionation schedules. If two fractionation schedules result in an equivalent clinical effect, they may be assumed to have the same BED and the linear quadratic model may be used to calculate the α/β ratio [21]. By setting BED1 = BED2, α/β is calculated as follows

$$\alpha/\beta = (\mathrm{D1d1} - \mathrm{D2d2})/(\mathrm{D2} - \mathrm{D1})$$

Douglas and Fowler estimated the α/β by using a reciprocal plot method (fraction equivalent plot, FE plot) based on several different fractionation schedules [22]. This method involves a rearrangement of the linear quadratic equation so that inverse total dose ($1/D$) may be plotted against dose per fraction (d):

$$-1/D = \alpha/\ln(\mathrm{SF}) + [\beta/\ln(\mathrm{SF})]d$$

The single best-fit line intercept on the abscissa provides a negative estimate of the α/β ratio.

Several other techniques have been described in the literature to derive α/β ratios from iso-effective radiation damage from clinical studies of different fractionation schedules. Methods based on graphical presentations include techniques developed by De Boer [23] and by Tucker [24]. Other methods are based on nonlinear regressions that include a weighting based on the standard deviation of the data points [24] or the "direct analysis" technique by Thames et al. [25].

FE plots are based on iso-effectiveness, generally considering *mean* iso-effective doses that are causing an equivalent effect induced by different fractionation courses. In practice, the iso-effectiveness is based on small intervals of tumor control probability and/or normal tissue complication rates.

In this study, the alpha/beta ratio of the optic pathways was assessed by analyzing the iso-effectiveness of *specific* doses. The FE plot in this study is based on the iso-effectiveness of SRS, HFSRS, and radiotherapy (RT) treatments, described in the literature, with specific doses to parts of the AVP, which had caused RION. Only the well-described maximum point doses to the optic pathways, which all caused RION for SRS, HFSRS, and RT fractionation courses, were accepted to be included in the fraction equivalent analysis. Although this approach reduced the available data, we did not derive a FE plot from much larger information in the literature on RION cases, which are mentioning only mean or median doses to the optic system. This approach was not feasible as widespread uncertainties were found. A mean optic nerve dose of a group of patients does not describe the amount of exposure in a certain patient.

The following criteria for diagnosing RION were defined by Kline et al. [26] and Parsons et al. [12]: irreversible visual loss with visual field defects indicating optic nerve or chiasmal dysfunction, absence of visual pathway compression due to tumor progression, radiation-induced neoplasm, arachnoid adhesions around the chiasm, radiation retinopathy or any other apparent ophthalmological disease, absence of optic disc edema, optic atrophy.

Data from literature

Data were extracted from (i) a meta-analysis of published studies on SRS, HFSRS, and radiotherapy treatments of perioptic lesions and (ii) from SRS and HFSRS treatments from our center.

Relevant publications were identified from the Medline database using PubMed with combinations of the search terms ("RION" or "visual impairment" or "visual field" or "visual acuity") and ("Gamma Knife" or "CyberKnife" or "Radiotherapy" or "Proton" or "Radiosurgery") and ("meningioma" or "adenoma" or "craniopharyngioma" or "chordoma"). The search includes studies indexed between January 2000 and June 2018. A total of 429 studies were found. To attain biological equivalency for the different fractionation courses of radiation-induced optic neuropathy, we applied the following inclusion criteria. Studies must present a least one well-documented RION case mentioning Dmax to the corresponding part of the optic pathway. FUP had to be limited to be longer than 24 months to account for RION as a late complication. Cases with tumor progression or prior radiation were excluded. Studies were considered only in case a detailed dosimetric analysis for the visual system was given for a specific RION case. Studies published before 2000 were discarded to take into account the improved imaging techniques utilized in recent years for treatment planning. From these criteria, we accomplished to include a total of 15 studies with a total of 21 well-described RION cases. FE plot data points extracted from these studies were considered iso-effective (Table 1).

Clinical data

Clinical data provided from our center were added to the fraction equivalent evaluation from both single-fraction and HFSRS treatments. This study was approved by the IRB of our center and informed consent was signed by each patient. Of a total of 229 patients with perioptic lesions that have been treated with a Leksell Gamma Knife unit (4C, Elekta) at our center, 2 cases were confirmed by ophthalmologic evaluations for RION, according to the criteria mentioned above.

Between June 2011 and November 2018, a total of 68 patients with perioptic lesions (36 pituitary adenomas, 19 meningiomas, nine craniopharyngiomas, one cavernoma, one AVM, one metastasis, and one sarcoma) were treated with HFSRS (seven treatments with five sessions with mean margin dose to lesion 5×6.93 Gy, 54 treatments with four sessions 4×5.32 Gy, and seven treatments with three sessions 3×6.31 Gy). The average maximum optic point dose for the three fractionation schedules was 5×5.79 Gy, 4×5.84 Gy, and 3×6.27 Gy. The mean FUP for ophthalmologic evaluation was 28 months [2–79 m]. An improvement in vision was observed in 10 cases, worsening of vision in two cases: one case of visual deterioration was caused by increased tumor volume, one case was confirmed for RION (maximum optic point dose was delivered in four fractions of each 5.60 Gy) (Table 1). A total of 161 patients with perioptic

Table 1 Studies describing cases of RION, which were included and applied to the fraction equivalent Fe plot method. Many studies, describing even treatment outcomes with relatively high doses applied to the AVP, had to be excluded from fraction equivalent evaluation, because of lacking observation of RION

First author	Year published	Mean or median optic FUP [month]	RION frequency [%]	RION case described		
				Number of fractions	Optic total dose [Gy]	Optic dose/fraction [Gy]
Astradsson, A. [27]	2017	39.6	6.30	30	60	2
Demizu, Y. [28]	2009	25	5.00	26	67.6	2.6
				26	40.1	1.54
Farzin, M. [29]	2016	75	0.90	29	57.3	1.98
				30	52.8	1.76
Grant, RA. [30]	2014	40.2	3.20	1	7.4	7.4
Hasegawa, T. [31]	2010	68	3.20	1	18	18
				1	15	15
Hauptmann, JS. [32]	2012	54	6.70	1	14.8	14.8
Hiniker, S. [3]	2016	36.8	0.40	5	23.9	4.78
Iwata, H. [33]	2011	33	1.70	3	20.8	6.93
Leavitt, J. [8]	2013	83	0.50	1	12.8	12.8
Park, K. [34]	2011	62	0.80	1	7.6	7.6
Ronson, B. [35]	2006	80	2.30	28	42	1.5
Skeie, BS. [36]	2010	82	2.00	1	8.6	8.6
Stafford, S. [37]	2003	40	1.90	1	12.8	12.8
Weber, D. [38]	2011	72.4	3.70	28	49.8	1.78
Wenkel, E. [39]	2000	73	8.70	31	62	2
				31	62	2
				31	62	2
				31	63	2.03
This study		36.3	0.60	1	10.2	10.2
		28	1.50	4	22.4	5.6

lesions were treated with single-fraction SRS, with a mean margin dose to the lesion of 15.48 Gy. The average dose to 1 mm^3 of the optic apparatus was 10.2 Gy, while the maximum optic point dose reached 18.4 Gy. The mean FUP for ophthalmologic evaluation was 36 months [7–81 m]. One case was confirmed for RION after delivering a maximum point dose to the AVP of 10.2 Gy (Table 1).

Both local control and tumor reduction were observed as significantly higher in the HFSRS group, compared to the single-fraction group; nevertheless, lesions in the HFSRS were located significantly closer to the AVP, according to our treatment protocol. After a mean imaging FUP of 23 months [2–72 m] of patients in the HFSRS group, 98.5% local control was achieved. Only one lesion progressed, caused by pituitary apoplexy. A mean volume reduction of 3.05%/month was observed. In the group of patients treated with single-fraction SRS, after a mean imaging FUP of 27 months [4–78 m], local control reached 95.7% and mean volume reduction of 1.52%/month was observed. The detailed treatment protocol and results surpass the scope of this analysis and will be published in a more comprehensive clinical focused study.

Results

The FE plot method revealed an alpha/beta ratio of the optic system of 1.03 Gy, 95% confidence limits for *x*-intercept [-0.38–1.60] (Fig. 1). To adjust for the large variation in the group of single-fraction schedules, parameters have been averaged resulting in a mean dose of 11.91 Gy for the group of single-fraction schedules, which accordingly weighted data point has been considered for FE analysis. Well-documented RION cases are rare in the literature; there is still not enough data to distinguish between alpha/beta ratios of the optic chiasm, the nerves, and the tracts.

This knowledge of α/β provides dose constraints for different fractionation schedules for a single fraction equivalent dose SFED of 12 Gy to the AVP, a single maximum dose that has been suggested as relatively safe for the AVP, with a low risk of development of RION in the order of 1% [4, 9]. SFED calculations offer the following equivalent doses: 16.68 Gy delivered in 2 fractions or 20.16 Gy in 3 fractions or 23.04 Gy in 4 fractions or 25.50 Gy in 5 fractions shall have the same biological effect as 12.0 Gy in one fraction delivered to the AVP (Table 2).

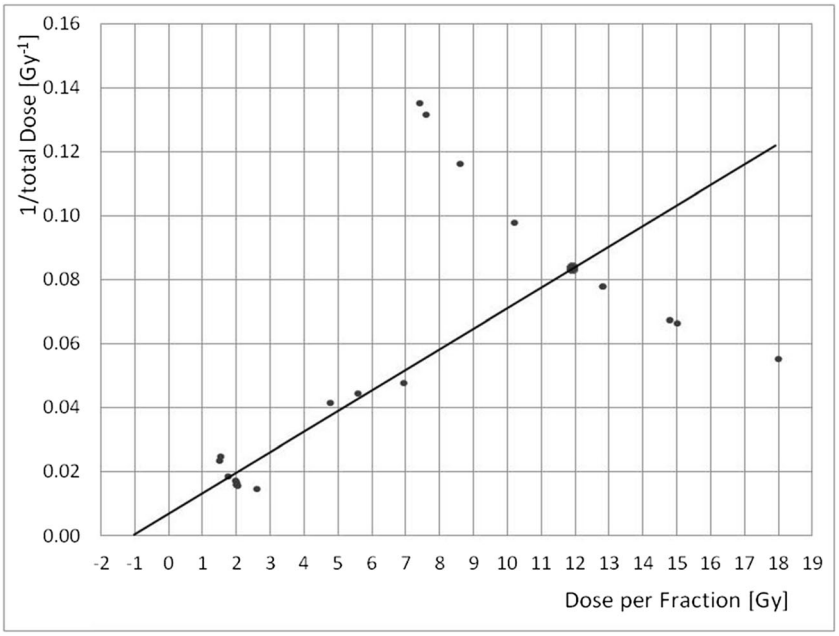

Fig. 1 The FE plot method revealed an alpha/beta ratio of the optic system of 1.03 Gy, 95% confidence limits for *x*-intercept [-0.38–1.60]

In the case of a lesion abutting the optic apparatus, it is frequently possible to limit the dose to 12 Gy to a 1 mm^3 volume of the AVP, and simultaneously achieving a 12-Gy margin tumor dose with a tumor coverage index close to 100%, by carefully planning the SRS treatment. In this case, the 12-Gy iso-dose line would fall perfectly into the junction between AVP and the tumor.

Based on this condition, one can calculate margin doses and SFEDs for different perioptic tumors, considering known α/β ratios. The α/β of benign meningiomas has been published as 3.76 Gy [40]. Instead of delivering 12 Gy in one fraction to this perioptic meningioma, 5.76 Gy in 4 fractions using the same treatment plan would give a maximum SFED of 12 Gy to the AVP, while an SFED of 13.1 Gy to the margin of the meningioma (Table 2). The α/β ratio of chordomas has been published as relatively low: 2.45 Gy [41]. The increase in equivalent dose from 12 Gy in one fraction to an SFED of 12.70 Gy in 5 fractions allows only a small benefit (Table 2). The benefit of increased SFED from hypofractionation for malignant tumors, including brain metastases, is much larger, as expected for fast responding tissues with high α/β ratios that are generally expected to be close to 10 Gy [42]. A treatment of 5 fractions of a perioptic metastasis allows for an SFED of 15.25 Gy to the margin of the metastasis, a significant increase compared to 12 Gy delivered in one fraction (Table 2).

Discussion

In radiosurgery of suprasellar lesions, several tissues are closely located and must be protected from high-dose levels.

Table 2 Different fractionation courses with doses that have the same biological effect on the optic pathways as 12 Gy applied during a single session

Optic apparatus					Meningioma (perioptic)			Chordoma (perioptic)			Metastasis (perioptic)		
Number of fractions [–]	Dose per fraction [Gy]	Total dose [Gy]	BED [Gy]	SFED [Gy]	BED [Gy]	SFED [Gy]	Relative dose increase vs. SRS [%]	BED [Gy]	SFED [Gy]	Relative dose increase vs. SRS [%]	BED [Gy]	SFED [Gy]	Relative dose increase vs. SRS [%]
1	12.00	12.0	152.0	12.0	50.3	12.0	0.0	70.8	12.0	0.0	26.4	12.0	0.0
2	8.34	16.7	152.0	12.0	53.7	12.5	3.8	73.5	12.3	2.1	30.6	13.2	9.9
3	6.72	20.2	152.0	12.0	56.2	12.8	6.5	75.5	12.4	3.6	33.7	14.0	16.9
4	5.76	23.0	152.0	12.0	58.3	13.1	8.7	77.2	12.6	4.9	36.3	14.7	22.5
5	5.10	25.5	152.0	12.0	60.1	13.3	10.6	78.6	12.7	5.9	38.5	15.3	27.1

Hypofractionation courses for benign meningiomas ($\alpha/\beta = 3.76$ Gy), for chordomas ($\alpha/\beta = 2.45$ Gy) and perioptic metastasis (expected $\alpha/\beta = 10$), that comply with the dose constraint of SFED = 12 Gy (as maximum point dose) for the AVP

An increase in SFED of up to 10% for meningiomas, 6% for chordomas and 27% for metastasis, allow for a higher tumor control probability with hypofractionation, maintaining an equal risk for the optic system

Because of its high radiosensitivity, of special concern is the AVP. Patients with tumors located within 3 mm of the optic structures ("perioptic" tumors) have been frequently excluded from SRS due to concerns for visual toxicity from radiation-induced optic neuropathy (RION) [3]. Vision loss may occur after SRS either if the optic dose is too high, or from tumor progression, in case the tumor dose is too low to yield control [43, 44]. For 2 decades, the maximum dose to the optic pathway has been limited to 8 Gy in a single fraction. For single-fraction doses necessary to control most benign tumors (12–16 Gy), a risk of blindness as high as 27% has been reported [45, 46]. However, more recent studies have shown that radiation doses of 10–14 Gy are well tolerated and have a low risk of RION [4, 9, 31].

In recent years, HFSRS is performed more frequently for the treatment of perioptic tumors. Several studies choose α/β ratios of 2.0 Gy for the visual system [3], while QUANTEC [4] and HyTEC [5] selected $\alpha/\beta = 1.6$ Gy, recently Xue et al. preferred $\alpha/\beta = 1.0$ Gy [47]. So far, to our knowledge, only 3 calculated α/β ratios have been published: In 1992, Goldsmith et al. published an α/β ratio of 3.06 Gy, which means that there would be no benefit of hypofractionation for most benign lesions, with an α/β ratio close to 3 Gy [48]. Two years later, Jiang et al. distinguished between optic nerve and optic chiasm and estimated, based on relatively few data, an α/β ratio of 1.6 Gy for the optic nerves and a negative value for the optic chiasm, mentioning that a negative value has no biological meaning [49]. In 2010, Vernimmen and Slabbert reported a negative value of − 0.6 Gy and remarked that a negative value is not permitted by the LQ model, though indicating that the optic α/β value should be very low [40]. In 2003, Flickinger et al. conclude that the optic alpha/beta ratio is supposed to be smaller than zero, mentioning that this finding stretches the theoretical basis [50].

A new analysis of the α/β ratio for the optic system seems to be justified for several reasons: During the past decade, more data has been accumulated; more studies have been performed with longer FUPs, particularly true for HFSRS series. In addition, many studies put more attention on dose-volume analysis. Probably the most impact comes from improved imaging techniques, providing higher accuracy for identification and delineation of the AVP, and therefore allowing more careful dose planning of the AVP and other structures. Exact imaging is of special importance in SRS compared to conventional radiotherapy, as SRS provides a theoretic spatial accuracy in the submillimeter range and moreover a steep dose gradient. Due to the steep dose gradient in SRS, a spatial variation of as little as 1 mm may theoretically differ the dose by up to more than 10 Gy (in case of a GKRS dose gradient in z-direction treating a hormone-secreting adenoma applying 30 Gy to the margin). In our center, the mean dose gradient within the optic chiasm was measured 1.3 Gy/mm, with a maximum of 5.1 Gy/mm for 105 patients with perioptic lesions treated with single session SRS, and 2.3 Gy/mm with a maximum of 8.5 Gy/mm for 54 perioptic HFSRS treatments. As SRS is especially affected by spatial accuracy, the complete chain from imaging to dose planning and treatment needs particular attention. During the last 2 decades, magnetic resonance imaging has been widely accepted as the imaging modality for SRS, substituting computed tomography for delineation of lesions and surrounding OAR not only limited to the suprasellar cistern. Though MRI provides much better clinical accuracy, still CT maintains an important advantage over MRI in spatial accuracy, even if spatial distortion corrections for MRI are applied. Particularly the optic chiasm and the optic tracts are much clearer presented on MR imaging than on CT. 3D imaging with slice thicknesses of 1 mm or 2 mm greatly improves exact delineation. The course and extension of the optic nerve, chiasm, and tracts are usually delineated on noncontrast-enhanced high-resolution T1-weighted images. However, in extensive space-occupying lesions surrounding, compressing, and displacing the optic structures as in cases of prior subtotal resection or recurrence, identification is not always possible, especially in lesions that involve high-signal areas such as small hemorrhages or fluid-containing cysts or areas with signal intensities similar to the optic system. A new inversion recovery MR sequence, based on the FGATIR sequence, is particularly helpful to identify the AVP in these special cases [51].

The estimation of the optic α/β in this study is based on the LQ model. The radiobiology and application of the LQ model to high doses applied in SRS continue to be a matter of investigation [20, 43, 52, 53]. Some authors argue that the LQ model represents adequately dose-response relationships at high doses and that clinical outcome is consistent with the predictions of this model [54–56]. Other authors conclude that the LQ model underestimates tumor control at the high doses and do not reflect other mechanisms involved in tumor cell kill, arguing that in addition to mechanisms of DNA strand breaks and chromosome aberrations by conventional radiotherapy, SRS with doses larger than 8–12 Gy per fraction are hypothesized to cause vascular damage resulting in decreased blood perfusion; additionally with antigen expression, these effects lead to indirect tumor cell death [26, 56–58]. Other authors reason that the LQ model overestimates cell killing for high-dose fraction schedules because it does not sufficiently account for the reduction of sublethal damage from the conversion of sublethal to lethal damage due to intensified irradiation [53]. Possibly these opposite effects of over- and under-estimation of cell killing may compensate each other to some extent, at least for doses not far beyond of the accepted limits for the correct prediction of the LQ model and may depend significantly on lesion vascularity.

Few α/β values are published for intracranial pathologies. For benign meningiomas, Shrieve estimated an α/β of 3.28 Gy based on relatively few data [21]; subsequently,

Vernimmen and Slabbert published an α/β of 3.76 Gy [40]. Two relatively small α/β values (2.4 Gy and 2.3 Gy) for schwannomas are mentioned in the literature [40, 59]. Henderson et al. estimated $\alpha/\beta = 2.45$ Gy for chordomas [41]. To the best of our knowledge, there is still no data published on α/β ratios of pituitary adenomas, or of craniopharyngiomas. The α/β value of metastasis is generally expected to be close to 10 [42]. Several α/β values for various types of gliomas are published in the literature with values in the range of 5–10 Gy [60–62].

Hypofractionation courses can be optimized and individualized for different pathologies. According to this study, the HFSRS treatment of benign meningiomas can benefit from hypofractionation from a dose increase of up to 10% maintaining the dose constraint of a single fraction equivalent dose of 12 Gy to the optic pathway. Malignant tumors with high α/β of expected 10 Gy may benefit from a dose increase of more than 25%, compared to single-fraction SRS, when located close to the AVP (Fig. 2) While still a margin dose of 12 Gy possibly causes an acceptable tumor control probability (TCP) for both meningiomas or chordomas, in case of brain metastases or functioning pituitary adenomas, a margin dose of 12 Gy may be considered insufficient. To our knowledge, α/β ratios for functional or nonfunctioning pituitary adenomas are not published in the literature, even so, these tumors are already frequently treated with HFSRS regimens.

In perioptic meningiomas, an SFED of 13.3 Gy given in 5 fractions probably leads to a superior tumor control probability, compared to single-fraction SRS, as doses in the range of 13–14 Gy are favored to permit a long-term control of at least 90% in meningiomas [63]. In the treatment of chordomas, dose fractionation will not allow a higher BED without increasing the risk of RION. A randomized study in brain metastasis comparing single fraction versus multiple fraction SRS indicated that HFSRS with a higher dose improves local control without additional toxicity [64]. Further clinical outcome studies validating the dose equivalence for single and hypofractionated SRS are needed to confirm the theoretical assumptions in this study.

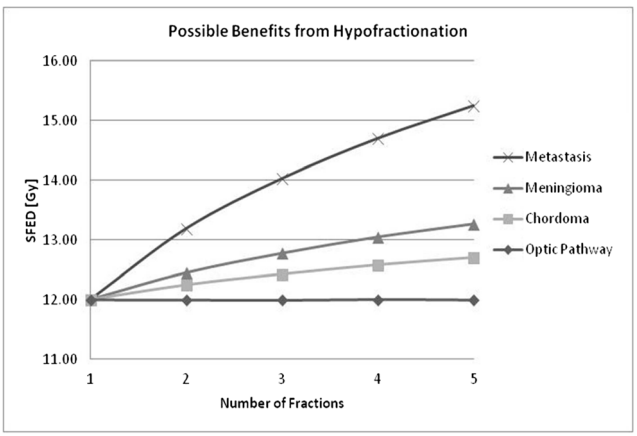

Fig. 2 Possible benefits from hypofractionation: While maintaining the SFED of the optic pathway at 12 Gy, the SFED for different benign and malignant tumors increases by a significant amount

According to the LQ model, higher SFED and BED benefits derived from differences of SFED/BED of the tumor versus the OAR can be achieved by increasing fraction numbers larger than 5; optimal fractionation would be the case of infinite fractions of infinite small doses. In practice, the fundamental principles of SRS, which include highly conformal plans, minimal margin, accurate and precise target localization, minimization of position deviation, and robust quality assurance, are still not perfectly realizable for large numbers of fractions. In order to judge for the optimal treatment, SRS or HFSRS or RT, of lesions close to OAR, an optimum dose/fraction scheme may exist for different tissue–OAR combinations. The LQ model does not account for factors as intense vascular damage that can effectively reduce tumor blood supply and changes in antigen presentation that can generate clinically important immune responses. Both effects increase with larger doses and reach high importance at doses larger than 8–10 Gy. Possibly HFSRS regimens, which deliver at least 8 Gy to large parts of the tumor while delivering that dose in a relatively high number of fractions, may get close to the optimal dose/fraction regimen.

Several dose recommendations for the optic pathway for hypofractionated regimens have been published in recent years. While applying different approaches, Timmerman [65], AAPM Task Group 101 [44], the QUANTEC group [4], the HyTEC group [5], and the study from Stanford University [3] reached similar results for the 5-fraction dose limits, while optic dose constraints vary considerably for 1–3 fractions (Table 3). Comparing the different approaches, including our study, dose constraints for the optic apparatus, derived from the LQ model, are relatively compliant with NTCP projections, while the comparison of conventional RT doses to other OAR, with SFED, may lead to conflicting clinical outcomes [47].

Limitations

All units and concepts applied in this study are based on the LQ model. Maximum doses to a small volume of the AVP presented in this study were in the range of 10–15 Gy, doses that to some extent fall outside of the commonly accepted dose region of the LQ model. However, the LQ has been proved for lesions treated generally with margin doses of 50–90%, with maximum doses being up to twice as high as margin doses.

RION can occur a long time after irradiation, up to 10 years [6]. FUP for visual impairments are commonly much shorter in most studies. Because of historic developments, SRS and RT series have longer FUP compared with the relatively new

Table 3 Dose limits to the optic pathway from published studies for 1–5 fractions, compared to the findings in this study. While dose constraints vary significantly for 1–3 fractions, the 5-fraction dose limits keep comparatively close together

Authors	Year published	Optic α/β used in study [Gy]	Constraint for optic pathway	Dose limit [Gy] for number of fractions				
				1	2	3	4	5
Timmerman [65]	2008		Maximum point dose	10.0		19.5		25.0
AAPM TG 101 [31]	2010		Suggested maximum point dose to 0.035 cc volume	10.0		17.4		25.0
QUANTEC [4]	2010	1.6–3.3	Dmax for 10% NTCP risk	12–15	"LQ model unreliable for extrapolating from RT to SRS"			
Hiniker et al. [3]	2016	2.0	Dmax for 1% NTCP risk	12.7	17.5	20.9	23.7	26.1
HyTEC [5]	2018	1.6	Dmax for 1% NTCP risk	10.0		20.0		25.0
This study		1.03	SFED equivalent of 12 Gy	12.0	16.7	20.2	23.0	25.5

HFSRS series, whose long-term efficacy and toxicities are less known. Most studies included in this estimation of the optic α/β had a similar FUP range; thus, errors caused by too short FUPs probably are similar and may cancel out.

A uniform application of a definition of RION and as well as the definition of the maximum point dose (Dmax) to the optic apparatus is still lacking in the literature, causing further limitations of this study. In part, the widespread maximum point doses between 7.4 and 18 Gy for RION cases within the SRS group considered in this study are owed to these uncertainties.

Conclusion

A significant benefit from hypofractionation relatively to single-fraction SRS can be expected not only for malignant tumors located in the sellar region but for benign lesions as well, because of the very low alpha/beta ratio of the optic system of 1.03 Gy, which is well below known alpha/beta ratios for benign and for malignant brain tumors. An increased SFED of up to 10% for perioptic meningiomas and of more than 25% for malignant tumors can be achieved with optimized hypofractionated stereotactic radiosurgery schedules.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Abbreviations BED, Biologically effective dose; SFED, Single fraction equivalent dose; NTCP, Normal tissue complication probability; TCP, Tumor control probability; RION, Radiation-induced optical neuropathy; FUP, Follow-up period; FE, Fraction equivalent; SRS, Stereotactic radiosurgery; HFSRS, Hypofractionated stereotactic radiosurgery; FSRT, Fractionated stereotactic radiotherapy; RT, Radiotherapy; OAR, Organ at risk; LQ, Linear quadratic; SBRT, Stereotactic body radiotherapy; Dmax, Maximum point dose; AVP, Anterior visual pathway; AVM, Arteriovenous malformation; GKRS, Gamma Knife stereotactic radiosurgery; FGATIR, Fast gray matter acquisition T1 inversion recovery

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