Research Square

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Radiosurgery treatment of Anterior Visual Pathway Meningioma (AVPM)

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Abstract

BACKGROUND

Most anterior visual pathway meningiomas (AVPM) are benign and slow-growing, but these tumors may affect visual functions, including visual acuity (VA) and visual field (VF). Due to location, most are treated non-surgically by fractionated stereotactic radiotherapy (FSRT), aiming to prevent tumor progression and visual functions deterioration. Unfortunately, FSRT in itself may affect visual functions. The current preferred treatment regimen (in terms of safety and effectiveness) is undetermined. While most cases are treated with conventional fractionation (cFSRT) – 50.4–54 Gy in 28–30 fractions of 1.8-2 Gy, advances in technology have allowed shortening of total treatment length to hypofractionation (hSRT) – 25-27Gy in 3–5 fractions of 5–9 Gy. Our aim was to evaluate the association of radiotherapy regimen for treating AVPM (cFSRT vs. hSRT) with visual function outcomes (VA, VF) at the last neuro-ophthalmologic evaluation.

METHODS

We conducted a retrospective cohort study of AVPM cases treated at Sheba Medical Center during 2004–2015. We compared cFSRT and hSRT regimens regarding visual function (VA, VF) outcomes at the last neuro-ophthalmologic evaluation. VA was determined by the logarithm of the minimum angle of resolution (LogMAR). VF was determined by the mean deviation (MD). A clinically relevant change in VA was defined as 0.2 LogMAR.

RESULTS

48 patients (13 receiving hSRT, 35 receiving cFSRT) were included, with a median follow-up of 55 months. No significant difference was evident regarding LogMAR or MD of involved eyes at the last evaluation. Six (17%) patients in the cFSRT group experienced clinically relevant VA deterioration in the involved eye, compared with six (46%) in hSRT ($p = 0.06$).

CONCLUSION

Our findings, using comprehensive and meticulous investigation of visual outcomes, suggest that hSRT may be associated with higher risk for VA and VF deterioration in AVPM especially in ONSM. We recommend the use of cFSRT for ONSM.

Introduction

Meningioma accounts for about one-third of adult brain tumors (population incidence 7.61 per 100,000). The incidence increases with age and is higher in women. In most cases, this is a benign tumor (WHO -

World Health Organization Grade I). Benign meningioma (as opposed to atypical (Grade II) or malignant (Grade III) meningioma) is not a significant cause of mortality but can cause severe morbidity[1]. Anterior visual pathway meningioma (AVPM) in most cases is benign and grows slowly over years but can impair one or more visual functions: visual acuity (VA), visual field (VF), or color vision. The injury can be unilateral or bilateral depending on the tumor's location relative to the anterior visual pathway (AVP): near the optic tract, the optic chiasm, optic nerve, or involving the optic nerve sheath. The tumor may cause diplopia due to compression of cranial nerves III, IV and VI in the cavernous sinus or in the orbit [2,3]. Without treatment, deterioration of vision functions[4] and finally blindness[5] occur.

In most cases, AVPM is diagnosed by imaging (without pathological verification) and is not operable. The common treatment is FSRT[6], accurate radiation therapy designed to stop tumor growth and prevent deterioration of visual functions. The method's stereotactic component relates to using a patient-specific immobilization system while assimilating a recent imaging test, thus producing a patient/tumor-specific 3D coordinate system used throughout the treatment[7]. The optimal fractionation scheme – the daily dose of radiation and the total number of doses – for safe and effective treatment of AVPM is undetermined[8–12]. In our institution, most AVPM cases receive conventionally fractionated stereotactic radiotherapy (cFSRT), employing 28–30 daily doses of 1.8-2 Gy per day for a total dose of up to 54 Gy.

AVP structures exhibit greater sensitivity to single-fraction irradiation than other cranial nerves in the cavernous sinus, perhaps more so in patients with a pre-existing visual deficit due to tumors or previous surgery[13,14]. In many AVPM cases, there is an impairment in visual functions (to varying degrees) even before treatment is given[4]. Radiation toxicity can damage optic pathways and impair their functions, particularly by radiation-induced optic neuropathy (RION). It is hypothesized that the mechanism of damage in RION is an ischemic disorder followed by necrosis of the optic nerve and the optic chiasm, typically occurring three months to several years after radiotherapy completion, with peak incidence after 1 to 1.5 years[15]. Important risk factors for RION include total radiation dose (over 50Gy), higher dose per radiation fraction, advanced age, previous exposure to chemotherapy, or optic nerve compromise at the beginning of radiation therapy.[15] No effective treatment for RION has been found, driving the need for careful consideration of radiation regimen, and raising the importance of estimating radiation toxicity risk for tumors adjacent to AVP. Other factors that have been described to influence meningioma treatment outcome include residual tumor volume after surgery and pathology report of WHO grade, with atypical and malignant tumors entailing worse prognosis [16,17].

Rogers et al. reviewed the treatment of meningioma and concluded that a total dose of up to 50Gy for optic nerve sheath meningioma (ONSM) and AVPM produced good results[16]. Stiebel-Kalish et al. reported their results and reviewed previous publications on cFSRT (1.7-2Gy / fraction, for a total of 50-60Gy) for AVPM[6]. In their study, tumor control was achieved in 14 of the 16 patients, with shrinkage of size in three patients during a mean follow-up of 39mo. Two cases progressed, one in an area that was outside the radiation field. Visual function improved or stabilized in 8 of the 16 patients and worsened in 2 (12%). In published data, we found permanent deterioration in visual acuity or visual field in only 23 out of 1191

patients after cFSRT (2.1%, see Additional File 1 for references). This rate corresponds to the risk of damage to optic nerves and chiasm summarized by Mayo et al.[18], based mostly on descriptive publications with relatively small samples. The differences between published studies in outcome variables, therapeutic equipment, and follow-up periods make it difficult to reach conclusions, especially since some studies did not consider tumor progression (PD) as a variable that may affect the outcome.

Radiobiological models suggesting that higher daily doses are at least as effective as lower daily doses, and possibly more effective, while shortening treatment courses, led to abbreviated radiation regimens, termed hypofractionation (hSRT)[19]. Compared to cFSRT, hSRT uses higher daily radiation doses with shorter treatment duration. Choosing between these regimens for meningiomas in direct contact with the AVP is a double-edged sword: high-dose fractions reaching the sensitive blood supply of the optical system could lead to vascular damage and late secondary toxicity with loss of vision; on the other hand, a suboptimal dose could cause visual function deterioration as a result of PD.

Several series of patients with AVPM treated by hSRT have been published, with the caveat of insufficient reporting of dosimetric analysis for AVP structures or detailed measurement of visual function: Conti et al.[8] reviewed previous publications reporting hSRT treatment of AVPM and described "controlled tumor growth" and lack of "optic nerve toxicity" in a series of 25 patients treated with 2–5 doses of 4-10Gy each. Hiniker et al.[20] summarized previous publications (including Emami et al.[21] and later information from QUANTEC[22]) and reported results of treating peri-optic tumors by hSRT in up to five fractions; they suggested both hSRT and SRS were safe treatment options. Marchetti et al.[23] reported the results of treating 143 patients with hSRT (25Gy in 5Gy sessions over five consecutive days). VA change (worsening or improvement) was defined as one or more Snellen lines. VF deterioration was defined as an increase in the defect area. The authors reported a visual worsening rate of 7.4% (5.1% after excluding cases with PD). Conti et al.[12] reported a multicenter retrospective heterogeneous cohort of 341 patients with skull-base meningiomas, and compared cFSRT to hSRT. Visual toxicity was reported for one case (0.49%) of mild visual disturbance in hSRT vs. one case (0.7%) of moderate optical pathway toxicity in cFSRT. Most recently, Marchetti et al.[24] published results of 167 patients treated with 5X5Gy hSRT. The authors reported an overall visual worsening rate of 5.5%, or 3.7% if excluding PD patients with no details regarding the test used.

In light of the paucity of sufficiently detailed information, the present study investigated the relationship between the radiation therapy regimen (hSRT vs. cFSRT) and the change in visual function (visual acuity and visual fields), measured at last neuro-ophthalmologic evaluation compared to pre-treatment.

Materials And Methods

We conducted a retrospective cohort study of patients with AVPM treated with hSRT or cFSRT at Sheba Medical Center during 2004–2015. After receiving the local IRB approval, the data were extracted from patients' computerized records. Statistical analysis was performed on anonymized data.

Patient population

Patients were entered into analysis according to the following inclusion criteria: 1) patient received a radiological diagnosis of meningioma. 2) the tumor involved or was in anatomical proximity to one or more of the following locations: medial sphenoid wing; cavernous sinus; orbital apex; optic nerve sheath; tuberculum sella. 3) the tumor was treated with radiotherapy using hSRT or cFSRT protocols at Sheba Medical Center during 2004–2015. 4) data on neuro-ophthalmology and neuroimaging were available. Exclusion criteria included: 1) Lack of visual acuity documentation in the involved eye before treatment, 2) patient underwent additional radiation therapy or surgery in the period between the first radiotherapy treatment and the first neuro-ophthalmologic assessment, 3) History of prior treatment with stereotactic radiosurgery (SRS), or 4) patient with no light perception (NLP) in the involved eye before treatment.

For each patient, we collected demographic variables (age at the time of treatment, gender, smoking history, and duration from symptom onset to diagnosis), pathology report of WHO grade of the tumor (if available), presenting signs and symptoms (headaches, seizures, blurred vision, ptosis, whether the tumor was an incidental finding) and medical history (previous surgery for the same tumor, prior radiation exposure, diagnosis of neurofibromatosis, vision-threatening systemic conditions such as diabetes, hypertension, collagen vascular disorders, chronic eye disease) (Table 1).

We also reviewed data from the neuro-ophthalmologic examination before and after the radiotherapy. Best corrected visual acuity was determined by a neuro-ophthalmologist using Snellen chart. Visual fields were examined by Humphrey automated static perimetry (HVF). The evaluation included optic disc abnormality (no/atrophy/swelling), other cranial nerve abnormalities (III, IV, V1, V2, V3, VI, VII), the diagnosis of RION, radiation retinopathy, and other radiotherapy complications.

Variable definitions

Visual acuity (VA) is a continuous quantitative variable, determined according to the logarithm of the minimum angle of resolution (LogMAR)[25]. We used a value of 1/400 Snellen chart (LogMAR = 2.6) to represent counting fingers (CF) and estimated values of LogMAR 2.7, 2.8, 2.9 to represent hand movement (HM), light perception (LP), and no light perception (NLP), respectively[26]. We defined variables related to change over the follow-up period to counteract the variance in pretreatment visual function evaluation. The VA change between pre-treatment evaluation and last evaluation was defined as: ΔLogMAR = last LogMAR minus pre-treatment LogMAR. A difference of 0.2 LogMAR (two lines on a Snellen chart) was defined as a clinically relevant change in VA.

The visual field (VF) is a continuous quantitative variable determined according to the mean deviation (MD) value in the last assessment documented[25]. The VF change from the pre-treatment evaluation to the last evaluation was defined as ΔMD = last MD minus pre-treatment MD. Radiotherapy treatment was defined as hSRT if it involved five fractions and as cFSRT if it involved 25–30 fractions. In cases of AVPM with bilateral effect, the worse eye (right or left) was determined according to the most recent

neuro-ophthalmological assessment before treatment or by the side involved in the last pre-irradiation imaging examination. Visual function results were analyzed separately for “worse” and “better” eyes.

For patients who underwent further treatment after the cFSRT/hSRT (surgery or additional cranial re-irradiation), visual acuity and visual fields were determined according to the most recent pre-treatment assessment.

Statistical analysis

Categorical variables were described as numbers and percentages. Continuous variables were reported as the median and interquartile (25%-75%) range (IQR). Categorical variables were compared between the groups using the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared between the groups using the Mann-Whitney U test. Changes in continuous variables - between baseline and last assessment - were evaluated using Wilcoxon's signed-rank test. All statistical tests were two-sided. P-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (IBM SPSS Statistics for Windows, version 25, IBM Corp., Armonk, NY, USA, 2017).

Imaging data

We documented tumor location (right/left/bilateral), orbital involvement, and tumor origin (optic nerve sheath, sphenoid wing, cavernous sinus, tuberculum sella (including parasellar/suprasellar), clinoid (either anterior or posterior)) from the brain and orbits Magnetic Resonance Imaging (MRI) reports before the treatment (Table 1).

Radiation therapy data

Computerized records of radiotherapy treatments were retrieved, and data were collected regarding the date of treatment, the number of fractions, the daily radiation dose, and the total radiation dose.

Results

Patient Inclusion

Of 288 patients with a radiological diagnosis of AVPM treated with radiotherapy at Sheba Medical Center during 2004–2015, 48 patients were included in the final analysis: 13 in hSRT and 35 in cFSRT. See Fig. 1 for detailed exclusion criteria.

Patient Characteristics

There was no statistically significant difference between the groups in patients’ demographic characteristics or medical background (Table 1). Eighteen patients showed evidence of optic nerve sheath involvement at baseline, 16 in cFSRT cohort and 2 in the hSRT cohort. Median follow up from radiotherapy to last neuro-ophthalmologic evaluation was 55 months (range 18–162 months for all patients), with a significantly longer follow-up in the cFSRT cohort: median 73mo (range 21–162 months)

in the cFSRT cohort vs. median 37mo (range 18–75 months) in the hSRT cohort ($p < 0.0001$). A neuro-ophthalmologist reviewed the medical records of all the patients known to have a systemic vision-threatening condition (e.g., diabetes mellitus, hypertension): No patient had evidence of ocular damage secondary to a systemic condition.

Table 1
Baseline characteristics of AVPM patients by treatment group

Characteristic	treatment group		
	cFSRT (n = 35)	hSRT (n = 13)	p-value
Demographic characteristics			
Median age at treatment onset (IQR)	58 (45, 64)	52 (43, 66)	0.917
Female gender	28 (80%)	11 (85%)	> 0.999
Smoker	11 (37%)	1 (8%)	0.128
Mortality until end of analysis	1 (3%)	0 (0%)	> 0.999
Medical history			
History of surgery for same tumor (not including biopsy(	13 (37%)	6 (46%)	0.571
History of radiation therapy for tinea capitis	3 (9%)	2 (15%)	0.612
Systemic condition associated with a risk for vision-related complications (diabetes mellitus, hypertension, collagen vascular disorder)	14 (42%)	5 (39%)	0.806
MRI Findings before treatment			
Optic nerve sheath inv. (ONSM)	16 (46%)	2 (15%)	0.092
Orbital inv. (including ONSM)	22 (63%)	6 (46%)	0.297
Planum sphenoidale inv.	3 (9%)	2 (15%)	0.602
Sphenoid wing inv.	9 (26%)	6 (46%)	0.293
Cavernous sinus inv.	15 (43%)	9 (69%)	0.104

AVPM, anterior visual pathway meningioma; hSRT, hypofractionated stereotactic radiotherapy; cFSRT, conventionally fractionated stereotactic radiotherapy; IQR, interquartile range; inv., involvement; ONSM, optic nerve sheath meningioma. *planum sphenoidale, cavernous sinus, tuberculum sella (including parasellar or suprasellar), clinoid (anterior or posterior); WHO, world health organization.

Characteristic		treatment group		
Tuberculum sella inv., including parasellar or suprasellar		11 (31%)	5 (38%)	0.735
Clinoid (anterior or posterior) inv.		19 (54%)	9 (69%)	0.351
Proximity to one or more midline* structure		26 (74%)	13 (100%)	0.090
Multiple masses		6 (18%) (n = 34)	1 (8%)	0.655
Radiographic laterality of tumor = right		16 (46%)	6 (46%)	0.978
Histopathologic classification (WHO Grade)				
WHO Grade	Unknown	9 (56%)	4 (40%)	0.840
	I	6 (38%)	5 (50%)	
	II	1 (6%)	1 (10%)	
	III	0 (0%)	0 (0%)	

AVPM, anterior visual pathway meningioma; hSRT, hypofractionated stereotactic radiotherapy; cFSRT, conventionally fractionated stereotactic radiotherapy; IQR, interquartile range; inv., involvement; ONSM, optic nerve sheath meningioma. *planum sphenoidale, cavernous sinus, tuberculum sella (including parasellar or suprasellar), clinoid (anterior or posterior); WHO, world health organization.

Pre-treatment data

Neuro-ophthalmological evaluation prior to treatment revealed higher proportion of cFSRT patients with optic disc abnormality (atrophy/edema): 76% (25 of 33) compared with 27% (3 of 11) in the hSRT group ($p = 0.009$). The median pre-treatment better eye LogMAR was 0.10 in hSRT vs. 0.00 in cFSRT ($p = 0.079$). There was no statistically significant difference between cFSRT and hSRT regarding pretreatment worse eye LogMAR ($p = 0.925$), worse eye MD ($p = 0.530$), or better eye MD ($p = 0.173$). Cranial Nerve (CN) V1 involvement was found in 33% (3 of 9) in the hSRT group compared to 4% (1 of 28) in the cFSRT group ($p = 0.038$). Three patients in the cFSRT group were diagnosed with chronic ocular disease, compared with no patients in hSRT, with no significant difference between the groups: see Table 2.

Analysis of MRI before treatment indicated that the proportion of patients with a proximity of the tumor to a midline structure was higher in the hSRT group, as was the proportion of ONSM, although these differences were not statistically significant (see Table 1).

Histopathologic classification (WHO tumor grade) was documented in 13 cases with WHO Grade I or II tumors with a significant difference between the groups (Table 1). 13 patients were classified as having "unknown histology" (radiologic diagnosis without pathologic verification): Nine patients (56%) in the cFSRT, compared with four patients (40%) in the hSRT group.

Table 2
Neuro-ophthalmologic findings by treatment group with all valid AVPM patients at each time point

Neuro-ophthalmologic finding	Treatment group				p-value
	cFSRT		hSRT		
	n	Median (IQR) or n (%)	n	Median (IQR) or n (%)	
ΔLogMAR, worse eye	35	0.00 (-0.05, 0.10)	13	0.05 (0.00, 0.50)	0.092
Clinically relevant VA deterioration (ΔLogMAR ≥ 0.2), worse eye	35	6 (17%)	13	6 (46%)	0.061
ΔMD, worse eye (dB)	16	2.4 (-0.2, 4.5)	4	0.1 (-4.2, 6.6)	0.682
ΔLogMAR, better eye	33	0.00 (-0.02, 0.03)	12	0.00 (0.00, 0.07)	0.869
Clinically relevant VA deterioration (ΔLogMAR ≥ 0.2), better eye	33	1 (3%)	12	1 (8%)	0.467
ΔMD, better eye (dB)	21	0.6 (-1.2, 1.7)	5	1.5 (-4.7, 2.4)	> 0.999
Optic disc abnormality (worse eye)					
Pretreatment	33	atrophy: 18 (55%) edema: 7 (21%) other: 0 (0%)	11	atrophy: 3 (27%) edema: 0 (0%) other: 0 (0%)	0.016
Final evaluation	31	atrophy: 20 (65%) edema: 0 (0%) other: 0 (0%)	11	atrophy: 3 (27%) edema: 0 (0%) other: 0 (0%)	0.043
Any optic disc abnormality (atrophy, edema, or other abnormality)					

AVPM, anterior visual pathway meningioma; hSRT, hypofractionated stereotactic radiotherapy; cFSRT, conventionally fractionated stereotactic radiotherapy; IQR, interquartile range; LogMAR, logarithm of minimum angle of resolution; MD, mean deviation; ΔLogMAR = final LogMAR minus pretreatment LogMAR; ΔMD = final MD minus pretreatment MD; VA, visual acuity; CN, cranial nerve.

Neuro-ophthalmologic finding	Treatment group				p-value
Pretreatment	33	25 (76%)	11	3 (27%)	0.009
CN V_1 involvement					
Pretreatment	28	1 (4%)	9	3 (33%)	0.038
Final evaluation	29	5 (17%)	12	2 (17%)	> 0.999
Chronic ocular disease	33	3 (9%)	12	0 (0%)	0.553
Radiation-induced Optic Neuropathy (RION)					
During 1st year after treatment	24	1 (4%)	10	0 (0%)	> 0.999
Final evaluation	31	1 (3%)	11	0 (0%)	> 0.999
Radiation retinopathy					
During 1st year after treatment	25	1 (4%)	10	0 (0%)	> 0.999
Final evaluation	31	4 (13%)	11	1 (9%)	> 0.999

AVPM, anterior visual pathway meningioma; hSRT, hypofractionated stereotactic radiotherapy; cFSRT, conventionally fractionated stereotactic radiotherapy; IQR, interquartile range; LogMAR, logarithm of minimum angle of resolution; MD, mean deviation; ΔLogMAR = final LogMAR minus pretreatment LogMAR; ΔMD = final MD minus pretreatment MD; VA, visual acuity; CN, cranial nerve.

Radiotherapy schedule and dose

The number of radiotherapy fractions was five in the hSRT cohort, compared with 28 in almost all patients in the cFSRT cohort. The daily dose in the hSRT cohort was 500 centiGray (cGy) compared with 180 cGy in the cFSRT cohort. Table 3 lists the radiation therapy characteristics.

Table 3
Characteristics of radiation therapy for AVPM by treatment group

Characteristic		Treatment group		
		cFSRT (n = 35)	hSRT (n = 13)	p-value
radiotherapy regimen	5 fractions of 450 cGy (80% IDL)		1	
	5 fractions of 460 cGy (80% IDL)		1	
	5 fractions of 500 cGy (80% IDL)		10	
	5 fractions of 600 cGy (80% IDL)		1	
	28 fractions of 180 cGy (80% IDL)	32		
	30 fractions of 180 cGy (80% IDL)	1		
	Missing regimen data*	2		
Treatment year	Median (IQR)	2010 (2006, 2012)	2014 (2013, 2015)	p < 0.001
	Range	2004 to 2015	2013 to 2015	
Time from pretreatment neuro-ophthalmologic evaluation to first day of radiation treatment (months)	Median (IQR)	3 (1, 6)	2 (1, 7)	p = 0.487

AVPM, anterior visual pathway meningioma; cFSRT, conventionally fractionated stereotactic radiotherapy; cGy, centigray; hSRT, hypofractionated stereotactic radiotherapy; IDL, Isodose Line; IQR, interquartile range

* These two cases were treated with cFSRT during 2007 and 2008. One of these cases experienced a clinically relevant visual acuity deterioration in the worse eye at the last neuro-ophthalmologic evaluation.

Neuro-ophthalmologic evaluation findings one year posttreatment

During the first year following treatment, 21 (66%) patients reported vision-related complaints or were found to have ocular complications, with no significant difference between the groups (p = 0.681). One patient in the cFSRT cohort developed retinal bleeding in the involved eye; we considered this case as radiation retinopathy, although it is unclear whether diabetic changes had a role in this complication. RION was diagnosed in one cFSRT patient (2% of all patients in the study) and no patients in the hSRT cohort (p > 0.999). This patient's visual acuity remained stable during follow-up (worse eye ΔLogMAR = 0.08), but the visual field deteriorated (ΔMD = -9.4) in the involved eye.

Last Neuro-ophthalmologic evaluation findings

No difference was found between treatment regimens in the last assessment worse eye LogMAR (p = 0.327), worse eye MD (p = 0.935), or better eye LogMAR (p = 0.115). The median of the last assessment better eye MD was − 1.6 (interquartile range, IQR: -4.4, -0.3. n = 26) in cFSRT, compared with − 4.7 (IQR: -11.3, -1.6. n = 8) in hSRT (p = 0.043), reflecting better VF results in cFSRT (but see later comments on missing MD data). The proportion of patients with involved side optic disc abnormality in the cFSRT cohort was higher (65%) than in the hSRT cohort (27%) (p = 0.043), similar to the proportion before irradiation (Table 2).

Five cases (12%) were diagnosed with radiation retinopathy: 4 patients (13%) in the cFSRT cohort vs. 1 patient (9%) in the hSRT cohort (p > 0.999).

Change in visual acuity and visual field between pre-treatment and final evaluation

The median change in visual acuity (ΔLogMAR) in the worse eye during the last neuro-ophthalmologic assessment compared to the pre-irradiation evaluation was 0.00 (IQR − 0.05, 0.10) in the cFSRT group and 0.05 (IQR 0.00, 0.50) in the hSRT group, suggesting a better long term outcome in the cFSRT cohort (p = 0.092). Of the 48 patients in the study, 12 (25%) had a clinically relevant deterioration in visual acuity (ΔLogMAR ≥ 0.2) in the involved eye in the last neuro-ophthalmologic assessment: six patients (17%) in the cFSRT cohort and six patients (46%) in the hSRT cohort (p = 0.061) (Table 4).

In the hSRT cohort, the median LogMAR of worse eyes in the final assessment was 0.30, compared with 0.10 at baseline, suggesting post-treatment VA deterioration after hSRT. However, this difference did not reach statistical significance (p = 0.068).

In the cFSRT cohort, the scores of the MD value of the worse eye in the last assessment were statistically significantly better than the scores of MD value of the worse eye at baseline (Wilcoxon Signed-Ranks test,

p = 0.034). However, this result is based on only 16 cases (of 35), and it may be biased due to the remaining cases' missing data.

Table 4
Change in visual functions between pretreatment evaluation and final evaluation in AVPM

Radiotherapy regimen		Final LogMAR (worse eye) minus pretreatment LogMAR (worse eye)	Final MD (worse eye) minus pretreatment MD (worse eye)	Final LogMAR (better eye) minus pretreatment LogMAR (better eye)	Final MD (better eye) minus pretreatment MD (better eye)
cFSRT	p-value*	0.726	0.034	0.740	0.434
		(n = 35)	(n = 16)	(n = 33)	(n = 21)
hSRT	p-value*	0.068	0.715	0.893	0.686
		(n = 13)	(n = 4)	(n = 12)	(n = 5)

cFSRT, conventionally fractionated stereotactic radiotherapy; hSRT, hypofractionated stereotactic radiotherapy; LogMAR, logarithm of minimum angle of resolution; MD, mean deviation

* Wilcoxon's signed-rank test, two-tailed.The proportion of tumors involving the optic nerve sheath in the cFSRT cohort was 46%, compared with 15% in the hSRT cohort (p = 0.092). To control for this potential confounder, we re-analyzed the data for all variables in a subset of patients (hSRT, n = 11, cFSRT, n = 19) in which *no optic nerve sheath involvement* was documented in the pre-treatment imaging test. No patient in this subgroup developed RION or radiation retinopathy. In this subgroup analysis no statistically significant difference was found between hSRT and cFSRT in the proportion of complications or complaints related to vision in the first year after radiation therapy (p = 0.628), change in visual acuity (ΔLogMAR) in the worse eye (p = 0.471), change in visual field (Δ MD) in the worse eye (p = 0.714), the proportion of patients with a clinically relevant deterioration (ΔLogMAR ≥ 0.2) in the involved eye VA (p = 0.417), or in the proportion of patients with PD in imaging (p > 0.999).

Imaging findings

Evidence of disease progression (PD) in imaging during the follow-up period was found in 5 patients (14%) in the cFSRT cohort, compared with 2 (15%) in the hSRT cohort (p > 0.999). Since the median duration from the last MRI scan to the last neuro-ophthalmologic assessment for all patients was two months, we believe that the imaging reports accurately reflect the tumor's state at the time of this evaluation.

Discussion

We studied patients treated with radiotherapy with a threat to visual function due to tumor location (in or near the AVP). The results are intended to support therapeutic decision-making in patients with AVPM not amenable to surgical treatment by pointing to a radiation therapy regimen associated with better post-treatment vision functions, to improve, even if only slightly, the prognosis of their vision. We examined the association between radiation regimen and visual function results and radiological PD, in patients with AVPM. Patients in the cFSRT group were more likely to have preserved VA after radiotherapy compared to hSRT group, although they had more optic disc abnormalities before and after the treatment (Table 2).

The proportion of patients (25%) who had a clinically relevant VA deterioration was higher than we expected from previous publications on cFSRT (see Additional File 1) and hSRT[5,7,26–30]. This may be due to differences in measured and reported variables (mainly VA), follow-up length, prognostic factors such as histology, equipment, and radiotherapy treatment plans.

While there was no difference in pre-treatment visual function between patients assigned to each radiotherapy regimen, VA deterioration was more evident in hSRT than in cFSRT, although findings did not reach statistical significance. This difference disappeared when we examined a subset of patients without optic nerve sheath (ONSM) involvement, suggesting a possible relationship between the treatment regimen, tumor location, and effects on visual functions. The use of hSRT in patients with optic nerve sheath involvement was associated with a worse visual outcome. This outcome relies on analysis of a small number of patients and should therefore be examined in further studies that will separate ONSM from other AVPM tumors.

RION rate in the first year after radiation therapy is consistent with the literature[18,31]. This impairment manifested in VF deterioration without an accompanying clinically relevant VA deterioration, demonstrating the importance of VF evaluation in the follow-up of patients with AVMP treated with radiotherapy. Most radiation retinopathy cases were not diagnosed in the first year post-treatment, consistent with previous publications about the delayed onset and slow progression of this condition[15].

Of the 48 cases in the study, WHO grade was documented in 13 cases, mostly WHO grade I. We assume that the vast majority of other tumors was also WHO Grade I meningioma. In this cohort we find that both radiation regimens were efficient in controlling AVPM in imaging, as 85% of patients were without PD at the last assessment, with no significant difference between hSRT and cFSRT at a median follow-up period of 4.5 years after treatment. This result agrees with previous publications stating that five to ten years after radiation therapy, a local control rate of 68–100% was reached in WHO Grade I meningioma (presumed or histologically verified)[12,16,24].

This study suffers several weaknesses due to its retrospective nature, including missing data for many patients, and the differences between study cohorts in treatment year and follow-up length. These may confound the results related to visual function and PD. However, unlike previous reports, our study has the strengths of using neuro-ophthalmologists' meticulous assessment of visual function and quantitative deterioration criterion, which allowed us to identify cases that may not have been identified if data relied

solely on patient reporting. Other strengths include evaluating prognostic factors such as pathology reports that are not available in many studies, having long-term follow-up of the patients, and employing a pre- and post-treatment analytic design.

Conclusions

Although the study did not confirm a statistically significant association between the radiation therapy regimen (hSRT vs. cFSRT) and visual function outcomes in post-treatment years, our findings using a comprehensive and meticulous investigation of visual outcomes suggest that cFSRT may be associated with less VA toxicity. Given the small sample and retrospective nature of our study, caution is needed in concluding which is the best regimen to be used. Based on our results, we chose to keep the traditional cFSRT regimen for ONSM and use hSRT only for tumors adjacent to the AVPM. We suggest this group of patients requires a multidisciplinary follow-up with meticulous pre- and post-treatment neuro-ophthalmologic evaluation, along with magnetic resonance imaging and patient-reported outcomes. Such information, along with well-designed prospective studies, may improve our understanding of the relationship between radiation regimen and long-term outcomes in AVPM. We believe our results indicate the importance of using thorough clinical investigation when adopting new radiation regimens.

Abbreviations

AVP
Anterior Visual Pathway
AVPM
Anterior Visual Pathway Meningioma
cFSRT
Conventional Fractionated Stereotactic Radiotherapy
cGy
centi-Gray
FSRT
Fractionated Stereotactic Radiotherapy
Gy
Gray
hSRT
Hypofractionated Stereotactic Radiotherapy
IQR
Interquartile Range
LogMAR
Logarithm of the Minimum Angle of Resolution
MD
Mean Deviation

MRI
Magnetic Resonance Imaging
NLP
No Light Perception
ONSM
Optic Nerve Sheath Meningioma
PD
Disease progression
RION
Radiation-Induced Optic Neuropathy
VA
Visual Acuity
VF
Visual Field
WHO
World Health Organization

Declarations

- Ethics approval and consent to participate: This retrospective study was approved by the Sheba Medical Center Institutional Review Board (Study 4275-17-SMC).
- Consent for publication: Since the images in Fig. 2 are entirely unidentifiable and there are no details on these individuals reported within the manuscript, we believe that consent for publication of images is not required.
- Availability of data and materials: the datasets analyzed during the current study are available from the corresponding author on reasonable request.
- Competing interests: All authors declare they have no competing interests.
- Funding: No external funding was used for this study.
- Authors' contributions: LZ and RHB conceived and supervised this study; MA, ZC, ZZ, ON, RS collected neuro-surgery related data; IBBM, GT, RHB collected neuro-ophthalmology related data; LZ collected radiotherapy related data; AA extracted data from medical records and performed analysis; AA, OF, LZ, RHB wrote the manuscript with input from all authors.

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Figures

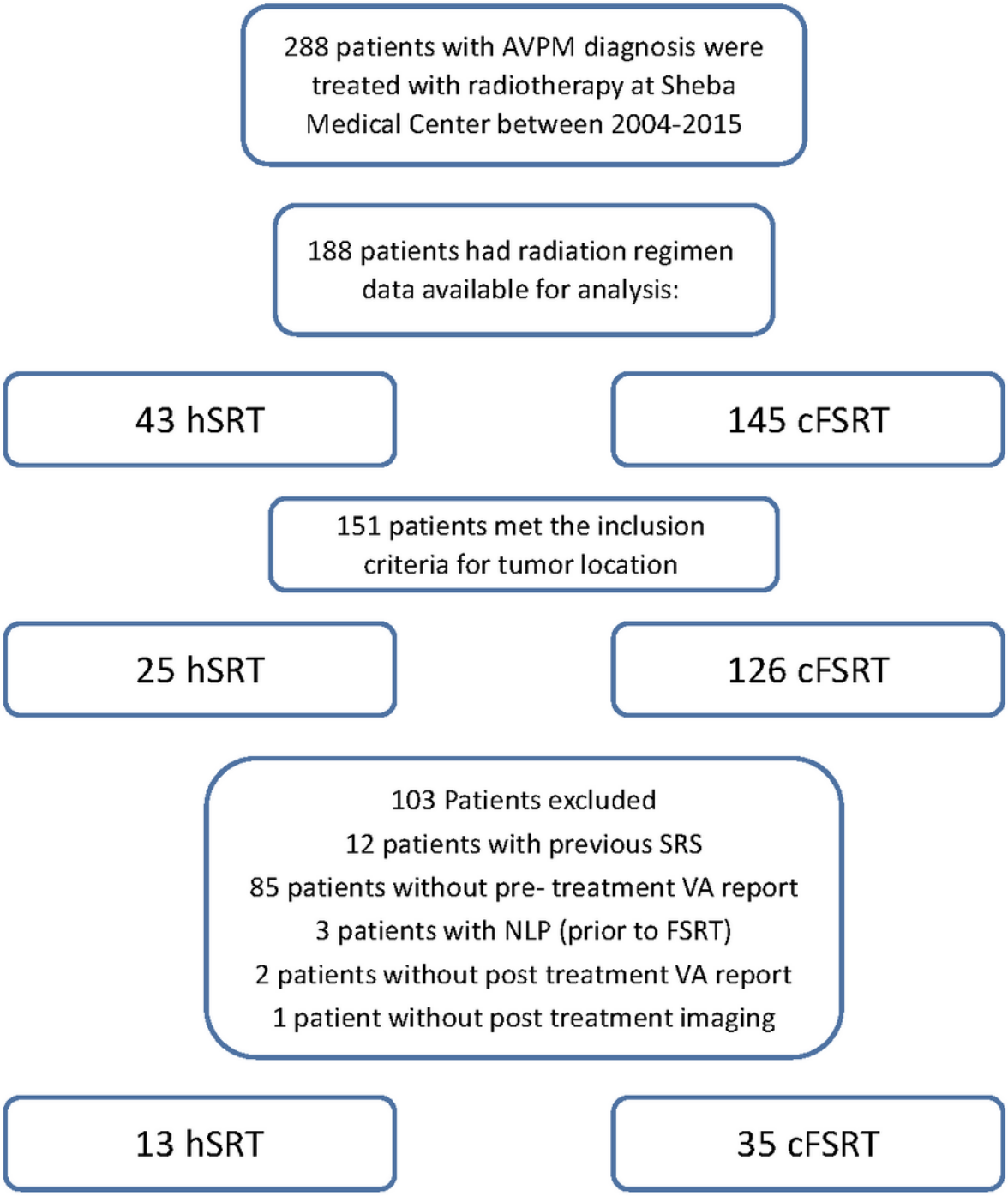

Figure 1

Inclusion and exclusion criteria of the study population. 288 patients with a radiological diagnosis of AVPM were treated with radiotherapy at Sheba Medical Center between 2004-2015. We included patients with a radiological diagnosis of meningioma whose tumors were in defined anatomical locations near the optic nerves and whose neuro-ophthalmology and neuroimaging data were available. We excluded patients having previous stereotactic radiosurgery treatment (SRS), lacking visual acuity documentation

before treatment, having no light perception (NLP) prior to treatment, or undergoing additional treatment before the first neuro-ophthalmologic assessment. hSRT, hypofractionated stereotactic radiotherapy; cFSRT, conventionally fractionated stereotactic radiotherapy.

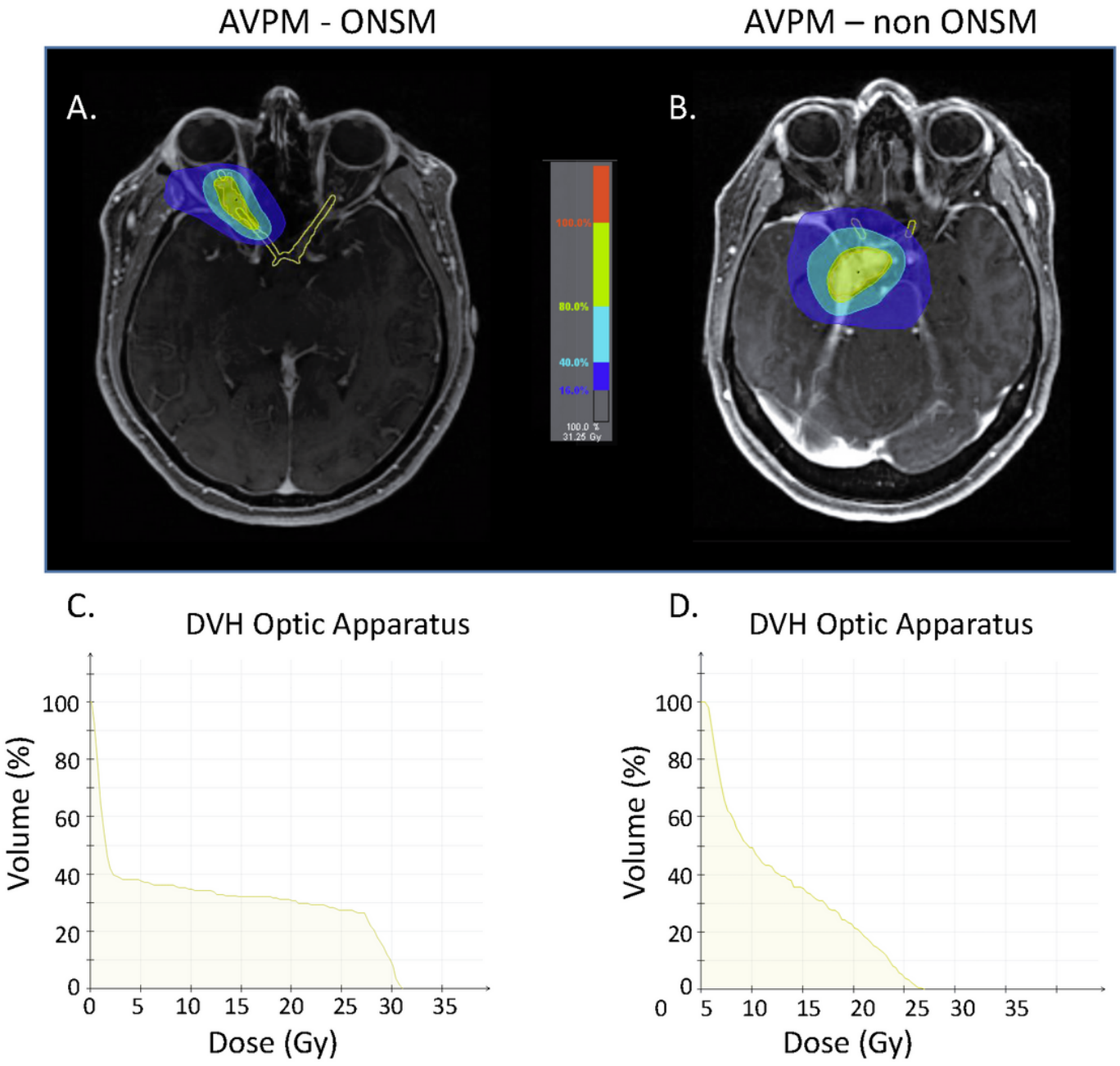

Figure 2

Radiation plan and Dose Volume Hisogram for AVPM patients with and without optic nerve sheath (ONSM) involvement. Both AVPM patients received hypofractionated radiosurgery (hSRT) in 5 sessions x 500 cGy, with maximum dose of 31.25 Gy. Optical apparatus (left and right optic nerve, optic chiasm) was marked in treatment plans of both patients and DVHs were calculated. A. Radiation plan for Optic Nerve Sheath Meningioma (ONSM) patient. B. Radiation plan for non-ONSM AVPM patient. Comparison of Optic apparatus DVH reveals that in the ONSM patient (C.) a higher radiation dose was absorbed by

the nerve sheath while in the perioptic non-ONSM AVPM patient (D.) the same radiation dose to the tumor resulted in smaller dose to the nerve sheath. We believe the combination of pre-treatment nerve damage and the high dose to the nerve explain the increased visual damage we see in ONSM patients treated with hSRT and suggest this cohort should be treated with cFSRT.

Supplementary Files

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