

Long-term response to fractionated radiotherapy of presumed optic nerve sheath meningioma

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ABSTRACT

Background/aims To review the long-term results of treatment of optic nerve sheath meningiomas (ONSMs) with conformal radiotherapy.

Methods Eleven patients with presumed ONSM were treated with fractionated conformal radiotherapy using 45–54 Gy in 25–30 fractions and followed for more than 5 years. Affected eye visual acuity in logMAR notation, colour vision, threshold perimetry, mean deviation (dB) and imaging were studied before and after treatment.

Analysis Included adverse effects of treatment and the frequency of affected eye maintained or improved vision.

Results There were nine women and two men with a mean age of 45.3. Vision or field loss was the most common presentation. All had abnormal MR imaging. The follow-up period after radiotherapy was 61–156 months (mean 89.6). Visual acuity was unchanged or improved in 10 patients (91%). The average difference between pretreatment and final logMAR visual acuity was 0.08, while the average difference in visual-field mean deviation was –4.63 dB. The radiographic appearance of the tumours was stable in size in nine patients and decreased in two. No major side effects from radiation were seen.

Conclusions Vision, MRI and complication outcomes are favourable for using fractionated conformal radiotherapy for ONSM.

INTRODUCTION

The natural history of optic nerve sheath meningiomas (ONSMs) is of progressive visual loss over a variable time course.^{1–3} Prior to the advent of the use of radiotherapy (RT), surgical excision or decompression were the only available treatment options, both of which were complicated by loss of visual function.^{1 2 4 5} Randomised clinical trials of medical therapy of meningiomas in all locations have shown no definite benefit.⁶

Several techniques have been developed to improve RT delivery and reduce toxicity by minimising the radiation absorbed by adjacent non-target tissue including immobilising the head, computer-based three-dimensional imaging, conformal targeting and precise-dose delivery.⁷ We report our long-term experience with conformal RT for 11 patients with ONSM who have been followed for more than 5 years.

METHODS

We reviewed the medical records databases of the Neuro-Ophthalmology services of The Eye Care Group and Yale University School of Medicine, New Haven, Connecticut, and The Institute for

Neurology and Neurosurgery of St Luke's Roosevelt Hospital and New York Eye and Ear Infirmary in New York for patients who underwent primary conformal RT for clinically diagnosed and radiologically confirmed primary ONSM. We identified 11 patients, between 1996 and 2009, who met our study criteria of having documented progressive loss of visual acuity (VA) or visual field or both, count fingers or better VA in the affected eye at the time of treatment, and no surgical intervention for the ONSM. All patients had a complete neuro-ophthalmological evaluation, detailed clinical history, visual-field testing and fat-suppressed orbital MRI without and with gadolinium contrast utilising a 1.5 T scanner.

Baseline and follow-up evaluations of the affected eye included best corrected Snellen VA (converted to logMAR notation, with 20/20=0.0, 20/400=1.30, finger counting at 2 feet (0.6 m)=1.50, hand motion=1.70), visual field expressed as the mean deviation (MD) in decibels (dB) using Humphrey automated perimetry (either 24-2 or 30-2 strategy) and colour vision testing using the number of pseudoisochromatic plates identified correctly.

All patients were treated with fractionated conformal RT techniques, including three-dimensional conformal RT, stereotactic RT and intensity-modulated RT. All techniques involved computer-assisted treatment planning and isodose calculations. Typical treatment plans included three to nine non-coplanar fields using photon energies of 6–18 MV from linear accelerators. The beam configurations were designed to minimise irradiation of normal structures including the optic chiasm, ipsilateral lens and retina, contralateral eye, pituitary and brain (figures 1, 2). The patients were treated with 45–54 Gy of external beam radiation in 25–30 daily fractions. Some patients had RT field reductions part way through treatment. Acute and delayed ocular, neurological or endocrinological adverse effects were recorded during and after therapy. Delayed toxicity was defined as occurring beyond 6 weeks after completing RT.

Patients were followed up by neuro-ophthalmological and MRI evaluations. VA deterioration of 10 letters (two lines) or visual-field worsening by 3 dB or tumour growth on MRI was defined as a treatment failure. Post-treatment final vision outcomes were compared with pretreatment using the Wilcoxon signed rank test.

RESULTS

There were nine women and two men with a mean age of 45.3 (range 16 to 58); all had visual

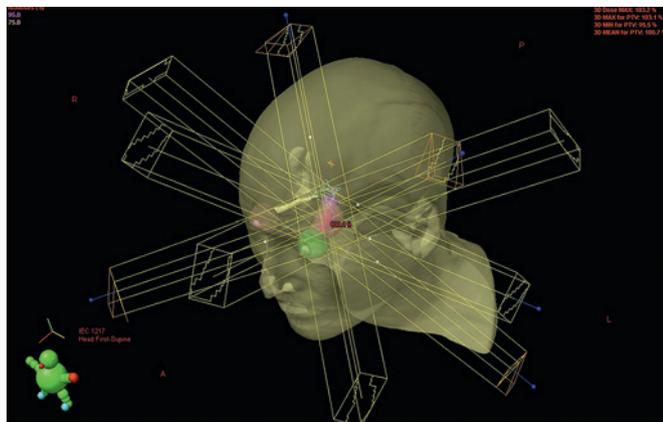


Figure 1 3D Representation of radiation beam geometry for optic nerve sheath meningiomas (ONSMs). This image shows a skin surface rendering of the patient with a left ONSM. The vantage point is from the patient's left side. Five beam apertures and pathways delimiting the volume irradiated are shown traversing the patient. All intersect only at the ONSM. Non-coplanar beams are used to severely limit dose to contiguous normal tissues. The surface of the volume receiving a dose of 75% of that prescribed to the ONSM can be seen behind the left globe.

disturbances, most commonly visual loss (tables 1, 2). At presentation, the mean VA was 0.20 and all patients had a visual-field defect with average MD of -14.09 dB (table 3). For colour vision, six patients were normal, and three saw no colour plates. No patients had an optociliary shunt vessel at presentation. Other ocular diagnoses that could affect the visual performance of the affected eye included low-tension glaucoma (bilateral) and cataract in one patient and amblyopia in one patient. All patients had abnormal MR imaging typical of ONSM. Six tumours in this series were intraorbital, but four extended into or were located entirely within the optic canal, and one extended intracranially along the prechiasmatic optic nerve. The pre- and post-treatment vision, and post-treatment radiological, and toxicity outcomes are summarised in table 3. Five patients (patients 2, 3, 6, 10 and 11) experienced progression of disease (ie, a decrease in VA of at least 10 letters or at least 3 dB worse MD) after their clinical diagnosis was made before the initiation of radiotherapy, and the others all had visual deficits at the time of their diagnosis. The



Figure 2 Axial optic nerve sheath meningioma (ONSM) CT slice with isodose contours. This axial CT slice shows a diffusely enlarged left optic nerve (same patient shown in figure 1). The ONSM is shown on this slice as a black contour contiguous with the optic nerve. The 25%, 50%, 75%, 95% and 100% isodose surfaces are shown as well. The dose delivered to the ONSM is uniformly high, and the dose drops off sharply as a result of the techniques used to plan and deliver this treatment.

mean time interval from presentation to diagnosis among all patients was 7.9 months (range 1–29 months). The mean length of follow-up after completing RT was 89.6 months (median 73 months; range 61–156 months). Case 9 (with underlying amblyopia) had an extension of the field defect without any change in VA and remained stable for the next 5 years. Of the 11 patients, seven had a final acuity of 0.0 (20/20) or better. The final VA improved by a mean of 0.08 logMAR units (0.11) compared with the pretreatment VA. Wilcoxon signed ranks were negative (improved) in seven eyes, tied in three eyes and positive in one eye ($p=0.04$). The final MD improved by a mean of 4.63 (SD 5.78) compared with pretreatment MD. For MD, Wilcoxon signed ranks were positive (improved) in eight, tied in one and negative in two patients ($p=0.02$). One patient (case 4) had pre-existing glaucoma with bilateral glaucomatous cupping and a characteristic arcuate visual-field defect that showed progression 34 months post-treatment in the eye with the meningioma as well as a new nasal step in the eye not affected by the meningioma. For colour vision, the mean difference from the pretreatment colour vision number of plates correctly identified was negligible (0.27). For colour vision, Wilcoxon signed ranks were positive in two and tied in nine patients ($p=0.18$).

All 11 patients had follow-up MRI available (the shortest follow-up time is 61 months after therapy) with a mean imaging follow-up time of 89.6 months. Imaging of the patients showed no radiographic evidence of progression of disease in nine patients; two ONSMs appeared smaller.

Temporary adverse effects included focal alopecia in four, fatigue in seven and headache in one. Case 1 developed bilateral dry eyes 4 years after treatment, which was presumed to be unrelated to lacrimal gland irradiation because of its bilaterality. No patient developed any overt RT-related complication involving either eye or the brain.

DISCUSSION

Smith *et al.*⁸ in 1981, reported the first series of patients with primary ONSM with demonstrated improvement in vision following treatment by RT using lower doses and less precise older delivery techniques. Subsequent reports of patients treated with fractionated conventional RT as primary therapy followed, confirming that visual control could be achieved through this modality.^{7, 9} In 2002, Turbin *et al.*¹⁰ reported a multicentre retrospective study of 64 patients treated with observation, surgery, surgery combined with radiation and radiation alone. Those patients treated with radiation alone had the best visual results, although one-third developed complications including radiation retinopathy, chronic iritis, temporal lobe atrophy and retinal vein occlusion. Unfortunately, the complications reported were not linked to details regarding the RT techniques, which varied widely over time and among centres.

The well-defined borders of many benign tumours including ONSM make them amenable to highly conformal RT, which permits higher radiation doses to be delivered to the tumour while decreasing the radiation dose to adjacent normal tissues.

Conformal RT techniques include three-dimensional conformal radiotherapy (3DCRT), stereotactic fractionated radiotherapy (SFRT) and intensity-modulated radiotherapy (IMRT). Because the tolerance of the optic nerve and of the retina for radiation is at approximately the same as the dose required to control an ONSM (approximately 50 Gy), a highly homogeneous radiation dose distribution is critical. Eng *et al.*¹¹ first reported a conformal ONSM RT technique using specific head positioning and a non-opposed beam configuration.

Table 1 Patient characteristics

Patient	Age/sex	Affected eye	Presenting symptoms	Location of optic nerve sheath meningioma	Time (months) to diagnosis
1	46/M	R	Metamorphopsia	Orbital	11
2	16/F	L	Blurred vision	Orbital/canalicular/intracranial	17
3	49/F	L	Blurriness	Canalicular	26
4	56/M	R	Blurred vision	Orbital	10
5	46/F	R	Transient blurriness, tenderness	Orbital/canalicular	5
6	51/F	L	Transient blurriness	Canalicular	29
7	58/F	R	Transient blurriness	Orbital/canalicular	1
8	60/F	L	Transient visual loss	Orbital/canalicular	9
9	47/F	R	Reduced vision	Orbital	4
10	36/F	L	Blurriness	Orbital	4
11	42/F	R	Blurriness	Orbital	1

F, female; L, left; M, male; R, right.

Table 2 Clinical signs and symptoms at presentation

Sign or symptom	No affected	Percentage
Visual loss or disturbance	11	100
Visual field abnormal (MD < -3 dB)	9	82%
Afferent pupillary defect	7	64%
Optic disc oedema	7	64%
Impaired colour vision	6	55%
Optic disc pallor	3	27%
Proptosis	2	18%
Optociliary shunt vessels	0	0
Initial visual acuity Mean, SD	0.200.33	
Initial mean deviation (dB) Mean, SD	-14.099.84	

Subsequently there were several individual case reports^{12–16} showing a high rate of visual preservation and a low rate of late toxicity. Several detailed case series using conformal RT have been published since 2002.^{17–22} Excluding patients who had antecedent surgery or had non-useful vision (ie, vision worse than count fingers), a total of 155 patients have previously been reported in the literature (see table 4). Our long-term results extend the findings of other studies that showed visual preservation and tumour control can be achieved in the vast majority with low late complication rates.

Seven patients with radiation retinopathy after conformal therapy have been reported to date.^{34–36} It is not known

whether or not these patients may have had inadvertent inhomogeneity in the radiation dose distribution that resulted in this radiation injury. In addition, the risk for vision complications may be increased if a radiation 'hot spot' within the retina occurs in the setting of poorly controlled hypertension or diabetic vasculopathy that exacerbates microvascular injury. Dry eye, iritis, cataract, pituitary dysfunction and, in one case, white-matter lesions in the cortex have also been reported as RT-related complications.

The results from our study are comparable with the overall published experience, with visual control achieved in 10/11 (91%) with no late complications. Most patients had stable or improved VA. At the time of the latest follow-up, seven of the 11 patients maintained a VA of at least 20/20, but of these, five patients had at least 20/20 when treatment was initiated. Although many of the patients in our series with pretreatment VA of 20/40 or worse did improve, only two had a final acuity of 20/20 or better. These findings suggest that RT should begin before the vision is severely compromised, but this must be balanced against the low but non-zero potential for retinal or optic nerve toxicity. Patients should be monitored using evaluations designed to show early worsening, particularly via threshold perimetry and retinal peripapillary nerve fibre imaging and MRI of the ONSM. Worsening would be a clear indication to initiate conformal RT.

Compared with the clinical characteristics reported in Dutton's 1992 review,¹ the patients in our series presented with

Table 3 Pretreatment vision and postradiotherapy outcomes

Patient	Pre-tx VA	Pre-tx MD (dB)	Pre-tx CV	Radiotherapy	Dose (Gy)	Final VA	Final MD (dB)	Final CV	Acute toxicity	Late complications	Optic nerve sheath meningioma by MRI	Follow-up (months)
1	0.0	+2.13	15	3DCRT	45.00	-0.1	+2.73	15	Alopecia* nausea	Bilateral dry eye syndrome	Decreased	114
2	1.0	-30.10	0	3DCRT	52.19	0.7	-23.27	0	Fatigue	None	Stable	73
3	-0.1	-19.52	15	3DCRT	50.36	0.0	NA	15	Fatigue	None	Stable	61
4	0.0	-6.42	15	3DCRT	50.30	-0.1	-8.22	15	Fatigue	None	Decreased	94
5	0.0	-1.37	15	3DCRT	50.25	0.0	+1.56	15	None	None	Stable	71
6	0.4	-22.61	0	3DCRT	50.36	0.3	-17.60	0	Fatigue	None	Stable	69
7	0.0	-1.78	15	3DCRT	50.41	0.0	-1.76	15	Alopecia* fatigue	None	Stable	67
8	0.0	-2.46	15	3DCRT	50.40	0.1	-2.05	15	Alopecia*	None	Stable	69
9	0.55	-20.78	11	IMRT	45.00	0.5	-23.51	12	Alopecia*	? Early Menopause	Decreased	91
10	0.1	-19.64	7	SFRT	52.20	0.0	-3.86	9	Headaches fatigue	None	Stable	156
11	0.5	-26.45	0	SFRT	54.00	0.3	-21.96	0	None	None	Stable	120

Case 4 had later worsening of vision due to pre-existing glaucoma.

*The alopecia described was focal and temporary only.

3DCRT, three-dimensional conformal radiotherapy; CV, colour vision; IMRT, intensity-modulated radiotherapy; MD, mean deviation; NA, not available; SFRT, stereotactic fractionated radiotherapy; tx, treatment; VA, visual acuity in logMAR notation.

Table 4 Summary of primary conformal radiotherapy series

Author	Period	RT technique (s)	Dose in gray and fractionation	Eyes with useful vision	Stable or improved	Worse	Radiographic regression	Progression	Late complications (0 = none reported)	Follow-up
Lee <i>et al</i> ²³		IMRT	50.4 (28×1.8)	1	1	0	0	0	0	1 wk
Klink <i>et al</i> ¹³	1995	Fract SRS	36 (6×6.0)	1	1	0	0	0	0	2 yrs
Grant and Cain ¹²		IMRT	50 (25×2.0)	1	1	0	0	0	0	3 yrs
Fineman and Ausburger ²⁴	1997 (?)	SFRT	54 (30×1.8)	1	1	0	0	0	0	6 months
Augsburger <i>et al</i> ¹⁵ (abstract)	1994–1998	IMRT	49.3–50.4 (1.7–2.0 Gray each fraction)	13	12	1	1	0	0	2–51 months (median 20)
Tsao <i>et al</i> ¹⁶ (abstract)	1989–1997	3DCRT	50.4–54.0	15	13	2	?	2	Two retinopathy	11–102 months (median 32)
Moyer <i>et al</i> ¹⁴	1996 (?)	3DCRT	50.4 (28×1.8)	1	1	0	1	0	0	2 yrs
Liu <i>et al</i> ²⁵	1994–2001	SFRT	50.4 (28×1.8)	5	5	0	0	0	0	1–7 yrs (mean 3)
Becker <i>et al</i> ¹⁸	1989–2000	SFRT	54 (30×1.8)	12	12	0	0	0	One functional hyperprolactinemia, One partial hypophyseal insufficiency	12–49 months (mean 32)
Andrews <i>et al</i> ²⁰	1996–2001	SFRT	50.4–54 (28–30×1.8)	11	11	0	0	0	0	9–284 wks (median 89)*
Narayan <i>et al</i> ¹⁹	1986–2001	3DCRT	54–55.8 (30–31×1.8)	13	11	2	1	0	Two iritis, one early radiation retinopathy, One dry eye, One orbital pain	8.9–86 months (mean 51)
Saeed <i>et al</i> ²⁶	1976–1999	SFRT	45 (28×1.6)	1	1†	0	0	0	One ischemic optic neuropathy	1 yr
Baumert <i>et al</i> ²⁷	1996–2003	SFRT	45–54 (25–? 30×1.8–2.0)	20	18	2	2	0	One radiation retinitis and vitreal haemorrhage	1–68 months (mean 22)
Subramanian <i>et al</i> ²⁸	1999–2004	SFRT	54 (30×1.8)	1	0	1	?	?	Initial improvement, and then progressive radiation retinopathy developed at 22 months VA 20/300	63 months
Richards <i>et al</i> ²⁹	1999–2002	SFRT	43.4–45 (25–27×1.67–1.75)	4	4	0	0	0	One cerebral punctate small vessel fallout	2–4 yrs (mean 2.5)
Sitathane <i>et al</i> ³⁰	1998–2005	SFRT	Mean 55.7 (30–31×1.8)	6	5	1	0	0	One vitreous haemorrhage	7–66 months (mean 34)
Romanelli <i>et al</i> ³¹	2004–2007	SRS	20 (4×5)	3	3	0	0	0	Treatment prescribed to the 80% isodose surface, maximum dose <30 gray	42, 32, and 30 months follow-up (mean 37 months)
Litré <i>et al</i> ³²	2000–2006	SFRT	45 (1.8×25)	8	8	0	0	0	0	37 months average
Llorente-González <i>et al</i> , ³³	1995–2006	SFRT	50 (1.67×30)	1	1	0	?	0	0	38 months
Smee <i>et al</i> ²¹	1990–2004	SFRT, 3DCRT, SRS	50 (1.8–2.0 ×25–28)	12	11	1	1	1	One patient became blind after treatment	5.5–157 months (median 86.4)*
Arvold <i>et al</i> ³⁴	1999–2006	CRT — Photon / Proton	50.4 (1.8×25–33) (45.0–59.4)	21/22	21	1	21	1	Three asymptomatic radiation retinopathy	3–168 months (mean 30)
Milker-Zabel <i>et al</i> ²²	1995–2007	SFRT	Median 54.9 50.4–57.6 (1.8×28–32)	32	31	1	6	0	0	6–204 months (mean 54)
Current series, 2009	1996–2009	3DCRT, SFRT, IMRT	45.0–54.0 (1.8×25–30)	11	10‡	1	2	0	0	61–156 months (mean 89.6)

Abbreviations: 3DCRT, three-dimensional conformal fractionated radiotherapy; F, fractions; IMRT, intensity-modulated radiotherapy; SFRT, stereotactic fractionated radiotherapy; SRS, stereotactic radiosurgery.

Only patients who were reported to have received primary radiotherapy (excluding biopsy) are included. Useful vision is defined as CF or better. Dose is indicated in the form: total (fractions × dose/fraction).

*Follow-up includes all patients in report including those who had prior surgery and/or those without useful vision.

†Patient had later worsening of vision due to ischemic optic neuropathy.

‡One patient had later worsening of vision possibly due to pre-existing glaucoma.

less severe signs and symptoms. None of our patients demonstrated the classic presenting triad of visual loss, optic atrophy and retinochoroidal (optociliary) shunt vessels.³ This may be related to an increased availability and use of cross-sectional imaging, particularly gadolinium enhanced fat-suppressed high-resolution MRI, as well as the broader recognition of the potential for early intervention to benefit the patient if the diagnosis is made while there is still useful vision.

In our series, immediate radiographic control was achieved in all but the one patient who had delayed loss of vision after treatment, and even this case showed no further growth 2 years later. There were no late complications definitely linked to RT in our series. The development of bilateral dry eyes 4 years following RT in one patient could not be ascribed to radiation injury of both lacrimal glands, given this patient's radiotherapy beam arrangement. Our follow-up period of 61–156 months (mean 89.6) is longer than the follow-up reported by other similar series.

Although the rarity of ONSM makes a randomised trial unlikely, the management of ONSM has changed considerably, supported by a growing body of case series. Current conformal RT techniques have been shown to be effective in halting or even reversing disease progression with a low rate of radiation toxicity. Acute side-effects are mild and temporary, while in our series the delayed complications were mostly treatable and infrequently affected vision. Our long-term experience supports the use of RT before severe permanent visual loss occurs. Even longer follow-up will be needed to fully evaluate the risk of complication and the durability of treatment response.

Competing interests None.

Ethics approval Ethics approval was provided by the Yale University School of Medicine Human Investigations Committee.

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