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Primary radiotherapy in progressive optic nerve sheath meningiomas: a long-term follow-up study

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ABSTRACT

Background/aims To report the outcome of primary radiotherapy in patients with progressive optic nerve sheath meningioma (ONSM).

Methods The clinical records of all patients were reviewed in a retrospective, observational, multicentre study.

Results Thirty-four consecutive patients were included. Twenty-six women and eight men received conventional or stereotactic fractionated radiotherapy, and were followed for a median 58 (range 51–156) months. Fourteen eyes (41%) showed improved visual acuity of at least two lines on the Snellen chart. In 17 (50%) eyes, the vision stabilised, while deterioration was noted in three eyes (9%). The visual outcome was not associated with age at the time of radiotherapy ($p=0.83$), sex ($p=0.43$), visual acuity at the time of presentation ($p=0.22$) or type of radiotherapy ($p=0.35$). Optic disc swelling was associated with improved visual acuity ($p<0.01$) and 4/11 patients with optic atrophy also showed improvement. Long-term complications were dry eyes in five patients, cataracts in three, and mild radiation retinopathy in four.

Conclusion Primary radiotherapy for patients with ONSM is associated with long-term improvement of visual acuity and few adverse effects.

INTRODUCTION

Optic nerve sheath meningiomas (ONSM) originate from meningeothelial cap cells of arachnoid villi inside the optic nerve. Whilst being slow-growing tumours, they are associated with gradual visual deterioration. Radiotherapy has been reported to prevent further disease progression and even result in improved visual acuity in 25–80% of the irradiated eyes.^{1–10} By contrast, surgical resection leads to significant or complete loss of any remaining vision.^{1–3} However, the majority of studies assessing radiotherapy have reported only short-term results in small numbers of patients.

This multicentre study evaluated the clinical characteristics and especially the visual outcome, in 34 patients undergoing primary radiotherapy to treat ONSM. Patterns of visual change, radiotherapy efficacy, complications and prognostic factors were assessed. This is believed to be the largest reported series to date.

MATERIALS AND METHODS

Patients

Thirty-four patients with a diagnosis of ONSM were treated primarily with radiotherapy between 1998 and 2008 at the orbital centres of the

University of Amsterdam ($n=12$), University of British Columbia ($n=10$), University of Adelaide ($n=8$), and the Universities of Utrecht/Rotterdam ($n=4$). Inclusion criteria were a diagnosis of ONSM based on clinical and imaging evidence or histopathology ($n=9$). Exclusion criteria were any surgical intervention other than biopsy, or no light perception by the involved eye before treatment.

Radiotherapy

Radiotherapy was offered as the primary treatment for ONSM in patients with progressive visual deterioration or visual field constriction. In Amsterdam and Vancouver, radiotherapy was offered only when the visual acuity was less than 20/40. In the other two centres eight patients underwent radiotherapy with visual acuities of more than 20/30.

Radiotherapy was mostly conventional ($n=22$), although stereotactic fractionated conformal radiotherapy ($n=12$) was used for smaller, well-defined ONSM.

The follow-up was uniform in all clinics at intervals of 6 weeks, 3 months and 6 months, and then annually. All patients underwent annual MRI.

Measurements

Retrospective data were collected at presentation, before radiotherapy and at all follow-up examinations, and included visual acuity, colour vision and visual fields, pupil examination, fundoscopy (with a detailed description of the optic disc combined with fundus photographs) and Hertel exophthalmometer measurements. Ocular motility was examined at presentation, before and at least once after radiotherapy. On neuroimaging, the location, configuration, extension and calcification before radiotherapy were documented, with the addition of progression and extension after radiotherapy.

Definitions

Dry eyes

All patients underwent a Schirmer test with signs of corneal dryness classified as: no corneal changes; corneal stippling limited to the inferior periphery; stippling more extended; ulceration; and clouding.

Cataract

Cataract was defined according to the Lens Opacity Classification System II (LOCS II) criteria. The classification system consists of four classes: nuclear colour, nuclear opalescence, cortical grading and posterior subcapsular (PSC). A lens was considered clear if the LOCS II classification rated maximal nuclear colour as 0 to 1, nuclear opalescence as 0 to 1,

cortical grading as 0 to 1, and PSC as 0. If higher ratings were registered, cataract was diagnosed. Patients who had undergone cataract surgery were not staged using the LOCS II system but were classified as suffering from cataract.^{11 12}

Possible retinopathy

The definition of possible retinopathy was the presence of at least one haemorrhage or microaneurysm on standardised 50° red-free, black and white retina photographs. We used 50° non-stereo, red-free photography, a technique slightly modified from that described and evaluated by the Eurodiabetes Study.^{11 13} In patients with a follow-up longer than 3 years, fundus fluorescein angiography was performed.

Visual improvement

Visual improvement was defined as improvement of at least two lines on the Snellen chart.

Statistical analysis

The results of the study were analysed using the SPSS statistical software package (version 14.0.2). Differences in baseline data between groups were compared with independent *t* tests for numerical data and Fisher's exact test for categorical data.

Variables with $p < 0.1$ were entered in a multivariate analysis, using logistic regression analysis. R statistical software (version 2.5.1) was used to analyse longitudinal patterns. Prognostic factors for improvement in visual acuity were analysed using a linear random effect model. If bilateral ONSM was present, the data were analysed for the first affected eye.

RESULTS

Sex distribution

There were 26 female and eight male patients. The mean age at onset was 44.9 (range 12–66) years and was 49.45 (range 29–69) years at the beginning of radiotherapy.

Follow-up

The mean total follow-up time was 110.8 (range 58–235, median 84) months. The mean follow-up time after radiotherapy treatment was 58.32 (range 51–156, median 55) months.

Symptoms and signs

All 34 patients presented with visual deterioration, among which 21 cases had a chronic onset (measured in months), 12 had a sub-acute onset (weeks) and only one had an acute onset (days). Transient visual obscuration was noted in five patients, 18 had evidence of proptosis, and diplopia was present in six patients. Eight patients presented with retrobulbar pain. Optic disc swelling was noted in 20 patients, optic atrophy in 11, optic swelling with segmental atrophy in one, and two patients showed no abnormalities (table 1).

Imaging

In 22 patients, the ONSM involved the full length of the optic nerve; in 11, the tumour had a posterior location; in one, the tumour involved the anterior aspect of the optic nerve. Optic canal extension was encountered in nine patients, with five also having intracranial extension. None had involvement of the optic chiasm.

Histopathology

Histology was available in eight patients: four tumours were meningothelial and four were transitional, of which one also had psammoma bodies.

Table 1 Clinical and demographic characteristics of patients ONSM RT

Demographic and clinical parameters	Value
Patients	
Male	8 (24)
Female	26 (76)
Age at presentation (years, mean±SD)	44.9±14
Age at time of RT (months)	49.5
Bilateral	3 (9)
Unilateral	31 (91)
Presenting signs and symptoms	
Visual deterioration	34 (100)
Proptosis	18 (53)
Pain/discomfort	6 (18)
Disc oedema	20 (59)
Disc atrophy	12 (35)
Normal disc	2 (6)
Limitations in ocular motility	4 (12)
Visual obscuration	5 (15)
Follow-up (months, mean)	110 (median 84)
Post RT time (months, mean)	58.32 (median 55)

ONSM, optic nerve sheath meningioma; RT, radiotherapy.
Values are n (%) unless state otherwise.

Radiotherapy

Twenty-one patients received 54 Gy in 30 fractions, six received 50.4 Gy in 28 fractions, and 13 received 45 Gy stereotactically in 25 fractions. One patient received simultaneous bilateral radiotherapy for bilateral involvement.

Visual outcome

The visual acuity at the onset of radiotherapy was between 20/20 or 20/30 in eight patients, 20/40 and 20/80 in 14 patients, 20/100 and 20/200 in eight patients, and between 20/200 and hand movement (HM) in four patients (table 2).

The visual deterioration characteristics were compared between follow-up and the period before radiotherapy. Twenty-one patients showed a chronic pattern of visual deterioration, 12 had sub-acute duration, and only one had an acute onset. After radiotherapy, 15 patients showed improved visual acuity of at least two Snellen lines, with 11 of this group improving by more than three lines. Among those with improvement, all except one had chronic deterioration of their visual acuity before treatment. In 17 eyes, the vision stabilised, while deterioration was noted in three eyes. We found the following patterns of visual changes during follow-up after radiotherapy:

Early visual improvement

Eleven patients showed significant improvement of their visual acuity (more than three Snellen chart lines) within the first few months after radiotherapy. Visual fields were significantly improved in seven patients and in two patients was no information available, while colour vision showed some improvement in five patients.

All of these patients had optic disc swelling at the time of radiotherapy and for months afterwards. All of these patients except one (sub-acute) had chronic onset of visual deterioration.

Two patients in this group after an initial improvement in a later stadium showed some deterioration of visual acuity. One, who was a 65-year-old woman with bilateral ONSM and optic atrophy, underwent only right-sided radiotherapy; despite an initial improvement in her vision from 20/80 to 20/30 in 2 months, her visual acuity deteriorated to 20/100 over 3 years. The cause of this secondary deterioration was a PSC cataract and epiretinal membrane. Another patient showed improvement of vision from 20/40 to 20/30 within 3 months after

Table 2 Visual outcome after radiotherapy on ONSM

Treatment modality	No of patients (n=34)	Outcome of treatment (no. of cases)		
		Improvement	Stable/no significant change	Significant deterioration
VA TX		14	17	3
20/20–20/30	8	1	7	0
20/40–20/80	14	6	6	2
20/100–20/200	8	5	2	1
20/400–HM	4	2	2	0
Optic disc TX				
Oedema	21	10	10	1
Atrophy	11	3	6	2
Normal	2	1	1	0
Type of RT				
Conventional	22 (33.3%)	9	11	2
Stereotactic	12 (12.5%)	5	6	1

HM, hand movement; RT, radiotherapy; TX, treatment; VA, visual acuity.

radiotherapy. This visual improvement was maintained for 3 years, but then deteriorated to 20/200, and finally to counting fingers (CF) in 8 years as a result of macular degeneration. In this group, three patients underwent biopsies, with two cases having meningotheelial meningiomas and one case a transitional meningioma.

Late visual improvement and stabilisation

Three patients showed delayed improvement of their visual acuity. Two had chronic and one had sub-acute visual deterioration. One patient with a biopsy-proven meningotheelial meningioma underwent radiotherapy when his visual acuity was 20/200. His visual acuity in the first 2 years fluctuated between 20/200 and 20/400. In the third year, his visual acuity improved to 20/40 and it then remained stable at that level for 6 years. The visual acuity remained unchanged within the first year in all three patients. Two of these patients had visual acuity of CF at the time of radiotherapy. Their vision improved in the second year to 20/80 and 20/200. The third patient improved from 20/200 to 20/100 in the second year. Neither colour vision nor visual fields were improved in these three patients.

No visual improvement and stabilisation

Seventeen patients showed any change in visual acuity, visual fields and colour vision during the mean follow-up period of 47 months. After this period, one patient had a marginal visual deterioration from 20/60 to 20/80 and a minor deterioration of colour vision. The only complication post-radiotherapy in this patient was dry eye.

Primary visual deterioration

Three patients showed visual deterioration and constriction of the visual fields within weeks of radiotherapy. Biopsies were performed in all of these patients at three different centres before radiotherapy. Histopathology showed meningotheelial tumours in two patients and a transitional meningioma in one. Radiotherapy in these patients consisted of 54 Gy in 1.8-Gy fractions. The only ocular abnormality at the time of visual deterioration was optic disc oedema.

Prognostic factors for visual outcome

There was no significant association between age at presentation or the timing of radiotherapy and visual outcome ($p=0.82$),

nor was sex ($p=0.43$) or the type of radiotherapy a prognostic factor ($p=0.35$). Optic disc atrophy and swelling were the only statistically significant prognostic factors found for visual outcome. Although optic disc swelling was associated with a better visual prognosis compared with optic atrophy ($p<0.01$), four patients with disc atrophy showed improvement in their visual acuity. In addition, chronic onset was associated with a better visual prognosis after radiotherapy, but this was not statistically significant ($p=0.11$), nor was visual acuity at the time of presentation a prognostic factor ($p=0.22$).

Risk factors

Hypertension was diagnosed in six patients before treatment. In two patients, this was combined with diabetes mellitus, and one had atherosclerosis. The mean follow-up in this group was 51 months post-radiotherapy, and none of these patients showed any sign of cataract, dry eyes or retinopathy.

Complications

Early complications

Sixteen patients during 6 weeks of radiotherapy showed signs of temporary erythema around the area of irradiation. In 12 patients, this was associated with temporary hair loss. Six patients had headaches during radiotherapy; of these patients four were treated with dexamethasone with good response.

Late complications

Dry eyes were noticed in five patients: three with sectoral stippling and two with extended stippling of the cornea. Three patients showed signs of a PSC cataract 2 years after treatment. In two patients, no signs of cataract were present before treatment. One patient had a pre-existing nuclear cataract that was unchanged 3 years after treatment.

Retinopathy

All patients followed for longer than 4 years underwent fluorescein angiography. In six eyes, areas of hyperfluorescence consistent with window defects were noted in the posterior pole. One patient had a microaneurysm and one had cotton wool spots at the posterior pole of the retina 4 years after treatment. In another patient, haemorrhage and microaneurysm first appeared at the posterior pole 3 years after treatment. Both of these patients were treated using conformal conventional radiotherapy with 54 Gy in 1.8-Gy fractions. In all of the patients with retinal changes after radiotherapy, ONSM involved the full length of the optic nerve (table 3).

Pituitary function

During follow-up, no signs or symptoms attributable to impaired pituitary function were noted. Detailed endocrinological testing is beyond the scope of this report, which focuses on visual outcome.

DISCUSSION

In the past 30 years, there have been several reports on the treatment of ONSM with radiotherapy.^{1–10} However, none of these studies were randomised, controlled or prospective, and few had a follow-up time that was sufficiently long for the true efficacy of irradiation and the incidence of delayed visual improvement or loss to be noted. However, a controlled, randomised study that compares surgery or observation with radiotherapy is unlikely to be undertaken.

In a retrospective study, Turbin *et al* compared 18 patients who received primary radiotherapy for ONSM with two

Table 3 Complications of primary radiotherapy for progressive ONSM

Variable	Number /total cases (%)	Details
Early complications		
Erythema	16/34 (47)	Transient
Hair loss	12/34 (35)	Transient
Late complications		
Dry eye	5/34 (15)	Inferior sectoral stippling in 3 Extended stippling in 2
Cataract	3/34 (9)	1 convincingly attributed to radiation 1 was in a 65-year-old patient 1 had nuclear cataract prior to treatment and developed a PSC
Retinopathy		
Window defect	6/34 (18)	
Epiretinal membrane	3/34 (9)	
Microaneurysm	2/34 (6)	

ONSM, optic nerve sheath meningioma.

separate groups who received surgery and radiotherapy or observation. The primary radiotherapy group was the only group that did not experience visual deterioration, with 44.4% showing at least two lines of improved visual acuity. A 33% incidence of radiation-induced toxicity was reported, without specifying the details.³

Our 34 patients were treated and assessed in four centres using comparable protocols, with a mean follow-up of 9 years and a median of 4 years. In this series, unlike earlier studies, no blind eyes were included.

Visual outcome and prognostic factors

Seventeen of the 34 patients in our study showed visual stabilisation, 14 showed improvement and three had visual deterioration. Two patients in the improved group showed visual deterioration 3 and 4 years later because of epiretinal membranes and cataracts, which were most probably caused by the irradiation. As we reported in an earlier study of 88 patients with ONSM, among 39 patients who were followed by observation, 24 (71%) had a visual acuity of 20/50 or better after a mean follow-up of 5.8 years. Fifteen (44%) patients in this group had stable vision of 20/20 or 20/50.² However, stabilisation or improvement in patients who received radiotherapy (91%) is undeniably a better result. The presence of disc swelling was associated with a significantly better response, while four of nine patients with disc atrophy showed some visual improvement. This was also the only significant prognostic factor. Chronic onset of visual deterioration was associated with a better response to radiotherapy, although this was not significant.

Complications

Retinopathy developed in three eyes, all after follow-up for more than 3 years. Turbin *et al.* reported four cases of retinopathy in 18 patients, although the time span was not stated.³ Other studies using only fractionated stereotactic radiotherapy have also reported retinopathy that appeared between 2 and 4 years afterwards.^{6 14 15} Recent studies have shown that in orbital radiotherapy, diabetes mellitus (DM) and hypertension are risk factors for the development of retinopathy.¹¹ Our two patients with retinopathy did not have DM or hypertension. Four patients with hypertension and one with hypertension and DM who received radiotherapy did not show any signs of retinopathy after a mean follow-up of 3.5 years.

Conventional versus stereotactic radiotherapy

Twelve patients in our study received stereotactic radiotherapy and 22 received conformal radiotherapy. There was no statistically significant difference in the visual outcome between the groups. Of our patients with complications, two with post-radiation retinopathy, two with cataracts and two with dry eyes were treated using conformal conventional radiotherapy techniques. Note that the stereotactic radiotherapy group included smaller tumours at a greater distance from the globe. Retinopathy has also been reported in patients who have undergone stereotactic radiotherapy.^{3 6 14 15} However, one would expect greater precision with this technique and thus avoidance radiation of vulnerable healthy tissue.¹⁶ Indeed, a primary concern of radiotherapy is its late effects on the adjacent brain parenchyma and other tissues. The risk of radionecrosis of the brain has a threshold of 50–54 Gy with standard fractions of 1.8–2 Gy per day. Combined data for irradiation of pituitary adenomas show an incidence of optic nerve or chiasm injury of 1.5% at a dose of 45–50 Gy in 1.8–2-Gy fractions.^{17–20} Late pituitary dysfunction has become a more recognised late effect of radiotherapy. However, with proper modern treatment planning, the pituitary gland can often be avoided in patients with ONSM. None of our patients showed any signs of radionecrosis of the brain or pituitary gland dysfunction.

Conclusion and recommendations

Primary radiotherapy is associated with improvement or stabilisation of visual acuity in the majority of patients with progressive ONSM. Only a small proportion will progress despite radiation, and most adverse effects are transient or minor. Although we individualise the treatment strategy, we recommend radiotherapy in patients with progressive visual deterioration and/or visual field constriction. Fractionated stereotactic radiotherapy might be considered for treatment, particularly for well-defined lesions.²

In our study, there was no significant correlation between visual acuity at the time of treatment and visual outcome after treatment. In general, imaging is done at 6- to 12-month intervals after disease activity has been assessed. Our strategy includes reassessment on a 6-month basis with serial neuro-ophthalmological and visual field examinations, unless progressive symptoms or unusual disease activity dictate more frequent evaluation.

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