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Clinical Characteristics and Treatment Response to Radiotherapy of Optic Nerve Sheath Meningiomas

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Abstract

CLINICAL CHARACTERISTICS AND TREATMENT RESPONSE TO RADIOTHERAPY OF OPTIC NERVE SHEATH MENINGIOMAS.

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Recent reports of success with conventional, conformal, and stereotactic radiotherapy in stabilizing or improving visual function in patients with primary optic nerve sheath meningiomas have reduced the controversy surrounding the optimal treatment of these rare tumors. To analyze trends in the clinical presentation and diagnosis of optic nerve sheath meningiomas and to evaluate the effectiveness and side-effect profile of three-dimensional conformal radiotherapy versus other treatment modalities, a retrospective chart review was performed on patients with optic nerve sheath meningiomas treated at The Eye Care Group and at the Department of Therapeutic Radiology, Yale University School of Medicine, in New Haven, CT, up to September 2006. Fourteen patients were identified, with a mean age of 45.6 (range 16-63). Abnormal color vision and proptosis were less frequent than in historical comparison with published series. Four patients had normal initial imaging, underscoring the importance of clinical suspicion and appropriate imaging protocols. One patient was observed only, and one received surgery as primary treatment. Nine patients were treated with three-dimensional conformal radiotherapy at Yale, one with conformal intensity-modulated radiotherapy at Yale, one with three-dimensional conformal radiotherapy at another center, and one with stereotactic fractionated radiotherapy at another center. The overall visual and radiographic control rate for patients treated with radiotherapy was 100% with one late complication of mild dry-eye syndrome and one of pituitary toxicity. Outcomes in this series compare favorably with those in the published literature.

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Abbreviations used in this paper

3DCFR, three-dimensional conformal fractionated radiotherapy.

APD, afferent papillary defect.

CF, count fingers.

CT, computed tomography.

HM, hand motion.

IMRT, intensity-modulated radiotherapy.

LP, light perception.

MRI, magnetic resonance imaging.

NLP, no light perception.

OD, right eye.

ONS, optic nerve sheath.

ONSM, optic nerve sheath meningioma.

OS, left eye.

OU, both eyes.

RT, radiotherapy.

SFR, stereotactic fractionated radiotherapy.

SRS, stereotactic radiosurgery.

VA, Snellen visual acuity.

VF, visual field.

Introduction

Introduction and epidemiology

Meningiomas are mostly benign tumors that represent 15% to 20% of all intracranial tumors in adults making them the second most common brain neoplasms after gliomas (1). Optic nerve sheath meningiomas (ONSM) may arise primarily from the optic nerve sheath (ONS) or extend secondarily from an intracranial site. A review by Dutton in 1992 (1) found primary ONSMs to represent 1.3% (22 of 1723) of all meningiomas with an identifiable site of origin. Most meningiomas in the orbit are secondary, extending mostly from the olfactory groove and sphenoid ridge; primary ONSMs represent only 9.5% of meningiomas involving the orbit (1). Primary ONSMs were found to represent between 1.7% (2) and 10% (3) of all orbital tumors and about 35% of primary optic nerve tumors (4). The apparent incidence has risen over the last few decades due to better detection and diagnosis by advances in imaging technology. Like most meningiomas, ONSMs are nearly all classified as benign under the World Health Organization grading system for meningiomas (5).

The mean age at presentation of ONSM was 40.8 years (range 2.5-78) with 4% of patients younger than 20 years in Dutton's review (1). ONSMs in children have been noted to be more aggressive, with a higher incidence and larger size of intracranial extension in younger patients (3). Females accounted for 61% of patients and males 39%. Most (95%) cases were unilateral, with an approximately equal distribution between right (52%) and left (48%) sides. A majority (65%) of bilateral cases involved the optic canal, while among unilateral cases only 5.7% had an intracanalicular component. ONSMs, like optic gliomas, occur more frequently in patients with neurofibromatosis, especially type 2 (1, 6).

A brief history of medicine pertinent to ONSM

1755 Spry provides a clinical and gross pathologic description of ONSM (7).

1816 Scarpa characterizes tumors of the optic nerve, including some ONSMs (7).

1835 Cruveilhier is the first to recognize meningiomas as a pathologic entity (8).

1912 Hudson's classification clearly separates optic gliomas from ONSM (9).

1972 Computed tomography (CT) imaging is first introduced (10).

1981 Radiotherapy (RT) is first reported to successfully treat ONSM (11).

1982 Magnetic resonance imaging (MRI) is first introduced (10).

1992 A technique now known as three-dimensional conformal fractionated radiotherapy (3DCFR) is first reported in the treatment of ONSM (12).

Clinical presentation and natural history

The classic clinical triad (13) of visual loss, optic atrophy, and optociliary shunt vessels, is almost (14) pathognomonic for ONSM, though the presence of the entire triad is relatively uncommon and usually occurs only with advanced disease (15).

Visual signs and symptoms

The most common presenting symptom of ONSM is a decrease in visual acuity (VA), which is seen in 96% (365 of 380) patients in Dutton's analysis. Visual loss at presentation is highly variable, with 45% of documented cases having a VA of 20/40 or better while 24% had a VA of less than 20/400 (1). Other signs and symptoms of optic neuropathy, including disturbances of color vision (73%) and visual field (VF) defects (83%), are also common (1). Any type of VF defect may be present, though generalized constriction may be more common with

canalicular tumors (16); Dutton reported that out of 112 reported VF defects, there was peripheral constriction in 35%; central, centrocecal, and paracentral scotomas in 29%; altitudinal defects in 16%; and increased blind spot size in 13% (1). Transient visual obscurations, which can be gaze-evoked, postural, or spontaneous, may be present or be the presenting complaint (14%) (1, 2).

A relative afferent papillary defect (APD) is present on the ipsilateral side of almost all patients with unilateral ONSM (17).

External orbital signs

Proptosis at presentation was found in 59% of patients in Dutton's review (1) of cases prior to 1992, though more recent series report a frequency of 14% to 38% (3, 18-20); it may occasionally be the presenting complaint. Proptosis is generally slowly progressive, and is generally mild to moderate (2 mm to 5 mm), rarely exceeding 10 mm (1). Stiffening of the ONS rather than cranial nerve palsy usually accounts for limitation of ocular motility, which is found in 47% (1) of patients at presentation, though it is often asymptomatic. Less commonly reported is periocular or retrobulbar pain or discomfort, which may be present in 4% to 50% of patients (2, 21).

Ophthalmoscopic findings

Chronic disc swelling without peripapillary hemorrhages or exudates is common, seen in 48% (1) of patients, though it is less common in canalicular tumors (16). Optic atrophy is generally a later finding, though it was noted in 49% (1) at presentation. Overall, 98% of patients have disc swelling or atrophy or both (1). Optociliary shunt veins, seen in 30% (1) of patients, have been demonstrated to be collaterals from the retinal to the choroidal venous circulation histologically (22) and by fluorescein angiography (13). These shunt vessels represent dilation of

regressed embryonic anastomoses that occurs when the central retinal vein is compressed. Macular edema contiguous with a swollen disc and choroidal folds may also be seen (17). In general, however, optic disc appearance has been shown to be highly nonspecific in identifying most causes of optic atrophy (23).

Natural history

Several case series describing patients who were followed by observation alone provide a picture of the natural history and progression of ONSM (1, 3, 20, 24, 25). The prognosis for life is excellent with an overall mortality rate due to ONSM of zero (among 228 patients over 4-11 years (1) and among 88 patients over 1-20 years (3)). ONSMs are also not associated with neurologic morbidity (other than on the visual system) or metastatic potential (17). In most patients, visual loss progresses slowly over many years, though VA may remain stable for many years (1, 3, 20, 24, 25). Vision has rarely been reported to improve spontaneously (25). Patients with better initial VA are more likely to remain stable or progress slowly than those with worse VA at presentation. A radiographic volumetric analysis of 74 patients found that on an annual basis, calcified tumors grew 3.38 mm^3 in volume and 0.12 mm in length, while non-calcified tumors grew 23.45 mm^3 and 0.6 mm respectively (3).

Relevant anatomy of the optic nerve

The optic nerve is generally divided into four portions: intraocular (optic disc, 1 mm), intraorbital (20-30 mm), canalicular (10 mm), and intracranial (10-15 mm) (26-28). The intraorbital portion is longer than the distance between the globe and the optic foramen, which provides redundancy to allow eye movements and proptosis (28). The intracanalicular portion

enters the lesser wing of the sphenoid bone through the optic foramen at the orbital apex. This portion is tightly fixed within the optic canal without redundancy; thus, compressive lesions may cause damage to the nerve even if small and radiologically invisible (28). The optic canal, about 4.5 mm wide and 5 mm high and narrower at its orbital end, runs medial to the anterior clinoid process and lateral to the sphenoid sinus (27). The intracranial portion of the nerve runs from the intracranial opening of the optic canal in the middle cranial fossa to the optic chiasm (27).

Radiographic diagnosis

Since the advent of CT in routine clinical practice, radiographic imaging has played an indispensable role in the diagnosis and observation of ONSMs by avoiding the need for potentially damaging exploratory surgery to obtain a tissue biopsy for diagnosis. The most commonly useful modalities are high-resolution CT (29), thin-section MRI (30), and ultrasonography (31). Three main morphologic patterns of ONSM have been described: tubular, globular, and fusiform with a respective distribution of 64%, 25%, and 10% in one series and 62%, 23%, and 11% in another (1, 3). The only association found between morphology and visual prognosis was a greater risk of becoming NLP in patients having the tubular pattern with apical expansion (3).

CT findings

In Dutton's review (1), CT findings were present in almost all (97% on initial exam and 99% on follow-up exams) patients presenting with clinical manifestations. Enlargement of the orbital optic nerve is seen in the vast majority of cases, except for entirely intracanalicular lesions (1). A "tram-track" appearance is a classic sign that is seen best on contrast-enhanced CT images

but only present in 26% of patients (3, 29). Tram-tracking is nonspecific, being seen in other diseases including orbital pseudotumor, perioptic neuritis, sarcoidosis, leukemia, lymphoma, metastases, perioptic hemorrhage, and Erdheim-Chester disease (i.e., systemic xanthogranulomatosis) (32). It is seen on images where the nerve is parallel to the slice and is produced by increased attenuation peripherally representing the thickened nerve sheath and decreased attenuation centrally representing the residual optic nerve (32). The corresponding appearance on coronal images where the nerve is perpendicular to the slice is a partial or complete annulus. In addition, a thin linear area parallel to and directly adjacent to the nerve has been described to be even more attenuating, and is thought to represent linear perineural spread of the tumor in the subarachnoid space unique to ONSMs (33). Calcification, when present (31%) (3), helps to differentiate ONSMs from optic nerve gliomas (29) and may indicate slow growth (3). Other features seen in ONSMs but not in gliomas are narrowly and diffusely enlarged nerves with polar expansions either at the orbital apex or immediately behind the globe, irregular excrescent margins signifying extradural invasion into the orbital soft tissues, tram-tracking, and bone erosion near the orbital apex, whereas gliomas but not ONSM may display kinks and bucklings of the optic nerve as well as infarctive cysts (29). Hyperostosis and bone remodeling, if present, can be seen on CT images (1). An occasional finding associated with intracanalicular ONSM is sphenoid pneumosinus dilatans, which is an enlarged, aerated adjacent sinus with thinning of the wall but without bony destruction, hyperostosis, or mucous-membrane changes (34). The pathophysiology of pneumosinus dilatans is unclear, but it can also be seen occasionally in meningiomas other than ONSMs (35).

MRI findings

MRI allows excellent visualization of the nerve and tumor, but routine imaging protocols (e.g., routine brain MRI) may be insufficient to detect very small ONSMs (36). High spatial resolution axial and coronal images of the orbits before and after administration of contrast with fat suppression should be obtained when there is any clinical suspicion of ONSM. A through-plane spatial resolution of less than 3 mm was required to detect intracanalicular ONSMs in a series of 6 patients whose diagnosis was missed despite multiple (2 to 6) prior MRI investigations (36). Multiplanar imaging or image reconstruction from volume acquisitions is helpful to define the tumors (36). On non-enhanced images, ONSMs are usually isointense to the optic nerve and brain, but they may appear hypointense to brain on T1- and proton-weighted images and hyperintense or hypointense to brain on T2-weighted images (37). Following administration of intravenous gadolinium-DTPA contrast, ONSMs show marked or moderate homogeneous enhancement, distinguishing it from the nonenhancing optic nerve and aiding in the evaluation of small, intracanalicular, or intracranial tumors (37, 38). A "tram-track" appearance (Figure 1) similar to that seen on CT may be seen, where the enhancing mass surrounds the relatively hypointense nerve. The high signal intensity of orbital fat surrounding the ONS complex obscures the interface between fat and the enhancing tumor, so the use of fat suppression in addition to contrast enhancement is necessary for the optimal detection and delineation of the size and extent of the tumor (1, 36, 38).

ONSMs do not have a smooth surface, but rather have very fine extensions into the adjacent orbital fat visible on detailed examination of fat-suppressed images (17). A "dural tail," often associated with meningiomas, may be seen as a linear enhancing structure extending and tapering along the dural surface away from the tumor (39). Intracanalicular ONSM is better visualized with MRI than CT because of the absence of MRI signal from the cortical bone forming

the optic canal (40). When present, hyperostosis in bone adjacent to meningiomas appears isointense to brain and enhances with contrast, reflecting infiltration of tumor (1). A "rose thorn" appearance on axial images may be produced by *en plaque* growth of intracanalicular ONSM along the wall of the sulcus chiasmaticus (36). Perioptic cysts may be seen between the globe and the anterior aspect of the tumor, and represent dilated portions of the ONS due to cerebrospinal fluid trapped by the tumor (38).

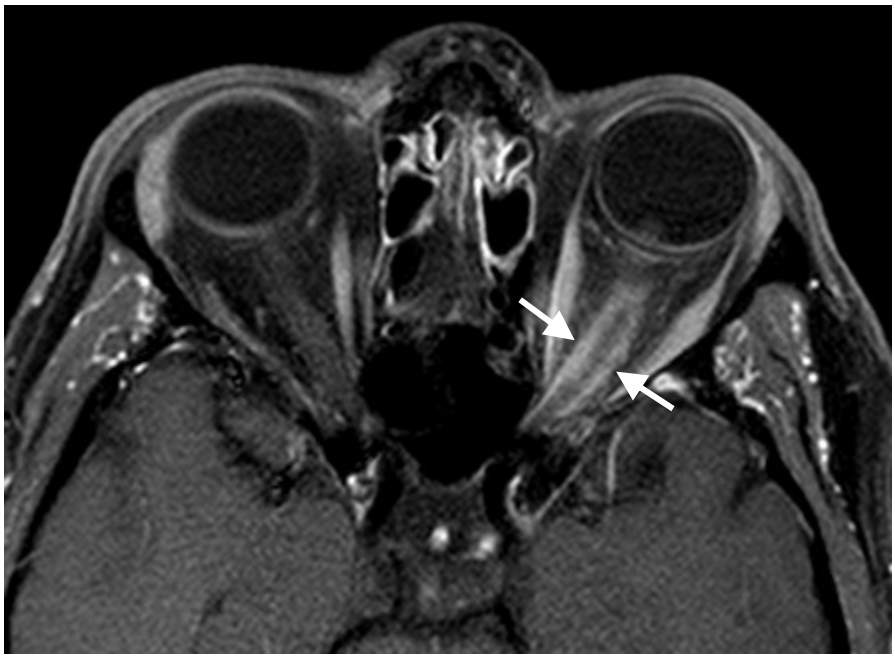


Figure 1. The tram-track pattern (arrows), formed by the enhancing tumor surrounding the relatively hypointense nerve, appears on this contrast-enhanced fat-suppressed T1-weighted axial image of patient 8.

Ultrasound findings

The characteristic echographic appearance is that of marked widening of the nerve with predominantly medium-high reflectivity and irregular acoustic structure (1). The 30 degree test may be performed by comparing the measured nerve diameter in primary gaze and at 30 degrees

of eccentric gaze. A negative test suggests a solid thickening of the nerve, while a positive test suggests increased subarachnoid fluid, which can be seen when a more posterior tumor traps cerebrospinal fluid anteriorly (1, 31). Three-dimensional ultrasonography used to generate coronal "C-scans" to measure ONS diameter has been described to correlate well with measurements obtained by CT in the setting of ONSM, though this technique can only image the anterior 15 mm of the optic nerve (the full coronal outline was only apparent for the anterior 7 mm) (41).

Octreotide scintigraphy

All meningiomas express somatostatin receptors, which allows them to be detected on ^{111}In-octreotide scintigraphic imaging (42). The high density of these receptors on meningiomas (versus other brain tumors) gives octreotide imaging a high level of sensitivity and allows the signal to be quantified (43). Unfortunately, octreotide imaging has low specificity (43) and thus can only support a diagnosis of ONSM that is already suspected clinically and radiographically. However, it has been suggested that ^{111}In-octreotide scintigraphy could provide a more sensitive and quantitative measure of tumor response after radiotherapy and also allow the differentiation of treatment failure from treatment-related morbidity (44).

Additional studies

Additional studies may provide more information but are usually performed in the pursuit of other entities. Optociliary shunt vessels that fill in the early venous phase may be visualized by intravenous fluorescein angiography or indocyanine green videoangiography (45). Visual evoked potentials show prolonged latency and decreased amplitude (27).

Differential diagnosis

The differential diagnosis of ONSM consists of other progressive optic neuropathies and/or causes of orbital syndrome, as well as entities with similar radiographic appearance (40). These include compressive, inflammatory, demyelinating, and infiltrative lesions. Toxic, nutritional, and hereditary optic neuropathies are also possible, though those tend to be bilateral (46). Tumors that can be confused with ONSM include optic nerve glioma (47), metastatic disease (48-50), lymphoma (51), schwannoma, neurofibroma, hemangiopericytoma (2), cavernous hemangioma, lymphangioma, and hemangioblastoma (40). Inflammatory or infectious conditions that may mimic ONSM include optic neuritis, optic perineuritis, sarcoidosis (52, 53), orbital pseudotumor, sclerosing orbital inflammation (54), and Wegener's granulomatosis (40). Other entities found during surgery include aspergillosis and benign lymphatic hyperplasia (55). Unilateral papilledema is usually associated with symptoms of elevated intracranial pressure (40).

Histopathology

Primary ONSMs are thought to arise from the meningothelial cap cells of the arachnoid villi (pacchionian granulations) that are uniformly present along the canalicular and intraorbital segments of the optic nerve (1). They may remain localized to one segment of the optic nerve or extend along the length of the nerve (17). They spread in the subarachnoid space along paths of least resistance: along dural septae of the optic nerve, around vessels, and into the haversian canal system of adjacent bone, which can induce hyperostosis and bone proliferation (1, 56). As the tumor grows, it may encircle and compress the optic nerve, obstructing axonal transport and interfering with the extradurally-derived pial blood supply of the nerve (1). The growth of the

tumor between the nerve and its blood supply makes sight-sparing surgery particularly difficult (17).

The main histopathologic patterns described for primary ONSMs are the meningothelial and transitional patterns (1). Of the histopathologic appearances described for meningiomas, fibrous and psammomatous patterns have also been described for primary ONSMs (57). All of these are benign in the World Health Organization classification (5). In the meningothelial or syncytial pattern, lobules of polygonal, largely uniform cells that appear under light microscopy to form a syncytium are separated by collagenous vascular septae, and mitoses are uncommon (1, 5). The fibrous or fibroblastic pattern features fibroblast-like spindle-shaped cells in wide fascicles among a matrix abundant in collagen and reticulin (5). The transitional or mixed pattern has features of both meningothelial and fibrous patterns, with lobular and fascicular arrangements of spindle or oval cells that can also be found in concentric whorl formations. Psammoma bodies, which develop from hyalinization and deposition of calcium salts in the degenerated centers of whorls, are common in the transitional pattern and are abundant in the psammomatous pattern, where they can become confluent. These psammoma bodies can be seen as calcifications on radiographic imaging (1, 5).

Overview of treatment options

Observation

Before the advent of RT and the imaging techniques that it depended upon, ONSMs were either observed or excised surgically. Since most ONSMs progress gradually over a period of many years and are not associated with mortality or metastasis, observation may be appropriate in patients with good vision, no significant progression of visual loss, and no evidence of

intracranial extension. The natural history of most ONSMs, however, is progressive visual loss (1, 3, 20, 24, 25, 58). Thus, patients being observed are monitored with regular exams and imaging, with intervention offered if there is evidence of progression of disease (17).

Surgical excision

Surgical excision was the most important treatment modality for well over a century. Lateral orbitotomy allowed the removal of anterior or mid-orbital tumors or biopsy of apical tumors, and craniotomy was employed for excision of apical or canalicular lesions (1). Since the recurrence rate for intracranial meningiomas decreases with increasing extent of resection (59), the nerve was often removed for ONSMs in an *en bloc* excision to prevent recurrence or intracranial extension. Even when an attempt was made to spare the nerve, however, surgery frequently resulted in blindness on the side operated on because of disruption of the pial blood supply (1, 17). It is rarely if ever possible to remove the entire tumor while sparing the nerve, even in extradural tumors, because of tumor remaining in the subdural or subarachnoid space surrounding the nerve (1). Other than disruption of vision, complications of surgical excision included central retinal artery occlusion, motility disturbance, and phthisis bulbi, though mortality from surgery is effectively zero (1).

Surgical decompression

Decompression of the optic nerve has been attempted by opening the dural sheath without removal of the tumor. Reports exist of successful decompressions arresting progressive visual loss (3, 60); however, most reports showed no benefit (3, 61-63). Furthermore, ONSMs have been reported to recur in the orbital fat and extraocular muscles following a decompression (2).

Medical therapy

Various forms of medical therapy have shown promise but randomized trials have been disappointing to date. High dose corticosteroids (prescribed in cases of presumed optic neuritis that were later identified as ONSM) have been reported to arrest temporarily visual decline, and hence have been proposed as a temporizing measure in cases of rapid visual deterioration pending definitive treatment (27, 36).

Among meningiomas, ONSMs in particular often express a variety of hormone receptors, most commonly estrogen or progesterone (64), and the growth of ONSMs has been reported to be initiated or accelerated by pregnancy (3, 62, 65). Thus, there has been interest in investigating the use of estrogen or progesterone antagonists to destroy or at least reduce the size of ONSMs. Clinical trials using tamoxifen and medroxyprogesterone on meningiomas have been negative, and mifepristone, after showing promising results in phase I and II trials, was evaluated in a phase III double-blinded randomized trial on meningiomas that was negative (66, 67).

Hydroxyurea, a ribonucleotide reductase inhibitor commonly used in the treatment of hematological malignancies, has been reported in several case series to have some effect in treating unresectable, residual, and recurrent meningiomas (68-71). Other studies have found only marginal or no beneficial effect (72, 73). However, there has only been one case report of the successful use of hydroxyurea in treating ONSM (74). A phase II study investigating the use of hydroxyurea in unresectable meningiomas was recently completed in 2005 by the South West Oncology Group but the results are not yet available.

Radiation therapy

Initially considered to be ineffective against meningiomas because of slow or no apparent response, RT is now considered a mainstay of treatment for ONSM. In 1981, Smith *et al.* (11) first

reported improvement in VA, VF, and funduscopic appearance in several patients treated with RT. Others subsequently confirmed the effect of conventional RT on producing an improvement in VA and VF in some patients that persisted for several years of follow-up (24, 75, 76). In 2002, Turbin *et al.* (20) retrospectively compared long-term (51 to 516 months) visual outcomes for patients treated with observation alone, surgery alone, surgery and RT, and RT alone. Treatment with radiation alone was associated with statistically significantly better visual outcomes versus the other three groups.

In general, the radiation may be in the form of heavy charged particle beams (helium, neon, protons), gamma-radiation (cobalt-60 source), and high energy photons (produced by heavily collimated linear accelerators) (77). Narrowly focused beams with a high dose gradient minimize the delivery of radiation to non-target tissues. Several techniques have been developed to minimize the radiation absorbed by non-target tissue, including accurate immobilization allowing for smaller field size, fractionation of irradiation, three-dimensional imaging, conformal targeting, and precise dose delivery (78). Several published series have reported patients with stable or improved vision after RT using protocols that incorporated advances such as these (see Discussion) (3, 19, 25, 46, 79-84).

Stereotactic irradiation implies the use of a highly accurate and reproducible three-dimensional coordinate system to locate the target, from imaging through treatment. Reproducible immobilization adequate for RT purposes has been achieved with a registration system based on a customized oral appliance that provides reproducible positioning based on maxillary dentition, with fiducial references implanted into the skull, and with image guidance systems. Neither a simple headholder nor a thermoplastic mask meets the submillimeter spatial accuracy and reproducibility requirements for true stereotaxy. Stereotactic radiosurgery (SRS), including Gamma Knife, uses a large single dose of radiation, and is not appropriate when any

residual vision is to be preserved because the tolerance of the optic nerve for single-fraction irradiation is below the dose required for durable long-term control of an ONSM (see below). Stereotactic fractionated radiotherapy (SFR) uses multiple fractions to reduce toxicity to non-target tissues by delivering doses safely tolerated by the optic nerve that will control the growth (and induce regression) of an ONSM.

The well-defined borders of many benign tumors including ONSM make them amenable to highly conformal RT (85). Conformality is achieved by techniques in dose planning and delivery. Eng *et al.* (12) described in 1992 the first use of a 3DCFR technique in the treatment of ONSM using a non-opposed beam configuration. The patient's head was positioned so that the optic nerve was aligned with the vertical axis, allowing for the use of smaller field sizes. In general, 3DCFR uses a three-dimensional anatomical image of the patient to define a tumor target volume that is irradiated by a set of beams shaped to conform to each beam's-eye-view projection of the target (86). Using a thermoplastic mask molded specifically to the patient's head allows the setup to be reproduced fairly accurately (less than 3 mm deviation between sessions in 92.5% of cases (12)), allowing a smaller margin around the tumor.

Another form of conformal RT, intensity-modulated radiotherapy (IMRT), uses computer optimization of intensity-modulated beams to maximize conformality, though generally at the expense of homogeneity (78).

In all cases where RT is used to treat ONSM, treatment planning images are obtained by CT and MRI; the CT scan is done with the patient immobilized using the device that will be used for immobilizing the patient in the same position for daily RT. These images are downloaded to the treatment planning computer and fused by software. The CT scan is used as the base image because it is not subject to distortion such as sometimes seen in MRI. The electron density information from CT allows for more accurate dose calculation, while the extent of the tumor is

usually best seen on fat-suppressed enhanced T1-weighted MRI images (78). Contouring and volume reconstruction are performed on the computer in the three-dimensional imaging data sets. The computer is then used to design a preferred arrangement for the treatment beams, which may be shaped by cylindrical cones, simple collimators within a cone, customized blocks, or micro-leaf collimators (78). This step involves the calculation of how intense each beam should be, along with the determination of whether any beam modifying devices are required to increase the dose homogeneity. The goal of RT planning is to construct a plan in which multiple beams of radiation are delivered from several angles to create a small conformal high-dose volume; alternatively, the beams may be arced around the target. The dose delivered can be calculated for any part of the target and non-target volumes.

Delayed toxicity is the major concern with RT. Nearby important structures include the optic nerve itself, the lens, the retina, the pituitary gland, and the brain. Radiation retinopathy has been described to have a threshold dose for increased risk of injury at a total of 45 to 50 Gy, with diabetes mellitus and concurrent chemotherapy increasing the risk (87, 88). There was no incidence of retinopathy in 33 retinas receiving less than 45 Gy, but above 45 Gy, the incidence of retinopathy increased with higher total dose or fraction size (i.e., 1.9 Gy or greater), and the mean time to onset of symptoms was 2.8 years (range 1-6.5 years) (88). Optic neuropathy was not seen in 106 nerves receiving 59 Gy or less of total radiation, but among those receiving 60 Gy or more, the dose per fraction was found to be more important in predicting damage than total dose, with fraction size of 1.9 Gy or greater associated with increased risk of damage (89). The risk of optic neuropathy was estimated to be less than 2% for total doses of 50 Gy or less (90, 91) The optic nerve is more sensitive to radiation than other cranial nerves (92), and single doses of greater than 8 Gy are associated with a risk of optic neuropathy (93). The incidence of severe dry-eye syndrome has a threshold of a total dose of about 40 Gy of fractionated radiation delivered to the

lacrimal gland (91), with a reported rate of 0% for doses less than 30 Gy, 19% for doses up to 45 Gy, and 100% for doses exceeding 57 Gy (94). Severe dry-eye syndrome was defined as that sufficient to produce visual loss from corneal opacification, ulceration, or vascularization, and developed 4 to 11 years after treatment with doses up to 45 Gy(94). The pituitary gland is also at risk for radiation toxicity; a total dose of 50 Gy or more is associated with increased risk of anterior pituitary dysfunction, most commonly hyperprolactinemia but also possibly hypothyroidism, hypoadrenalism, or hypogonadism (95). The hypothalamus may be more susceptible than the pituitary as it does not seem to exhibit a threshold response (95). The risk of brain necrosis has been reported to have a threshold of 50 to 54 Gy when given in 1.8 to 2.0 Gy fractions (96, 97).

Statement of purpose and hypothesis

Recent reports of success with conventional, conformal, and stereotactic RT in stabilizing or improving visual function in patients with ONSM have reduced the controversy surrounding the optimal treatment of primary ONSM. Surgery is now considered only in cases of intracranial extension, incipient extension, and proptosis in a blind eye. Until the time that effective medical therapy is found, it appears that RT will form the mainstay of therapy. However, the relative rarity of this disease makes it unlikely that any controlled randomized trial could ever be carried out directly comparing one treatment regimen with another, forcing clinicians to rely on case series where the patients number in the dozens. This study aims to (1) analyze trends in the clinical presentation and diagnosis of ONSM; and (2) evaluate the effectiveness and side-effect profile of 3DCFR versus other treatment modalities. The hypotheses of this study are that (1) improved imaging techniques and increased awareness of ONSM have led to earlier diagnosis while the manifestations of disease are more subtle; and (2) 3DCFR provides equal or better tumor control and visual outcomes with comparable or better side-effect profile than conventional fractionated RT and other treatment modalities.

Methods

Approval was obtained from the Human Investigation Committee of the Yale Institutional Review Board to identify, review the records of, and contact for follow-up those patients treated or followed at Yale University (the proposal was written with James Yu, MD, Department of Therapeutic Radiology). A search of the patient database of The Eye Care Group as well as of the transcription database computer servers of the Department of Therapeutic Radiology of the Yale University School of Medicine was performed. A retrospective review was performed of the medical records of the 14 patients with a clinical, radiologic, or pathologic diagnosis of ONSM who were treated or followed in the neuro-ophthalmologic clinic of Robert Lesser, MD (The Eye Care Group, New Haven, CT) and/or primarily treated in the therapeutic radiology clinic of Jonathan Knisely, MD (Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT) in the period up to September, 2006. Clinical reports, treatment plans, and imaging studies were reviewed.

A review of the published literature was performed to provide historical data for comparison with the current series. The clinical and radiologic presentation of ONSM in the current series was compared with those reported in the literature to identify trends and deficiencies in diagnosis. The outcomes of these patients were compared with those reported in the literature of patients treated with 3DCFR, SFR, and other modalities.

At Yale, patients are usually treated with a 3DCFR technique using thermoplastic mask immobilization after planning CT and MRI are obtained to create a treatment plan, as described above. The dose prescribed is usually 50.4 Gy in 28 1.8-Gy daily fractions. One patient in this series was treated with an IMRT technique using the Peacock system with a dose of 45 Gy in 25 fractions prescribed to the 85% isodose surface.

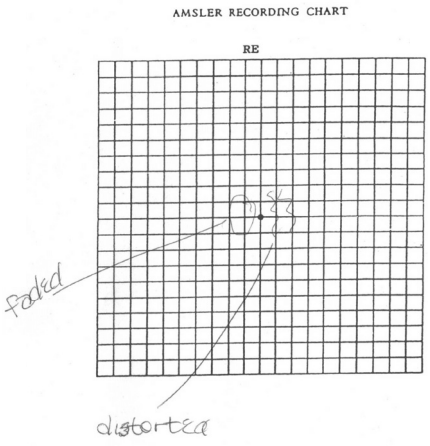
Results

Case histories

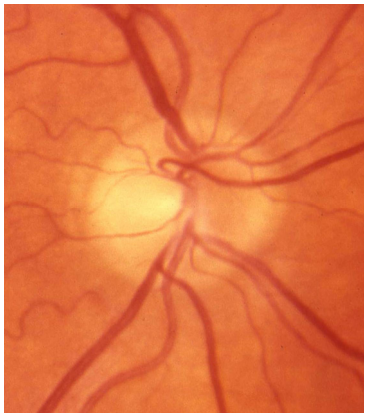
Patient 1

A 46-year-old man was referred for evaluation of progressive metamorphopsia in the central vision of his right eye. He was initially referred to a retina specialist who documented a normal exam and fluorescein angiogram. At a second retinal consultation, a repeat fluorescein angiogram showed some staining and slight leakage of the capillaries along the nasal aspect of the right optic nerve, which prompted a neuro-ophthalmic evaluation. The patient had no symptoms other than the metamorphopsia. A review of systems was positive for convergence insufficiency and also included mitral valve prolapse and depression; his medications included fluoxetine, aspirin, and multivitamins. Examination revealed VA of 20/20 in the right eye (OD) and 20/15 in the left eye (OS), no relative APD, intact color vision, and no limitation of motility with a small exophoria. A slight proptosis of the right eye of 3 mm was seen on Hertel exophthalmometry. Amsler grid testing showed a slight irregularity just nasal to fixation. The right optic disc appeared somewhat elevated and hyperemic nasally with fairly superficial vessels, but no definitive optociliary shunt vessels were seen. Ultrasound examination showed an elevated disc OD with enlargement of the retrobulbar optic nerve and a positive 30-degree test (indicating increased subarachnoid fluid). Automated static perimetry was normal. Head CT showed a diffuse enlargement of the orbital portion of the right optic nerve with some enhancement. Brain and orbital MRI showed enhancement of the right ONS extending from about 1 cm posterior to the globe into the orbital apex without intracranial abnormality, but no

discrete mass was seen. A workup for sarcoidosis was negative and a short course of corticosteroids provided no benefit. The patient reported continued progression of his metamorphopsia during the period prior to treatment, but his VA and VF remained normal. He was treated with 3DCFR, receiving 45.00 Gy in 25 fractions over 36 days. He experienced some mild nausea and a small area of alopecia during treatment. His optic disc swelling has resolved and temporal pallor has developed; his slight proptosis has also resolved. He has been followed for 96 months (8 years) with no late radiation side effects except for the onset of dry eye syndrome about 4 years after treatment. His paracentral metamorphopsia has been stable, with maintenance of his VA at 20/15 in both eyes (OU) and normal VF OU. On MRI, the enhancement around the optic nerve diminished slightly and has since stabilized.



A. Amsler grid at initial presentation showing central metamorphopsia in the right eye.

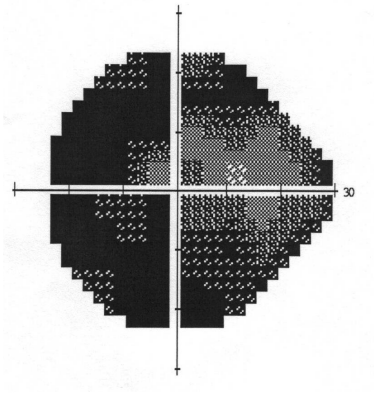


B. Right optic disc 36 months after completion of treatment, showing a flat disc with temporal pallor.

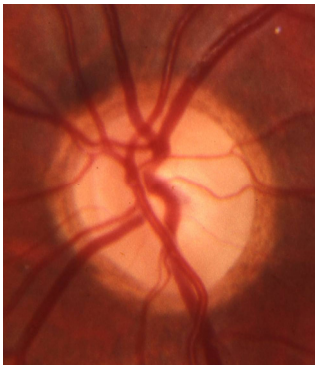
Figure 2. Clinical images from patient 1.
Fundus photographs at presentation were not available.

Patient 2

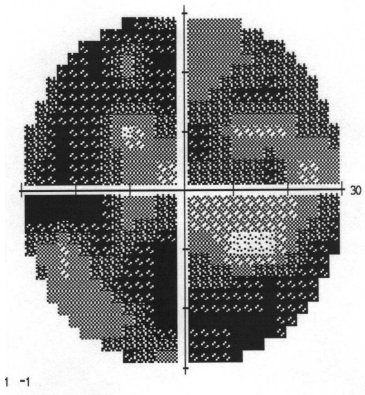
A 16-year-old girl was referred for evaluation of an asymptomatic decrease in vision and visual field found on routine driver's license eye exam. She had not previously noticed the problem and had no other symptoms. A review of systems revealed a history of chronic headache. Her medications included butalbital/acetaminophen/caffeine. Examination revealed a VA of 20/15 OD and 20/80 OS, a 0.9 log density relative APD in the left eye, and a normal external exam without exophthalmos or limitation of mobility. She identified 15/15 Ishihara color plates with the right eye but none with the left eye. Automated static perimetry showed diffuse loss in the left eye. The left disc was flat and diffusely pale with a peripapillary halo and a cup to disc ratio of 0.7. MRI showed asymmetric thickening and tram-track enhancement of the left ONS extending 6 mm from the globe almost to the chiasm, with atrophy of the intracanalicular and intracranial nerve with enlargement of the anterior clinoid process. A CT scan without contrast showed faint linear calcification involving the superior mid-portion of the left optic nerve; a scan with contrast showed nodular and linear tram-track enhancement of the left optic nerve. Also seen was enlargement of the left anterior clinoid process without hyperostosis causing narrowing of the optic canal. A workup for other etiologies including sarcoidosis and vasculitis was negative. She was referred for RT after she experienced progression of visual loss to 20/200 OS. She was treated with 3DCFR, receiving 52.19 Gy in 29 fractions over 42 days, with the last 9 fractions as a conedown. She experienced no acute side effects other than mild fatigue. She was followed for 58 months. Her VA initially improved to 20/60 but later declined and stabilized at 20/100 . Her VF and MRI have been stable, and she has not had any signs of late radiation toxicity.



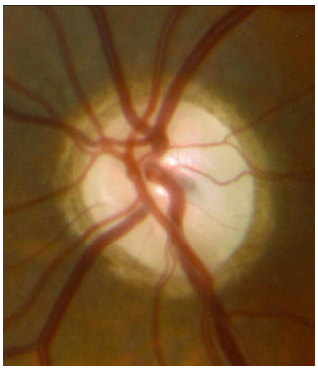
A. Static perimetry of the left eye at presentation showing diffuse loss.



B. Left optic disc at presentation showing a flat, atrophic disc with a peripapillary halo.



C. Static perimetry of the left eye 58 months after completion of treatment showing diffuse loss, though with slight improvement.



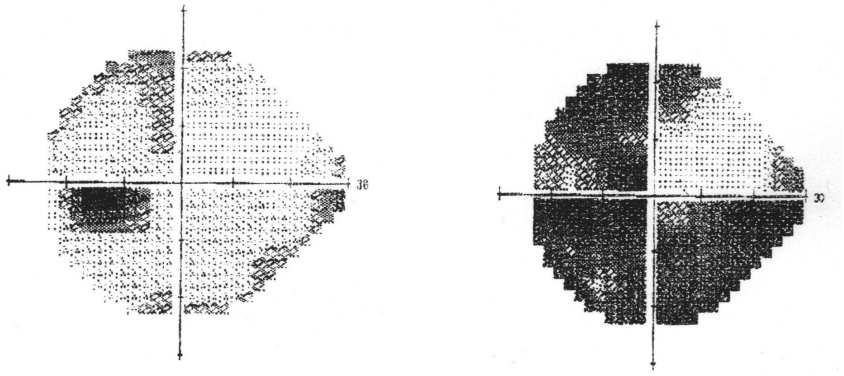
D. Left optic disc at 46 months after completion of treatment showing a flat, atrophic disc with a peripapillary halo as before.

Figure 3. Clinical images from patient 2.

Patient 3

A 49-year-old woman was referred for evaluation of an 18-month history of subtle visual loss in the left eye after a relative APD and progression of visual field defects in that eye were

noted by an ophthalmologist. The patient described feeling that her vision was not as sharp in the left eye as in the right, which she described as being similar to looking through a sheet of plastic wrap. She also reported decreased color perception in the left eye. She had no transient obscurations of vision or pain on movement of the eye. She had an open MRI that only found an incidental small cyst in the temporal lobe. Her past medical history and review of systems included migraine-type headaches for many years, depression, anxiety, carpal tunnel syndrome, and rhinoplasty. Her medications included ibuprofen, acetaminophen, and pseudoephedrine. Examination revealed VA of 20/15 OU but slower on the left, a 0.9 log density relative APD OS, a mild deficit in color vision OS by Hardy-Rand-Rittler color plate testing, and a normal external exam with no exophthalmos or limitation of motility. The left optic disc was diffusely pale most markedly temporally; the right disc was normal. Automated static perimetry showed temporal depression in the left eye with no definite respect for the vertical meridian. A repeat MRI was read as showing no abnormal enhancement of the optic nerves. About 5 months later, after progression of her symptoms, another MRI was ordered, which demonstrated left optic atrophy but no abnormal enhancement. Two months later a fourth MRI found a pattern of ONS enhancement that was suspicious for ONSM, and a retrospective review of the previous imaging found that this pattern had been subtly present. A workup for sarcoidosis was negative, and a diagnosis of ONSM was made on the basis of radiographic appearance and clinical presentation. The patient was treated with 3DCFR, receiving 50.36 Gy in 28 fractions over 37 days. She tolerated the therapy well with some fatigue during the course but no other symptoms. She has been followed for 24-1/2 months with no further progression of visual loss and no delayed radiation side effects. Her VA has been stable at 20/15 OD and 20/20 OS, her APD has disappeared, her left optic disc shows temporal atrophy, and her VF has improved.



A. Static perimetry of the left eye at presentation 18 months after onset of symptoms, showing temporal depression with no definite respect for the vertical meridian.

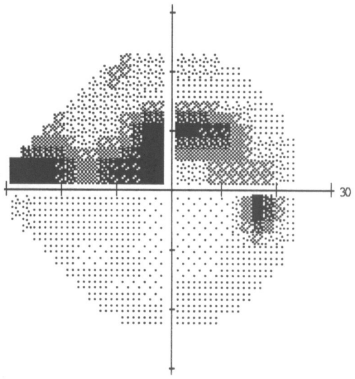
B. Static perimetry of the left eye before treatment, 23 months after onset of symptoms, showing diffuse loss with sparing of the superonasal quadrant.

Figure 4. Clinical images from patient 3.
Perimetry images after treatment and fundus photographs were not available.

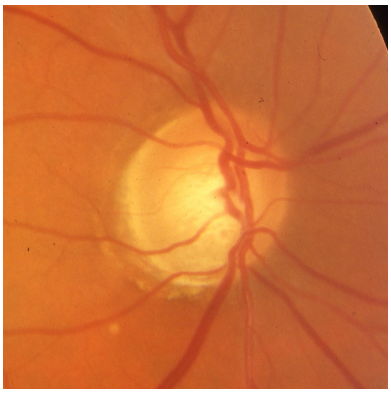
Patient 4

A 56-year-old man was referred for evaluation of an 8-month history of subjective progressive enlargement of existing visual field defects in the right eye that was also seen on automated perimetry by an ophthalmologist, who then ordered an orbital CT that showed a punctate calcification in the right ONS. A review of systems included a history of low-tension glaucoma in the right eye, strabismus surgery for exotropia 17 years prior, and peripheral neuropathy; his medications included bimatoprost 1 gtt qhs, omeprazole, and simvastatin. Examination revealed visual acuity of 20/20 OU, both pupils equal and reactive with no APD, intact color vision, no exophthalmos, and a small anterior subcapsular cataract OD. The right optic disc had a cup-to-disc ratio of 0.9, notching most marked inferiorly, pallor temporally, and an intact rim but sloping superiorly and absent inferiorly. Optociliary shunt vessels were not

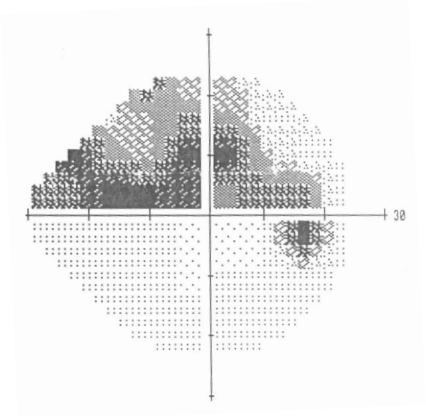
seen. The left optic disc had a cup-to-disc ratio of 0.8 with sloping in the margin with intact rim. Automated static perimetry showed a superior arcuate defect with respect for the horizontal meridian in the right eye and a normal field in the left. Although these findings were consistent with low-tension glaucoma, MRI was ordered because of the significant pallor in the right eye along with the calcification seen on CT. Orbital MRI revealed a focal 3 mm enhancement along the inferior right ONS just posterior to the globe, corresponding to the area of calcification on CT and suspicious for tiny ONSM. A pulmonology evaluation found no evidence for sarcoidosis, and a tuberculin skin test was negative. The patient was treated with 3DCFR, receiving 50.3 Gy in 28 fractions over 39 days. He reported no side effects during the treatment course other than feeling minor fatigue. He has been followed for 57 months with no delayed radiation side effects and a stable clinical course, with visual acuity remaining 20/20 OU or better. His visual field improved slightly at 8 weeks after the end of treatment and remained stable until beginning to worsen at 34 months, but this is likely due to progression of his glaucoma. At 45 months it was noted that the focal enhancement on MRI that had been previously stable was no longer seen, likely representing regression of the meningioma beyond the limit of imaging resolution.



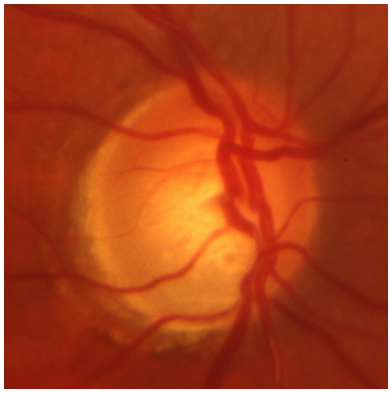
A. Static perimetry of the right eye at presentation showing superior arcuate scotoma.



B. Right optic disc at presentation showing marked cupping and temporal pallor.



C. Static perimetry of the right eye at 40 months after completion of treatment showing increasing superior arcuate scotoma due to progression of glaucoma.

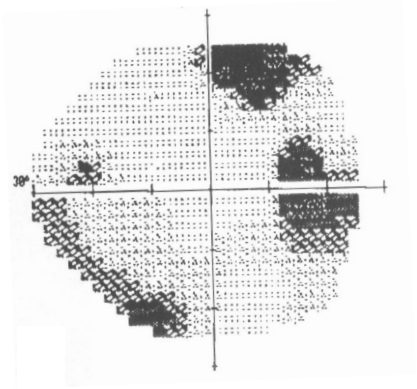


D. Right optic disc at 34 months post treatment showing stable course since presentation.

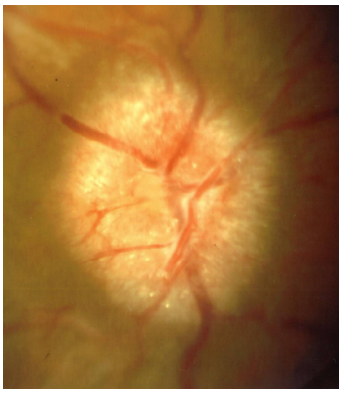
Figure 5. Clinical images from patient 4.

Patient 5

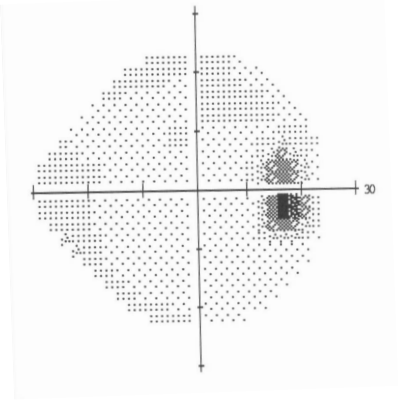
A 46-year-old woman was referred for evaluation of an 8-month history of transient fogging of vision in her right eye. An ophthalmologist had seen unilateral disc swelling and ordered an orbital MRI, which was suspicious for an ONSM or other tiny mass. The patient experienced episodes in her right eye of blurriness often associated with change in position, lasting several seconds, and occurring on a daily basis. She also complained of eye tenderness. A review of systems was unremarkable except for a history of migraines since childhood and cluster headaches, and her medications included Excedrin as needed. Examination revealed VA of 20/20 OU, a relative APD in the right eye neutralized by a 0.3 log unit neutral density filter, intact color vision, no exophthalmos, and no limitation of motility. There was edema of the right optic disc with 360° elevation and obscuration of vessels consistent with grade III elevation; pseudodrusen were also seen on the right optic disc. No optociliary shunt vessels were seen. Automated static perimetry showed an enlarged blind spot and minimal superotemporal and nasal depression in the right eye. MRI was repeated and showed enhancement of the sheath extending from a level 7 mm posterior to the globe posteriorly through the optic canal nearly to the level of the optic chiasm. A diagnosis of ONSM was made on the basis of radiographic and clinical presentation. Between initial neuro-ophthalmic evaluation and time of treatment, her symptoms became more frequent, more spontaneous, and longer in duration. She was treated with 3DCFR, receiving 50.25 Gy in 28 fractions over 40 days. She reported no side effects during the treatment course other than minor mucous membrane inflammation, and she enjoyed an immediate subjective improvement in her vision. She has been followed for 38 months with no delayed radiation side effects. She has had resolution of disc edema with development of temporal pallor, significant subjective improvement in vision, maintenance of VA at 20/20 or better OU, complete improvement in the visual field to normal, and stable MRI appearance.



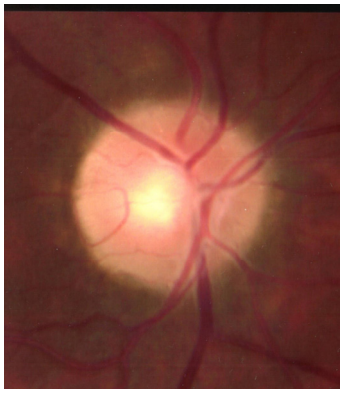
A. Visual field of right eye at presentation showing enlarged blind spot and scotomas superotemporally and nasally.



B. Right optic disc at presentation showing grade III papilledema and pseudodrusen.



C. Visual field of right eye at seven weeks post treatment, showing improvement to within normal limits.



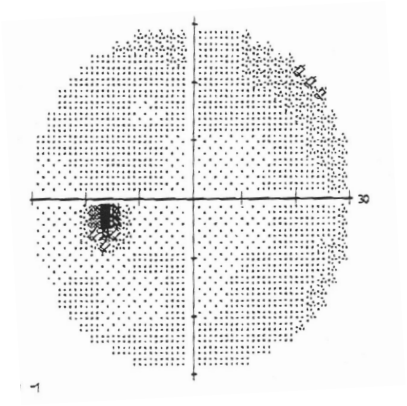
D. Right optic disc at 19 months post treatment, showing resolution of edema with development of temporal pallor.

Figure 6. Clinical images from patient 5.

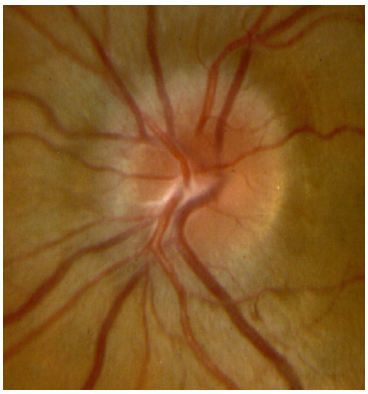
Patient 6

A 51-year-old woman was referred for evaluation of a 6-month history of intermittent episodes of decreased vision in the periphery of the left eye after seeing a retina specialist who found edema of the left optic disc and fullness of the left optic nerve on ultrasound. The patient described discrete episodes lasting up to 10 seconds during which the periphery of the inferonasal quadrant of her visual field became "fuzzy," occurring 2 to 3 times in a day and without associated symptoms or identified triggering events. She had an MRI that found enhancement without enlargement of the left optic nerve. Her past medical history was significant for stage I breast cancer that was treated with lumpectomy, EBRT, and tamoxifen about 1 year prior, nephrectomy secondary to traumatic damage, and hysterectomy for uterine fibroids. A review of systems was otherwise negative. Her only medication was anastrozole (an aromatase inhibitor) for her breast cancer. Examination revealed VA of 20/15 OU, no relative APD, intact color vision, and a normal external exam with no exophthalmos or limitation of motility. The left optic disc was hyperemic with edema of the nerve fiber layer most markedly superiorly and nasally, with absence of spontaneous venous pulsations, and without hemorrhages, exudates, or optociliary shunt vessels seen. Her right optic disc was normal. Automated static perimetry showed a questionably enlarged blind spot in her left eye and a normal field in her right. A CT scan showed enhancement and mild enlargement of the left optic nerve without masses, calcifications, or bony changes. A repeat MRI showed a tram-track pattern of enhancement of the left optic nerve extending from about 5 mm posterior to the globe to the orbital apex. A diagnosis of ONSM was made on the basis of the clinical presentation and radiographic appearance. The patient was treated with 3DCFR, receiving 50.34 Gy in 28 fractions over 41 days. She tolerated the therapy well with no alopecia or other side effects, and she noted a subjective improvement in her symptoms during the treatment course. She has been followed

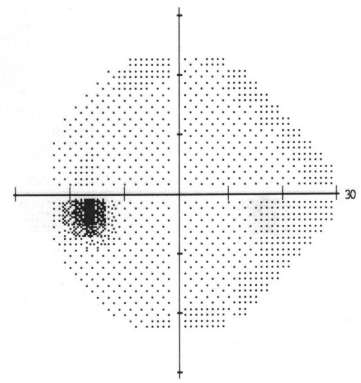
for 30 months with maintenance of 20/15 VA OU, full VF OU, resolution of her optic disc edema, cessation of the episodes of "fuzzy" vision, no delayed radiation complications, and a stable MRI appearance.



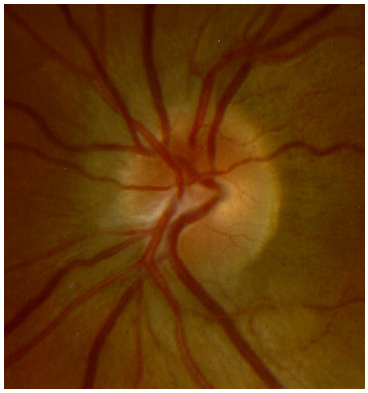
A. Static perimetry of the left eye at presentation showing a questionably enlarged blind spot.



B. Left optic disc at presentation showing hyperemia with edema of the nerve fiber layer most markedly superiorly and nasally.



C. Static perimetry of the left eye at latest follow-up showing a normal field.



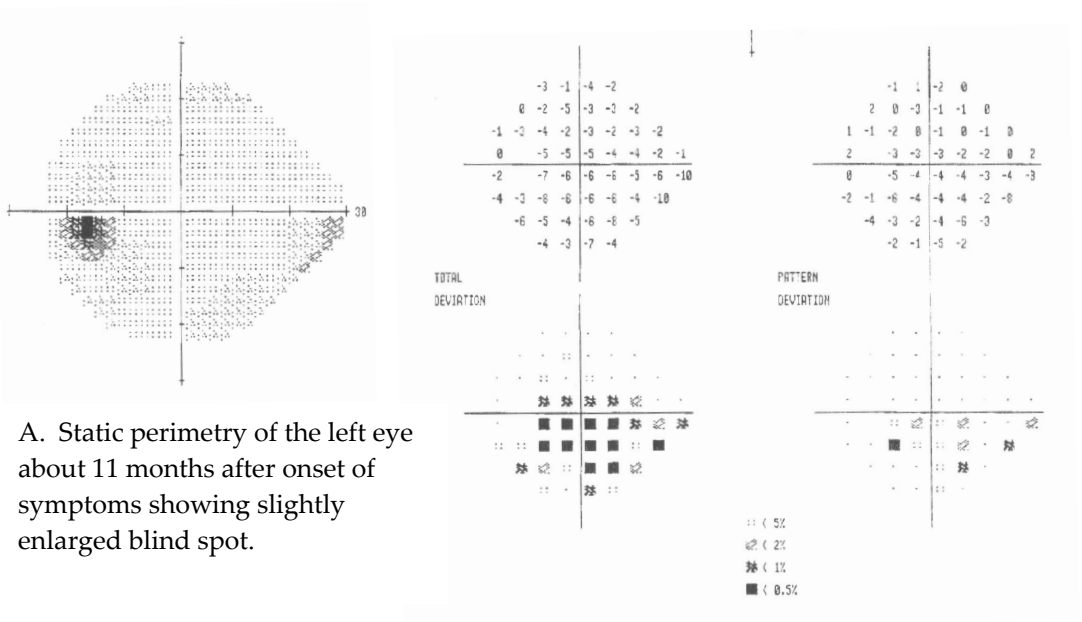
D. Left optic disc 1-1/2 months after completion of treatment showing dramatic reduction in disc edema.

Figure 7. Clinical images from patient 6.

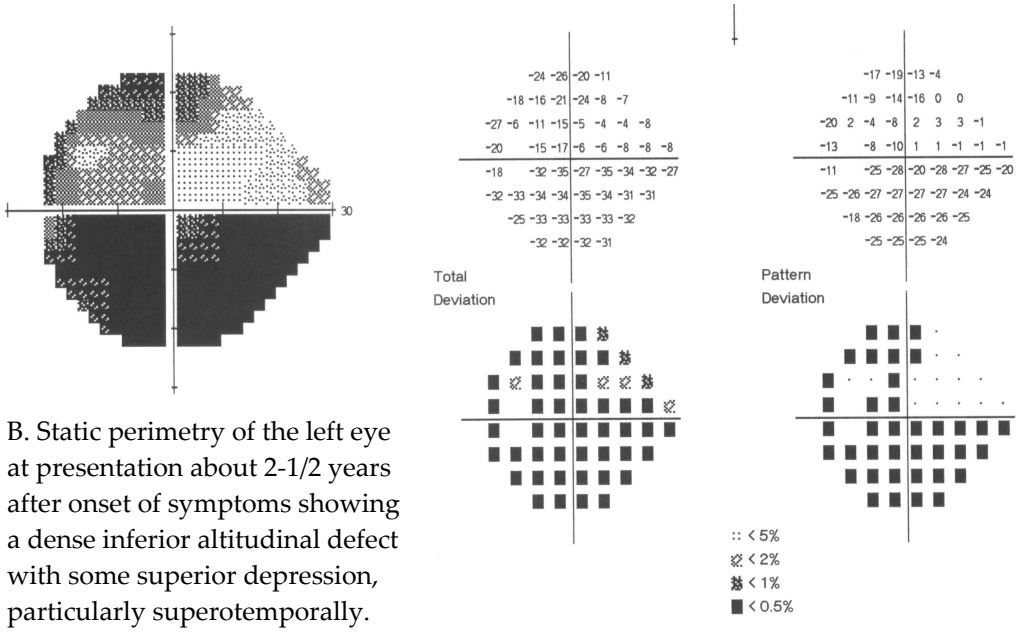
Patient 7

A 51-year-old woman was referred for evaluation of an approximate 2-1/2 year history of progressive visual loss in her left eye. She also described transient blurring of vision while lifting weights. About 6 months after the onset of symptoms, an optometrist noted a unilateral swollen elevated disc with mild vessel tortuosity but her VA was 20/20 OU. She was subsequently evaluated by a neurologist and two neuro-ophthalmologists, and she underwent an inconclusive diagnostic workup that included two negative orbital MRIs, a normal lumbar puncture, a negative vasculitis workup, negative Lyme titers, and a multifocal electroretinogram showing diffuse depression. During this time her vision continued to decrease slowly, progressively, and painlessly. About 2 months prior to presentation, she was seen by another ophthalmologist for a corneal abrasion and referred again for neuro-ophthalmic consultation. A review of systems was negative except for sporadic bitemporal headaches of moderate intensity relieved by ibuprofen, and joint pain; she took no medications. Examination revealed VA of 20/15 OD and 20/50 blurred OS, a 1.8 log unit left relative APD, normal motility, and a normal external exam without proptosis. She correctly identified 15/15 Ishihara color plates with her right eye but 0/15 with her left eye, and red saturation in the left eye was only 5% relative to the right. There was diffuse elevation of the left optic disc without hemorrhages but with some temporal atrophy, minimal venous tortuosity most markedly inferiorly, and gliosis most marked nasally. No optociliary shunt vessels were seen. Automated static perimetry showed a dense inferior altitudinal defect with some superior depression, particularly superotemporally, in the left eye. Brain and orbital MRI now showed a subtle focal enhancement of the left optic nerve at the level of the optic canal and the annulus of Zinn; the enhancement on a subsequent repeat MRI was noted to have a tram-track appearance. CT imaging of the head revealed no abnormalities. The patient underwent 3DCFR, receiving 50.36 Gy in 28 fractions over 38 days. She experienced mild fatigue that

resolved, and noted some subjective improvement in her vision toward the end of her treatment course. She has been followed for 15 months with no delayed radiation side effects. On examination, her best corrected VA was 20/15 OD and 20/40 OS, she had a 0.6 log unit left relative APD, her color vision was unchanged, her left disc was flat and atrophic, and her VF showed slight improvement compared to her pre-treatment VF. Her MRI appearance has been stable without progression in the size of her tumor.

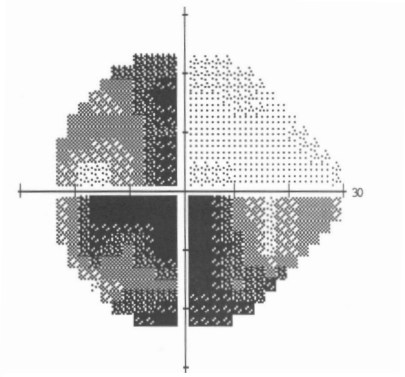


A. Static perimetry of the left eye about 11 months after onset of symptoms showing slightly enlarged blind spot.

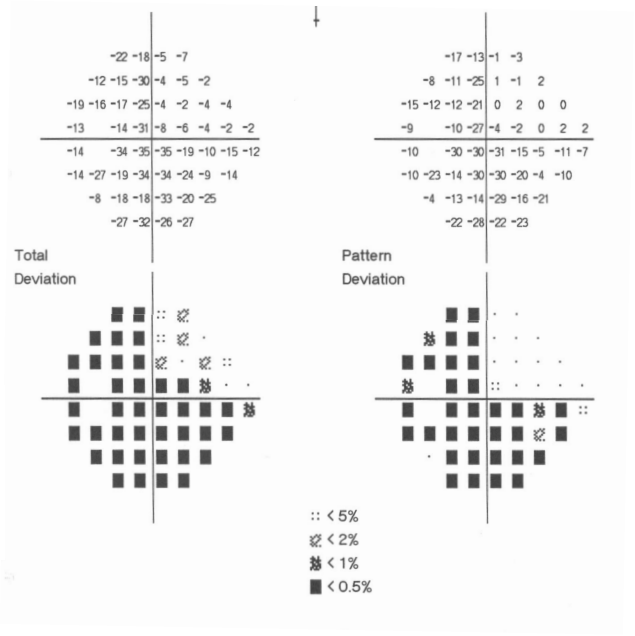


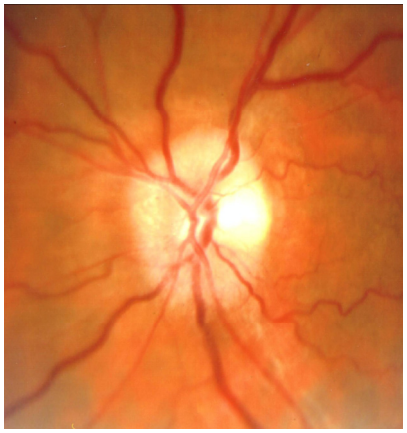
B. Static perimetry of the left eye at presentation about 2-1/2 years after onset of symptoms showing a dense inferior altitudinal defect with some superior depression, particularly superotemporally.

Figure 8. Clinical images from patient 7.

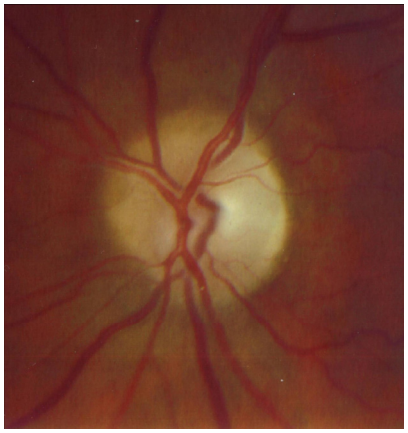


C. Static perimetry of the left eye 11 months after completion of treatment showing slight improvement.





D. Left optic disc at presentation showing diffuse elevation of the left optic disc without hemorrhages but with some temporal atrophy, minimal venous tortuosity most markedly inferiorly, and gliosis most marked nasally.



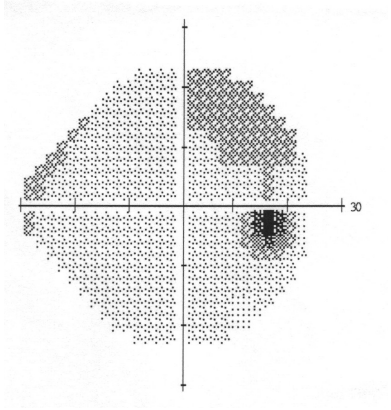
E. Left optic disc 1 month after completion of treatment showing resolution of edema with development of optic atrophy.

Figure 8. Clinical images from patient 7. (continued)

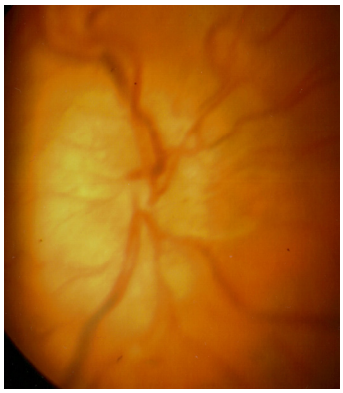
Patient 8

A 58-year-old woman was referred emergently by a comprehensive ophthalmologist for evaluation of the sudden onset of transient blurred vision. Two weeks prior to presentation, she noted painless transient blurred vision in each eye, lasting for about an hour. She also noted white lights in the peripheral field of vision lasting for a few seconds associated with standing from a seated position; these continued to occur intermittently. She had no headache or diplopia associated with any of these symptoms. She had a history of episodes of scintillating scotomas consistent with a migraine, but those were dissimilar to these symptoms. Her past medical history included Graves' disease treated with radioactive iodine, hypercholesterolemia, and osteoporosis; she had no history of hypertension. A review of systems was negative other than skin rash and dizziness. Her medications included atorvastatin, alendronate, and levothyroxine. Examination revealed VA of 20/20 OU, no relative APD, intact color vision OU, normal external exam with no proptosis, and full motility. There was diffuse 360-degree edema of the right disc, most marked inferiorly, without hemorrhages, as well as a question of a plaque in the inferior arcade. No optociliary shunt vessels were seen. Fundoscopy of the left eye was normal other than a question of minimal temporal pallor. Automated static perimetry showed some superotemporal depression with slight enlargement of the blind spot in the right eye, and a normal field in the left. Initial diagnosis favored non-arteritic anterior ischemic optic neuropathy, but an orbital MRI was ordered and showed an enlarged right optic nerve with nodular peripheral enhancement in a tram-track pattern along nearly all of the intraorbital optic nerve as well as along the cisternal portion of the nerve extending almost up to the chiasm. A head CT showed enhancement surrounding the right optic nerve correlating with the MRI findings. A pulmonology evaluation, including a chest CT, ruled out sarcoidosis, making ONSM the presumed diagnosis. The patient continued to experience episodic transient blurry vision but her

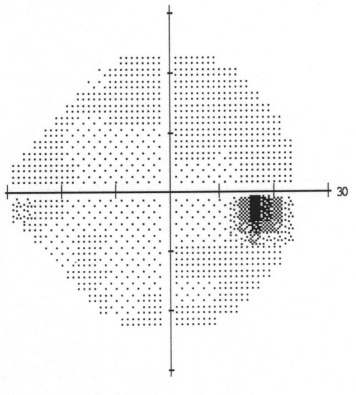
VA continued to be normal. She was treated with 3DCFR, receiving 50.41 Gy in 28 fractions over 45 days. She had focal alopecia and mild fatigue associated acutely with RT, and she noted a subjective improvement in her symptoms after treatment. She has been followed for 26 months with no late complications from RT. Her right disc edema resolved with no or minimal pallor and minimal nasal fullness. Her visual symptoms have resolved, her VA has remained at 20/20 OU, her VF has improved in her right eye, and the MRI appearance of her optic nerve has been stable.



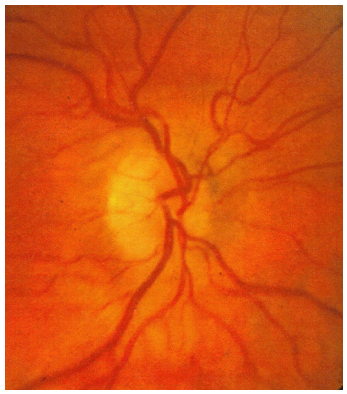
A. Static perimetry of the right eye at presentation showing some superotemporal depression with slight enlargement of the blind spot in the right eye.



B. Right optic disc at presentation showing diffuse 360-degree edema of the right disc, most marked inferiorly.



C. Static perimetry of the right eye 2 months after completion of treatment showing improvement.



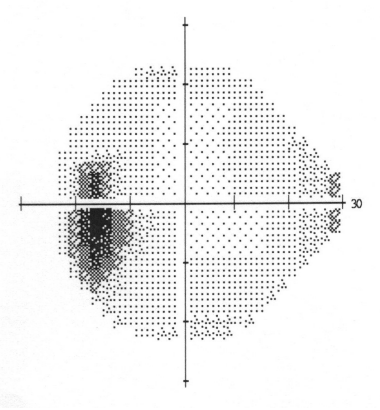
D. Right optic disc 2 months after completion of treatment showing significant clearing of edema.

Figure 9. Clinical images from patient 8.

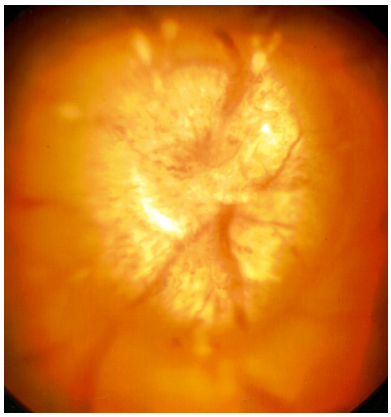
Patient 9

A 60-year-old woman was referred for evaluation of a 9-month history of episodic transient monocular visual loss in the left eye. She described episodes of abrupt-onset complete loss of vision in her left eye that rapidly subsided within seconds, occurring up to a dozen or more times in a day without any apparent trigger and with no other associated symptoms. She underwent a cardiologic workup that included an electrocardiogram, echocardiogram, stress test, Holter monitoring, serum studies, and chest CT; only an incidental pericardial effusion and moderate tricuspid insufficiency were found. She was also referred for neurologic evaluation, which included an MRI/MRA, carotid duplex ultrasound, visual evoked potentials, and lumbar puncture. Her MRI revealed a circumferential enhancement along entire length of the left ONS, and her visual evoked potential latency was significantly greater in her left nerve versus her right nerve. On the diagnosis of atypical optic neuritis, she was given a short trial of oral methylprednisolone during which the episodes of transient visual loss subsided. However, a repeat MRI revealed that the degree of enhancement of the ONS had worsened with new soft tissue thickening, and she was referred for neuro-ophthalmic evaluation. Her past medical history and review of systems revealed the cardiac abnormalities mentioned, dry eyes, resection of an ovarian cyst, appendectomy, gestational diabetes, and nephrolithiasis. Her medications included artificial tears, alendronate, calcium, and multivitamins. Examination revealed VA of 20/15 OD and 20/20 OS, no relative APD, intact color vision, and a normal external exam with no exophthalmos or limitation of motility. The left optic disc was markedly elevated with multiple hemorrhages and exudates consistent with grade IV edema. Optociliary shunt vessels were not seen. The right optic disc was normal. Automated static perimetry showed an enlarged blind spot with some inferonasal depression OS. A diagnosis of ONSM was made on the basis of clinical presentation and a review of the patient's MRIs. She was treated with 3DCFR, receiving

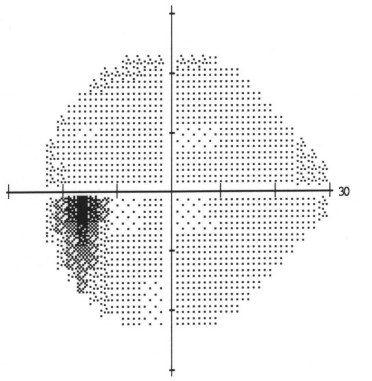
50.4 Gy in 28 fractions over 37 days. She reported that her symptoms subjectively began to improve during the course of treatment. She had no acute side effects other than transient focal alopecia. She has been followed for 7 months with a stable VA, full VF, cessation of her episodes of visual loss, and resolution of her optic disc edema with no development of atrophy. She has had no late complications from RT and her MRI appearance has been stable.



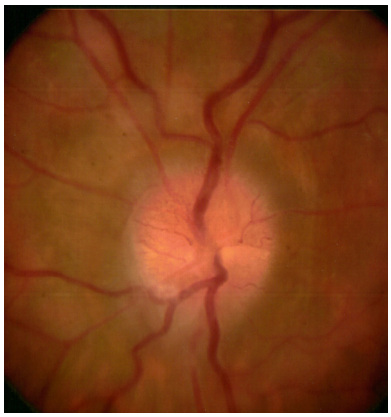
A. Static perimetry of the left eye at presentation showing an enlarged blind spot with some inferonasal depression.



B. Left optic disc at presentation showing marked elevation with multiple hemorrhages and exudates consistent with grade IV edema, and the presence of Weiss' line.



C. Static perimetry of the left eye 7 months after completion of treatment showing improvement.



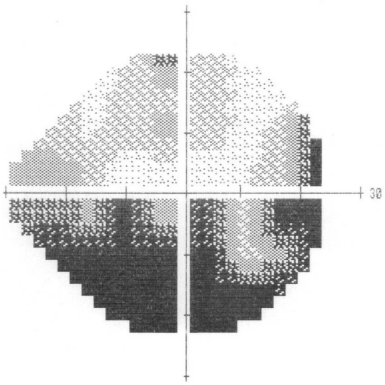
D. Left optic disc 1 month after completion of treatment showing dramatic improvement with grade II edema. The appearance was further improved at 7-month follow-up.

Figure 10. Clinical images from patient 9.

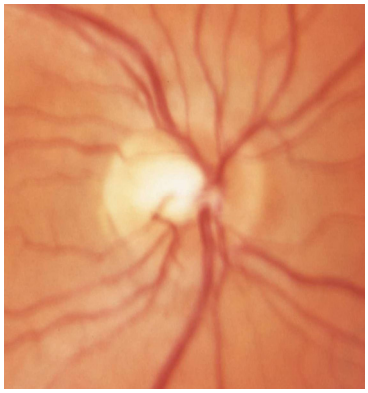
Patient 10

A 47-year-old woman was referred for evaluation of a 4-month history of awareness of a visual field defect inferiorly in her right eye. She described a new intermittent awareness of the visual field defect, as well as some associated sensation of retro-orbital pressure and discomfort. She had a history of amblyopia with decreased vision in that eye, but her visual symptoms were of new onset, and she reportedly had 20/20 corrected VA previously. Her medical history included hypertension, migraine headaches, and arthritis. A review of systems was otherwise negative. Her medications included verapamil and estrogen/medroxyprogesterone hormone replacement therapy. Examination revealed VA of 20/70 OD and 20/15 OS, a minimal relative APD OD, intact color vision, and a normal external exam with no exophthalmos or limitation of motility. The right optic disc was flat and pink with hyperemia nasally and no hemorrhages, exudates, or optociliary shunt vessels; the left disc was normal. Amsler grid testing was abnormal OD with the inferotemporal field appearing blurry. Automated static perimetry showed an inferior defect in the right eye, denser nasally, respecting the horizontal meridian. An orbital MRI was ordered, which showed an enlarged right ONS with diffuse enhancement in a tram-track pattern extending from the retrobulbar region into the optic canal. A diagnosis of ONSM was made on the basis of the radiographic appearance and clinical presentation. She was treated with conformal IMRT, receiving 45 Gy to the 85% isodose surface in 25 fractions over 36 days. Acutely she had minor alopecia that resolved, and she reported some subjective improvement in her field of vision and brightening of her vision in the right eye while in the course of treatment. One month after completion of treatment, her VA had improved to 20/30 OD and her VF defect was less dense than prior to treatment, although she continued to have a 0.6 log density relative APD OD. However, she subsequently noticed a gradual decrease in vision; by 5 months after her treatment, her VA had decreased to 20/80 OD, her VF showed

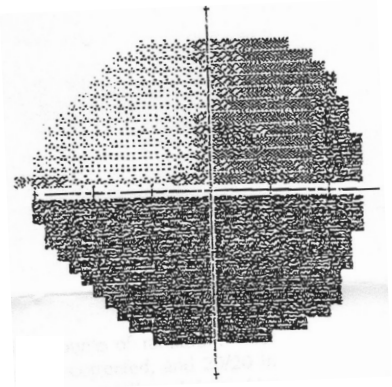
further loss superonasally OD, and she developed diffuse disc edema OD. She also developed retro-orbital discomfort. Repeat MRI revealed increased contrast enhancement in the region of her ONSM. She was given a course of oral dexamethasone with a dramatic recovery of VA and VF as well as improvement in retro-orbital discomfort. Additionally, during this time she experienced the recrudescence of her menstrual periods and the onset of continually feeling warm, which her endocrinologist attributed to hypothalamic dysfunction due to radiation, though details of her endocrinologic workup were unavailable. Subsequent MRI follow-up demonstrated no further increase in the size of her tumor, and the most recent follow-up MRI 87 months after completion of RT in fact demonstrated a slight decrease in the size of the ONSM. She has been followed for 95 months after the completion of her RT with a stable clinical course with a VA of 20/60 OD and a persistent stable inferior defect in her VF.



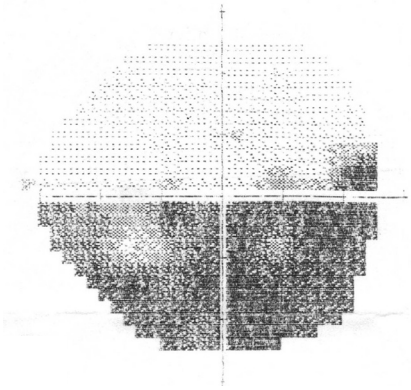
A. Static perimetry of the right eye at presentation showing an inferior defect in the right eye respecting the horizontal meridian.



B. Right optic disc at presentation showing hyperemia nasally.



C. Static perimetry of the right eye 3 months after completion of therapy showing further loss of visual field.



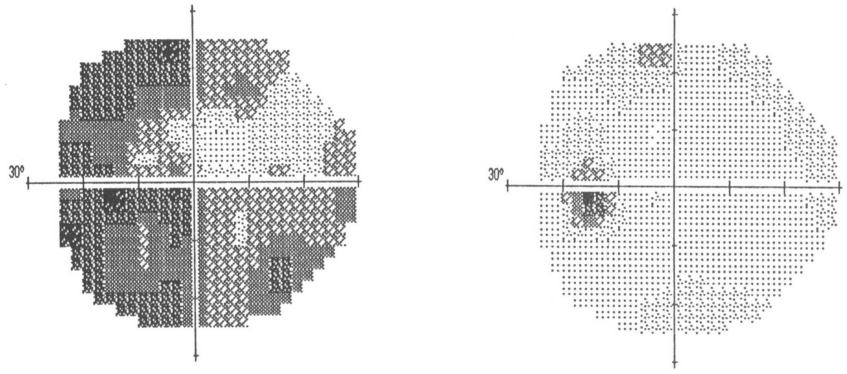
D. Static perimetry of the right eye after a short course of corticosteroids showing marked recovery.

Figure 11. Clinical images from patient 10.
Fundus photograph after treatment were not available.

Patient 11

This patient was evaluated and treated in Cincinnati, and followed at Yale.

A 36-year-old woman was referred for evaluation of a 2-month history of unilateral blurred vision in the left eye. She was otherwise asymptomatic and only became aware of the blurred vision when she tried to perform direct ophthalmoscopy. A comprehensive ophthalmologist noted an APD, proptosis, and optic disc swelling, and ordered CT and MRI scans that were consistent with an intraorbital ONSM. Her past medical history included hypothyroidism not secondary to treated hyperthyroidism, and her medications included levothyroxine. Examination revealed a VA of 20/20 OD and 20/200 OS, a moderate left relative APD, 3 mm of proptosis and periorbital edema on the left side, and no gross limitation of motility. She identified 15/15 Ishihara color plates with the right eye but none with the left. Her left optic disc was mildly swollen without optociliary shunt vessels; the right disc was normal. Automated static perimetry of the left eye showed marked abnormalities with deficits in the temporal field worse than in the nasal field. A diagnosis of ONSM was made on the basis of radiographic and clinical presentation. She was treated with 3DCFR, receiving 50.40 Gy in fractions. She reported no side effects during the treatment but experienced subjective improvement in vision very quickly. Her VA subsequently improved to 20/15 OU, which has remained stable over the 124-month follow-up period. She had a residual minimal early pupillary escape, and her proptosis resolved. Her optic disc swelling resolved with development of temporal disc pallor and diffuse nerve fiber layer loss. The radiographic appearance of her ONSM has remained stable.



A. Static perimetry at presentation showing marked abnormalities with deficits in the temporal field worse than in the nasal field.

B. Static perimetry 3 months after completion of treatment showing marked improvement to an almost normal field.

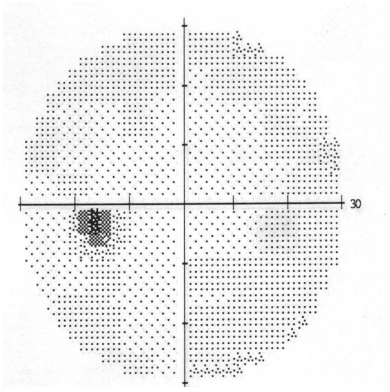
Figure 12. Clinical images from patient 11.
Fundus photographs at presentation were not available.

Patient 12

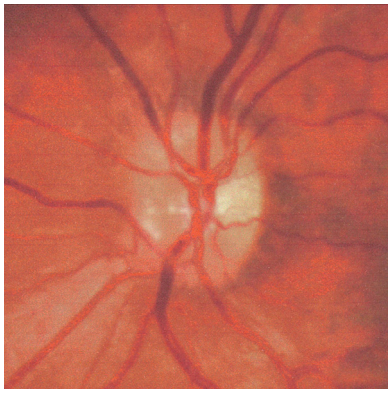
This patient did not receive her radiation treatment at Yale.

A 22-year-old woman was referred for evaluation after an MRI, performed in the workup for secondary amenorrhea, showed a mass involving the left optic nerve that was consistent with an ONSM. She had no other symptoms, and she reported that an initial endocrine workup had been normal. Her past medical history included depression and anxiety, and she was taking no medications other than vitamins, flaxseed oil, and cod liver oil. Examination revealed a VA of 20/15 OD and 20/20 OS, no relative APD, intact color vision, and a normal external exam without exophthalmos or limitation of motility. Her left optic disc was elevated, most markedly nasally, superiorly, and inferiorly, and showed no atrophy or optociliary shunt vessels; her right disc was normal in appearance. Automated static perimetry of the left eye showed a spot of depression

inferonasal to central fixation, of unclear significance. MRI showed a left periclinoidal enhancing lesion about 15 mm in greatest diameter extending into the optic canal with a dural tail tracking along the dura through the optic canal. CT imaging showed some abnormal calcification in the lesion, which produced mass effect on the adjacent sphenoid sinus and an enlarged optic foramen without bony reaction in the anterior clinoid or sphenoid. A diagnosis of ONSM was made on the basis of radiographic and clinical presentation. The patient was treated with SFR, receiving 46.80 Gy in 26 fractions over 33 days. She reported no acute side effects, and she has been followed for 12 months with no delayed side effects. She has had resolution of her optic disc swelling without evidence of atrophy, maintenance of her VA at 20/20 or better OU, full visual fields, and stable MRI appearance. Interestingly, her menstrual periods returned about 9 weeks after completion of RT.



A. Static perimetry of the left eye at presentation showing a spot of depression inferonasal to central fixation, of unclear significance.



B. Left optic disc at presentation showing elevation, most markedly nasally, superiorly, and inferiorly.

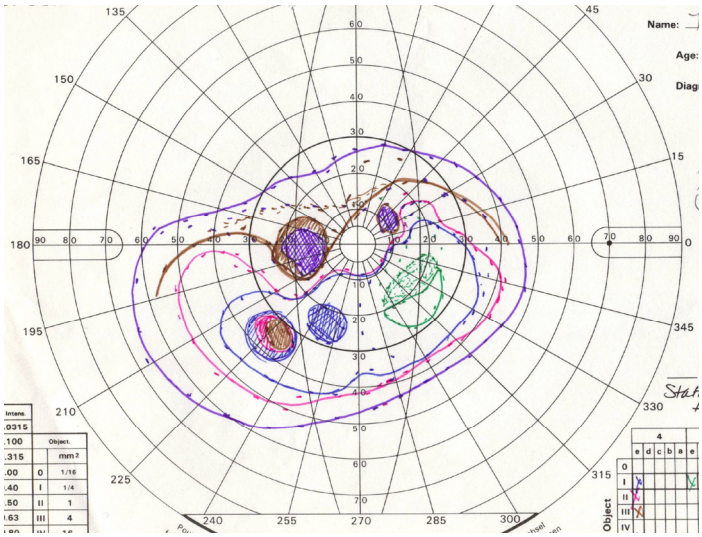
Figure 13. Clinical images from patient 12.
Fundus photographs from after treatment were not available.

Patient 13

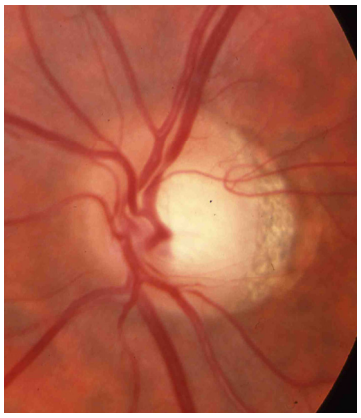
This patient underwent surgical resection followed by SRS for recurrence.

A 38-year-old man was referred for a second opinion in the evaluation of an 8-month history of progressive visual loss in the left eye. He initially had a VA of 20/15 OU when his visual loss began as a small scotoma; it progressed to cause blurry vision in the left eye with an abnormal visual field test. An initial MRI was negative, but repeat scans showed a small focal area of enlargement of the intracanalicular portion of the left optic nerve with abnormal enhancement. A review of systems was negative other than a minor head injury from a motor vehicle accident, and the patient was on no medications. Examination revealed VA of 20/15 OD and 20/40 OS with difficulty, a 1.8 log unit left relative APD, normal motility, and 2 mm proptosis of the left eye on Hertel exophthalmometry. On color testing, the patient identified 15/15 Ishihara plates correctly OD but only 10/15 OS, and red saturation on the left was only 30% that on the right. The left optic disc was tilted with a diffuse temporal crescent but no atrophy, edema, or optociliary shunt vessels were seen. Goldmann perimetry demonstrated multiple paracentral scotomas and superotemporal depression in the left eye. A repeat MRI showed abnormal signal enhancement through the entire cross section of and along a 10 mm length of the left optic nerve, an appearance uncharacteristic of meningioma. A short corticosteroid trial did not halt the progression of visual loss. A workup for sarcoidosis, occult malignancy, vasculitis, and other inflammatory etiology including silent endocarditis was negative. An electroretinogram and echocardiogram were normal. A lumbar puncture showed slightly elevated protein that could be associated with demyelinating disease or tumor. With a negative workup, clinical suspicion favored an ONSM, and a decision was made to obtain a biopsy. By the time the biopsy was performed, 7 months since presentation, the patient's VA had deteriorated to light perception only (LP) in the left eye, and his left optic disc showed temporal pallor. A left frontotemporal

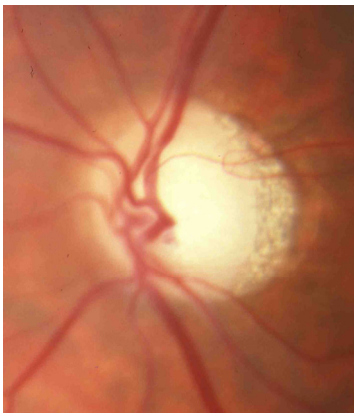
craniotomy was performed and a gross total resection was performed. Microscopic examination revealed both interlacing bundles of spindle cells and nests of cells with poorly delineated cytoplasm, with occasional whorls and psammoma bodies seen; a histologic diagnosis of ONSM was thus made. The patient recovered from surgery uneventfully, but he lost all vision in the left eye within a year. A slight increase in size of the residual intracanalicular tumor was seen 62 and 74 months after surgery on follow-up MRI. The recurrence was treated by gamma knife SRS, with 20 Gy prescribed to the 50% isodose surface in one fraction. The patient has been followed for 98 months after SRS without late complications or radiographic progression.



A. Goldmann perimetry of the left eye at presentation showing multiple paracentral scotomas and superotemporal depression.



B. Left optic disc 1-1/2 months after presentation, showing a tilted disc with a temporal crescent with 0.7 sloping, and inferior sector pallor without edema.



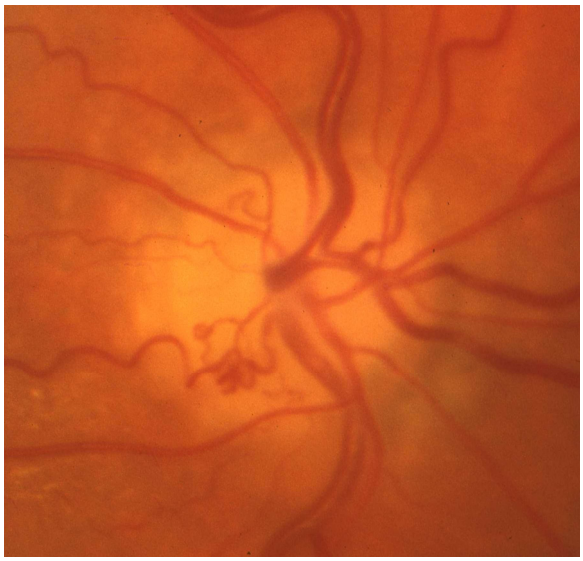
C. Left optic disc 1-1/2 months after surgery showing diffuse atrophy.

Figure 14. Clinical images from patient 13.

Patient 14

This patient was followed by observation only.

A 63-year-old man was referred for evaluation of unilateral blindness in the right eye after an ophthalmologist ordered a MRI and CT scan that were consistent with ONSM. He had amblyopia OD due to strabismus in childhood, and as an adult his best vision in that eye was LP. However, he became aware that he had lost all vision in the right eye after he sustained a corneal abrasion in the left eye. He had no other symptoms. A review of systems was unremarkable other than chronic nephritis, a history of headaches, osteoarthritis, and hypertension; his medications included nifedipine, hydrochlorothiazide, atenolol, potassium chloride, nabumetone, and aspirin. Examination revealed no light perception (NLP) OD with an amaurotic pupil, a VA of 20/20 OS, no exophthalmos, and no limitation of motility with a 60 prism diopter right exotropia. The right optic nerve was elevated with early branching of the disc and diffuse pallor, with optociliary shunt vessels seen most markedly in the inferotemporal disc margin; the left optic nerve was unremarkable. MRI showed enlargement and faint enhancement of the mid and posterior thirds of the right optic nerve extending into the optic canal but not involving the chiasm; there was atrophy of the intracranial portion of the nerve. An incidental 1-cm right frontoparietal convexity meningioma was also seen. CT imaging showed calcifications in the lesion. A diagnosis of ONSM was made on the basis of radiographic and clinical presentation. The patient elected to be followed conservatively with MRI and VF testing in the uninvolved eye. He was followed for 11-1/2 years with no morbidity from the ONSM except for minimal proptosis. There was no radiographic progression in the size of his ONSM, although the frontal convexity meningioma did increase in size. He was deceased of unrelated causes at the age of 75.



A. Right optic disc at presentation showing elevation with early branching of the disc and diffuse pallor, with optociliary shunt vessels seen most markedly in the inferotemporal disc margin. This appearance was unchanged in follow-up.

Figure 15. Clinical image from patient 14.

Summary of cases

The clinical characteristics, testing and imaging characteristics, dose prescriptions, and treatment outcomes are summarized in Table A, Table B, Table C, and Table D. Fourteen patients with primary ONSM were identified (follow-up 7 mos to 11.5 yrs). Nine patients (patients 1-9) were treated at Yale with 3DCFR and received 45.00 to 52.19 Gy in 25 to 29 fractions and were followed for 7 to 96 months (mean 43.3 mos, median 34 mos). One was treated with IMRT at Yale, receiving 45.00 Gy in 25 fractions (patient 10, follow-up 95 mos). One received 3DCFR at a total dose of 50.40 Gy at another center (patient 11, follow-up 124 mos), and one received 46.80 Gy in 26 fractions using SFR at another center (patient 12, follow-up 12 mos). One patient received surgery followed later by 20 Gy by single-fraction SRS due to recurrence, and one was followed by observation only. For the 10 patients who received 3DCFR, the follow-up was 7 to 124 mos (mean 46.2 mos, median 34 mos). None of the patients had an associated history of neurofibromatosis, and only patient 14 had another meningioma, in the frontal convexity.

The mean age at presentation was 45.6 (range 16-63) with 10 female and 4 male patients. Initial VA in the affected eye were: 20/20 or better, 10; 20/25 to 20/200, 3; and NLP, 1. The most common presenting symptom was blurred vision, which affected 7 patients. Other presenting symptoms were awareness of VF loss in 2, transient visual loss in 1, complete loss of vision in 1, discomfort or tenderness in 2, and metamorphopsia in 1. One patient presented because of secondary amenorrhea, and one was initially asymptomatic but had decreased vision found on a routine screening exam. In the affected eye, relative APD was present in 8 patients, abnormal color vision was present in 4, and proptosis was noted in 3; none of these correlated with VA. Optic disc swelling or edema was present in 9, pallor or atrophy was present in 5, and optociliary shunt vessels were seen in 1. Only patient 14 had the classic triad of visual loss, pallor, and shunt vessels. One patient had a normal VF; the others had abnormalities. Other ocular diagnoses that affected VA and/or VF in the ONSM-affected eye in this cohort include low-tension glaucoma and cataract in 1 patient and amblyopia in 2 patients.

Radiography played an important role in diagnosis and follow-up; however, 4 patients (patients 3, 6, 7, and 13) initially had imaging that was read as normal. All patients eventually had abnormal imaging. The radiographic appearance of the ONSM was tubular in 8 patients, fusiform in 3, and focal in 3. Most patients (10 of 14) had involvement of the orbital portion of the optic nerve; of those, 5 were entirely intraorbital. Three patients had entirely intracanalicular tumors.

Antecedent diagnoses given before the final diagnosis of ONSM included: optic neuritis, optic disc drusen, large blind spot syndrome, non-arteritic anterior ischemic optic neuropathy, and retinal disease.

Outcomes were generally favorable with stable or improved vision and radiographic appearance in 12 of 12 patients overall who received primary RT, 10 of 10 patients who received

3DCFR, and 9 of 9 patients who received 3DCFR at Yale. For those 11 patients who received primary RT and for whom data are available, the mean deviation on automated static perimetry improved slightly from -8.86 dB pre-treatment to -6.87 dB post-treatment but was statistically stable ($p = 0.1$, two-tailed paired *t*-test). Subjective evaluation of the VF defects were also stable or improved in all patients after treatment (though it did later worsen in patient 4 from glaucoma). Three patients had radiographic improvement: one (patient 1) with a slight decrease in enhancement, one with disappearance of the tumor from imaging (patient 4), and one (patient 10) with a decrease in the size of the tumor after initial enlargement followed by a period of stabilization. The other 11 patients had stable radiographic appearance without progression.

Acute toxicity was generally mild, with focal alopecia in 4 patients, fatigue in 5, mucositis (limited inflammation of mucous membranes) in 1, and nausea in 1. These side effects were all transient and self-limited. Patient 10, who received IMRT, developed optic nerve edema that resolved with a course of corticosteroids; she also had mild pituitary axis toxicity diagnosed by an endocrinologist on the basis of recrudescence of her menstrual periods and development of heat intolerance. One patient (patient 1) developed dry eye syndrome 4 years after treatment.

Table A. Clinical characteristics of the patients in the current series.

Patient	Age/sex	Side	Initial VA*	Presenting symptoms	APD*	Color vision*	Proptosis*	Optic disc abnormalities*	Time to diagnosis	Ocular/neurologic history
1	46 M	R	20/20	Metamorphopsia	No	Normal	3 mm	Swelling, hyperemia	11 mos	Convergence insufficiency
2	16 F	L	20/80	Asymptomatic	Yes	0/15	None	Pallor, peripapillary halo	17 mos	Headache
3	49 F	L	20/15	Blurriness	Yes	Mild defect	None	Pallor	26 mos	Migraine headache
4	56 M	R	20/20	VF loss	No	Normal	None	Pallor, cupping	10 mos	Low-tension glaucoma*, cataract*
5	46 F	R	20/20	Transient blurriness, tenderness	Yes	Normal	None	Swelling, pseudodrusen	5 mos	Migraine headache
6	51 F	L	20/15	Transient blurriness	No	Normal	None	Swelling, hyperemia	6 mos	
7	51 F	L	20/20	Transient blurriness	Yes	0/15	None	Swelling, pallor	29 mos	Headaches
8	58 F	R	20/20	Transient blurriness	No	Normal	None	Swelling	1 mo	Ocular migraine, Graves' disease
9	60 F	L	20/20	Transient visual loss	No	Normal	None	Swelling, hemorrhages, exudates	9 mos	Dry eye syndrome
10	47 F	R	20/70	VF loss, discomfort	Yes	Normal	None	Hyperemia	4 mos	Amblyopia*, migraine headache
11	36 F	L	20/200	Blurriness	Yes	0/15	3 mm	Swelling	2 mos	Headache
12	22 F	L	20/20	Amenorrhea	No	Normal	None	Swelling	1 mo	

13	38 M	L	20/15	Blurriness	Yes	Normal	2 mm	Crescent	15 mos	
14	63 M	R	NLP	Blindness	Yes	NLP	None	Swelling, pallor, shunt vessels	7 yrs	Amblyopia*

Abbreviations: APD, afferent papillary defect; F, female; L, left; mo, month; M, male; NLP, no light perception; R, right; VA, Snellen visual acuity; VF, visual field; yrs, years.

*in the eye affected by ONSM.

Table B. Visual field and radiographic characteristics of the patients in the current series.

Patient	Initial VA	Initial VF mean dev	VF defect	Location	Morphology	Tram-tracking	Initial imaging
1	20/20	+2.13 dB	Normal	Orbital	Tubular		Abnormal
2	20/80	-29.64 dB	Diffuse	Orbital/cananicular/intracranial	Tubular	Yes	Abnormal
3	20/15	-8.36 dB	Temporal	Canalicular	Focal		Normal
4	20/20	-6.24 dB	Superior arcuate	Orbital	Focal		Abnormal
5	20/20	-5.72 dB	Multiple scotomas	Orbital/canalicular	Tubular	Yes	Abnormal
6	20/15	-0.91 dB	Enlarged blind spot	Orbital	Tubular	Yes	Normal
7	20/20	-2.72 dB	Inferior altitudinal	Canalicular	Tubular	Yes	Normal
8	20/20	-7.68 dB	Superotemporal	Orbital/canalicular	Tubular	Yes	Abnormal
9	20/20	-2.46 dB	Inferonasal	Orbital/canalicular	Tubular	Yes	Abnormal
10	20/70	-21.25 dB	Inferior	Orbital	Fusiform	Yes	Abnormal
11	20/200	-14.55 dB	Diffuse	Orbital	Fusiform		Abnormal
12	20/20	-1.91 dB	Scotoma	Intracranial	Tubular		Abnormal
13	20/15	-9.72 dB	Multiple scotomas	Canalicular	Focal		Normal
14	NLP	NLP	NLP	Orbital/canalicular	Fusiform		Abnormal

Abbreviations: dB, decibel; dev, deviation; NLP, no light perception; VA, Snellen visual acuity; VF, visual field.

Table C. Dose prescriptions to target and dose-limiting structures for 3DCFR performed at Yale.

Patient		1	2	3	4	5	6	7	8	9	Mean	Median	Range
Prescribed dose		45.0	52.2	50.4	50.4	50.4	50.4	50.4	50.4	50.4	50.0	50.4	45.0-52.2
Maximum dose		45.5	51.7	51.2	49.6	51.8	50.6	51.3	50.9	51.3	50.4	51.1	45.5-51.7
Absorbed dose		45.0	52.2	50.4	50.3	50.2	50.3	50.4	50.4	50.4	50.0	50.4	45.0-52.2
MDPD		1.01	0.99	1.02	0.98	1.03	1.00	1.02	1.01	1.02	1.01	1.01	0.98-1.03
Fractions		25	29	28	28	28	28	28	28	28	27.8	28	25-29
Beams		3	3	3	3	3	3	3	4	4	3.2	3	3-4
Contralateral ON dose	Maximum	0.4	2.3	11.8	13.2	1.8	14.8	14.0	20.6	7.0	9.6	11.8	0.4-20.6
	Average	0.4	1.1	11.5	13.0	0.5	5.3	13.5	12.5	1.4	6.6	5.3	0.4-13.5
Optic chiasm dose	Maximum	24.9		49.3		50.5	50.0	10.1	50.5	50.6	40.8	50.0	10.1-50.6
	Average	3.7		23.0		28.4	20.1	2.5	34.0	19.3	18.7	20.1	2.5-34.0
Ipsilateral eye dose	Maximum	20.2	50.5	47.5	50.0	49.6	19.3	51.1	50.2	50.5	43.2	50.0	19.3-51.1
	Average	3.1	11.2	7.2	19.6	8.8	1.7	5.8	8.5	13.4	8.8	8.5	1.7-19.6
Pituitary dose	Maximum	0.8	0.9	31.2		48.5	19.1	2.6	23.4	44.4	21.4	21.3	0.8-48.5
	Average	0.5	0.6	25.3		26.0	14.6	2.1	15.1	19.4	12.9	14.8	0.5-26.0

Abbreviations: 3DCFR, three-dimensional conformal fractionated radiotherapy; MDPD, ratio of maximum dose to prescribed dose; ON, optic nerve.

Table D. Treatment outcomes of the patients in the current series.

Patient	Initial VA	Pre-tx VA	Initial VF mean dev	Pre-tx VF mean dev	Treatment	Dose	Post-tx VA	Final VF mean dev	Acute toxicity	Late complications	MRI follow-up	Follow-up
1	20/20	20/20	+2.13 dB	+2.13 dB	3DCFR	45.00 Gy (1.8 x 25)	**20/15**	**+2.73 dB**	Alopecia*, nausea	Dry eye syndrome	Slight decrease in enhancement	96 mos
2	20/80	20/200	-29.64 dB	-30.10 dB	3DCFR	52.19 Gy (1.8 x 29)	**20/100**	**-23.27 dB**	Fatigue	None	Stable	58 mos
3	20/15	20/15	-8.36 dB	-19.52 dB	3DCFR	50.36 Gy (1.8 x 28)	**20/20**	NA	Fatigue	None	Stable	14.5 mos
4	20/20	20/20	-6.24 dB	-6.42 dB	3DCFR	50.30 Gy (1.8 x 28)	**20/15**	**-8.22 dB**	Fatigue	None	Tumor no longer seen	57 mos
5	20/20	20/20	-5.72 dB	-1.37 dB	3DCFR	50.25 Gy (1.8 x 28)	**20/20**	**+1.56 dB**	Mucositis	None	Stable	38 mos

6	20/15	20/15	-0.91 dB	-0.91 dB	3DCFR	50.34 Gy (1.8 x 28)	**20/15**	**+1.23 dB**	None	None	Stable	30 mos
7	20/20	20/50	-2.72 dB	-22.61 dB	3DCFR	50.36 Gy (1.8 x 28)	**20/40**	**-17.60 dB**	Fatigue	None	Stable	11 mos
8	20/20	20/20	-7.68 dB	-1.78 dB	3DCFR	50.41 Gy (1.8 x 28)	**20/20**	**-1.76 dB**	Alopecia*, fatigue	None	Stable	26 mos
9	20/20	20/20	-2.46 dB	-2.46 dB	3DCFR	50.40 Gy (1.8 x 28)	**20/25**	**-2.05 dB**	Alopecia*	None	Stable	7 mos
10	20/70	20/70	-21.25 dB	-20.78 dB	IMRT	45.00 Gy (1.8 x 25)	**20/30, later 20/60**	**-23.51 dB**	Alopecia*, optic nerve edema	Pituitary axis toxicity	Enlargement, then stabilization, then decrease in size	95 mos
11	20/200	20/200	-14.55 dB	-11.58 dB	3DCFR	50.40 Gy (1.8 x 28)	**20/15**	**-2.13 dB**	None	None	Stable	124 mos
12	20/20	20/20	-1.91 dB	-1.55 dB	SFR	46.80	**20/20**	**-2.55 dB**	None	None	Stable	12 mos

						Gy (1.8 x 26)						
13	20/15	LP	-9.72 dB	LP	Surgery + SRS		NLP	NLP	None	Recurrence	Stable since SRS	98 mos
14	NLP	NLP	NLP	NLP	Observation		NLP	NLP	None	None	Stable	11.5 yrs

Abbreviations: 3DCFR, three-dimensional conformal radiotherapy; dB, decibel; dev, deviation; Gy, Gray; IMRT, intensity-modulated radiotherapy; LP, light perception only; mos, months; MRI, magnetic resonance imaging; NA, not available; NLP, no light perception; SRS, stereotactic radiosurgery; VA, Snellen visual acuity; VF, visual field; tx, treatment; yrs, years.

Boldface indicates improvement or stabilization after treatment. VF was considered stable if within ±3 dB of pre-treatment mean deviation.

*Alopecia described was focal and temporary only.

Discussion

Clinical characteristics

The clinical characteristics of the patients in this series are summarized in Table A. In Table E they are compared with the patients reported in the literature up to 1992 as compiled by Dutton (1) and with several other recent series where such data were provided (3, 18-20, 25, 44, 81, 84, 98). The mean age of 45.6 and the female predilection in this series are consistent with published reports. Improvements in imaging technology as well as increasing awareness of ONSM should lead to earlier, more frequent, and more accurate diagnosis, an observation that others have made (3, 17, 19, 24). This should lead to a more subtle clinical presentation on average. Compared with the data from Dutton, patients in this series were more likely to have swelling or edema (64% vs 48%) and less likely to have pallor or atrophy (36% vs 49%) or optociliary shunt vessels (7% vs 30%), though these differences are not statistically significant due to the small sample size of the current series. Impairment of color vision, however, was seen in fewer patients in the current series (31% vs 73%, $p < 0.001$, χ^2 test), as was proptosis (21% vs 59%, $p < 0.01$, χ^2 test); however, proptosis is also a function of tumor location in addition to tumor size. The presenting VA tended to be better in the current series (20/20-20/40, 71% vs 45%; 20/50-20/400, 21% vs 31%; counting fingers [CF] to NLP, 7% vs 24%), though this difference also was not statistically significant. Decreased vision was present at initial evaluation in 93%, comparable to the 96% in Dutton's review. VF defects were present in 92%, also comparable to the reported rate of 83%, though there are also differences in the method of perimetry between the historical group and the present series.

The largest recent series are those by Turbin *et al.* (20) (64 eyes, 2002) and Saeed *et al.* (3) (88 eyes, 2003). More frequently seen in the current series was swelling or edema (64% vs 43% in Turbin or 42% in Saeed). Less frequently seen were pallor or atrophy (36% vs 55%, data unavailable for Turbin), optociliary shunt vessels (7% vs 25%, data unavailable for Turbin), and proptosis (21% vs 38% for Turbin and 30% for Saeed). However, none of these were statistically significant differences. Impairment of color vision was again significantly less frequent in the current series (31% vs 82% in Turbin, $p < 0.001$, χ^2 test, data unavailable for Saeed).

In summary, when compared with patients reported before 1992, patients in this series were more likely to have a less severe presentation on clinical examination, though not statistically significantly so, except for color vision and proptosis. The same was true in comparison with patients reported more recently except only color vision had a statistically significant difference. The classic triad of visual loss, atrophy, and shunt vessels was rare in this series.

Table E. Clinical characteristics of the patients in the current series compared with those of selected series reported in the literature.

Authors		**Dutton (1)**	**Turbin et al (20)**	**Egan et al (25)**	**Liu et al (84)**	**Pitz et al (98)**	**Andrews et al (44)**	**Saeed et al (3)**	**Narayan et al (19)**	**Baumert et al (18)**	**Richards et al (81)**	**Current series**
		1992	2002	2002	2002	2002	2002	2003	2003	2004	2005	2007
					1994-2001	1989-2000	1996-2001	1976-1999	1986-2001	1996-2003	1999-2001	1998-2006
Patients		**498**	**64**	**16**	**5**	**15**	**30**	**88**	**14**	**23**	**4**	**14**
Laterality	Unilateral	475 (95%)	58 (90.6%)	16 (100%)	4 (80%)	14 (93.3%)	27 (90%)	84 (95.5%)	13 (92.9%)	21 (91.3%)		14 (100%)
	Bilateral	23 (5%)	6 (9.4%)	0	1 (20%)	1 (6.7%)	3 (10%)	4 (4.5%)	1 (7.1%)	2 (8.7%)		0
Side	OD	111 (52%)	30 (51.7%)	10 (62.5%)	0 (0%)	8 (57.1%)	17 (63.0%)	40 (47.6%)	8 (61.5%)			6 (42.9%)
	OS	102 (48%)	28 (48.3%)	6 (37.5%)	4 (100%)	6 (42.9%)	10 (37.0%)	44 (52.4%)	5 (38.5%)			8 (57.1%)
Sex	Male	139 (39%)	9 (14.1%)	6 (37.5%)	2 (40%)	3 (20%)	12 (40%)	18 (20%)	1 (7.1%)	4 (17.4%)	1 (25%)	4 (28.6%)
	Female	217 (61%)	55 (85.9%)	10 (62.5%)	3 (60%)	12 (80%)	18 (60%)	70 (80%)	13 (92.9%)	19 (82.6%)	3 (75%)	10 (71.4%)
Age	Mean	40.8	45.2	50	57.2	44.8	47.9	40.3	44	Med 44	35	45.6
	Range	2.5-78	19-81	26-74	40-73	13-67	20-76	7-71	14-65	9-71	26-51	16-63
Swelling/edema	**Present**	**100 (48%)**	**22 (43.1%)**	**9 (56.2%)**				**42% (37)**	**7 (50%)**		**4 (100%)**	**9 (64.3%)**
	Absent	108	29	7					7		0	5
	Unknown	290	13		5	15	30					
Pallor/atrophy	**Present**	**87 (49%)**		**7 (43.8%)**				**55% (48)**	**6 (42.9%)**		**0 (0%)**	**5 (35.7%)**
	Absent	90		9					8		4	9
	Unknown	321	64		5	15	30					
Shunt vessels	**Present**	**71 (30%)**	**4**	**2 (12.5%)**	**2 (40%)**			**25% (22)**			**0 (0%)**	**1 (7.1%)**
	Absent	167		14	3						4	13
	Unknown	260	60			15	30		14			
Proptosis	**Present**	**142 (59%)**	**23 (37.7%)**		**1 (20%)**			**30% (26)**	**2 (14.3%)**	**6 (26.1%)**	**0 (0%)**	**3 (21.4%)**
	Absent	99	38		4				12	17	4	11
	Unknown	257	3	16		15	30					
APD	**Present**		**56 (93.3%)**									**8 (57.1%)**
	Absent		4									6
	Unknown	498	4	16	5	15	30		14		4	
Color vision	**Abnormal**	**33 (73.3%)**	**46 (82.1%)**									**4 (30.7%)**
	Normal	12	10									9
	Unknown or NLP	453	8									1

Time to diagnosis

The relative rarity of ONSMs combined with the often nonspecific presenting signs and symptoms of the disease contribute in many cases to a substantial amount of time elapsing between the onset of symptoms and the diagnosis and treatment of ONSM. Visual loss, the most common presenting symptom, is typically gradual, which could cause patients to delay being evaluated. ONSM is sometimes missed by clinicians other than neuro-ophthalmologists due to the rarity and nonspecific presentation of ONSMs. Symptomatic ONSM may have a subtle radiographic appearance or may be below the limit of detection, particularly if there is not high clinical suspicion to obtain appropriate imaging protocols (i.e., high-resolution orbital MRI with contrast enhancement and fat suppression).

In the current series of 14 patients, the mean time from onset of symptoms to diagnosis was 10.3 months with a range of 1 month to 29 months, not including patient 14 who had no useful vision (LP only) due to amblyopia and became NLP about 7 years prior to diagnosis. Including patient 14, the mean time to diagnosis was 15.6 months (range 1 month to 7 years). Patient 14 was the only one who had symptoms for five years or more before diagnosis.

In the 1992 review, Dutton (1) reported that the mean length of time between initial symptoms and presentation was 41.9 months (n = 119, range 1 month to 17 years). Thirty-two percent had symptoms for less than one year, 46% for one to five years, and 22% had symptoms for five years or more. The difference in time to diagnosis from the current series is statistically significant (χ^2 test, $p < 0.01$).

The duration of symptoms before diagnosis was reported by Pitz *et al.* (98) in 2002 of 15 patients. The mean time to diagnosis was 33.5 months with a range of 5 months to 120 months; 4 patients (26.7%) had symptoms for five years or more. The difference in time to diagnosis from

the current series is statistically significant whether patient 14 is excluded (one-tailed Student's *t*-test, p = 0.01) or included (p = 0.049).

The time to diagnosis was also reported by Egan and Lessell (25) in 2002 of 16 patients. The mean time to diagnosis was 40.2 months with a range of 1 month to 144 months; 5 patients (31.3%) had symptoms for five years or more. The difference in time to diagnosis from the current series is statistically significant whether patient 14 is excluded (one-tailed Student's *t*-test, p = 0.01) or included (p = 0.03).

Compared with the reported data from Dutton (cases up to 1992) and Pitz *et al.* (cases from 1989 to 2000), patients in this series (cases from 1992 to 2006) were diagnosed much more rapidly after the onset of symptoms. This may reflect improvements in radiographic techniques contributing to earlier detection as well as increased awareness of ONSM leading to higher levels of suspicion. Other possible factors may include local familiarity with ONSM at this center or better access to ophthalmic care.

Radiographic diagnosis

The advent of CT and subsequently MRI has revolutionized the use of imaging in detecting and diagnosing ONSMs, as well as in planning for treatment. It is appropriate to proceed to RT based on radiographic appearance and clinical presentation without a tissue diagnosis, after other potentially confounding diagnoses such as sarcoidosis have been ruled out. None of the patients in the current series who received primary RT underwent confirmatory biopsy. Nevertheless, because even a tiny ONSM can have a detectable effect on optic nerve function, symptomatic ONSMs can at times fall below the imaging resolution of CT and MRI. In the current series, 4 of 14 (28.6%) patients initially had imaging that was read as normal; all later had abnormal imaging. In some cases the initial scans were ordered by non-neuro-

ophthalmologists, who may not have had the clinical acumen to order a protocol sensitive enough to detect the patients' ONSMs. Cases have been reported of intracanalicular ONSM where the diagnosis was missed for years despite evaluation with MRI because of repeated use of an inappropriate imaging protocol (36). In other cases the ONSM may truly have been beyond the limit of imaging resolution. All four of these patients with initially normal imaging had VA of 20/20 or better, but their VF defects were not significantly milder than the others'. Thus, despite the value of CT and MRI in the diagnosis of ONSM, it remains essential to maintain a strong suspicion of ONSM in the face of negative imaging when the clinical presentation is appropriate. To maximize the sensitivity of imaging, CT images should be thin-slice orbital sequences without and with contrast enhancement, and MRI images should be high spatial resolution sequences with contrast enhancement and fat suppression. On the other hand, ONSMs may be detected incidentally in the absence of visual deficit or abnormal exam. One patient in the current series (patient 12) had no visual symptoms or signs; her ONSM was discovered during the workup for secondary amenorrhea.

The 2003 report by Saeed *et al.* (3) examined closely the radiographic appearance of ONSMs for associations with prognosis. In the series of 88 patients reported, 74 nerves had films available for review, and 47 tumors were examined histologically. MRI was more sensitive than CT for intracranial extension, with 4 cases of intracranial involvement not seen on CT but clearly demonstrated on MRI. On imaging, a tubular pattern with apical expansion (14.8% of nerves) was associated with worse visual prognosis, with 6 of 11 (55%) losing vision compared with a 27% rate of ending up NLP overall. No other correlation was found between radiographic configuration and VA. There was also no correlation between configuration and location on imaging and histopathologic type. All 8 cases with invasion of orbital fat (demonstrated histologically) showed irregular margins on CT, suggesting that the presence of irregular margins

may indicate a need for more aggressive resection if surgery is performed. Volumetric studies found that calcified tumors (31%) grew by 3.38 mm^3 in volume and 0.12 mm in length annually, while non-calcified tumors grew by 23.45 mm^3 and 0.6 mm respectively. In the current series patients were not observed for a significant length of time after diagnosis as they were offered RT as primary therapy, except for patient 14, who was already NLP at diagnosis. None of the patients in the current series became NLP during the period of observation. Thus it is not possible in this series to draw conclusions on any association between morphology or calcification and visual prognosis.

Greenfield *et al.* (99) reported in 1998 that none of 52 eyes with low-tension glaucoma had an occult compressive lesion of the anterior visual pathway. In a comparison with a group with non-glaucomatous cupping, the non-glaucomatous nerves were associated with age younger than 50 years, male gender, worse VA, temporal neuroretinal rim thinning, and vertically-oriented VF defects. In the current series, patient 4 (56 M, 20/20) had a prior diagnosis of low-tension glaucoma with a characteristic arcuate VF defect, but imaging (CT) was ordered on the basis of progressive enlargement of his existing VF defects. His CT revealed a calcification that was later identified to be an ONSM. Thus, despite the rarity of anterior visual pathway compression in patients with low-tension glaucoma, radiographic evaluation remains important when there is any suspicion for another entity based on clinical features.

Response to radiotherapy and side effects

The treatment outcomes for the patients in the current series are summarized in Table D. For the 10 patients who received 3DCFR (including one at another institution), the overall visual control rate was 100%, with all patients maintaining stable or improved VA and/or VF. Of the patients with less than 20/20 vision prior to treatment (patients 2, 7, and 11), all improved after

treatment (20/50 to 20/40, 20/200 to 20/60, 20/200 to 20/20). One patient (patient 4) had later worsening of his VF due to his pre-existing low-tension glaucoma, though his VA remained stable. The radiographic tumor control rate was also 100%, with 2 patients experiencing radiographic improvement (patients 1 and 4) and the others stabilization. Thus, 3DCFR has been very effective in this series of patients in arresting the growth of ONSMs and arresting or partially reversing visual decline, even though radiographic regression was not common.

Acute toxicity for 3DCFR was generally mild and transient; side effects included focal alopecia in 3 patients, nausea in 1, fatigue in 5, and minor mucous membrane inflammation in 1. With a follow-up period of 7 to 96 months (mean 46.2 mos, median 34 mos) for all 12 patients treated with primary RT, late complications included the development of dry eye syndrome in 1 patient after 4 years. Two patients (patients 1 and 11) had a follow-up of more than 5 years, and two others had a follow-up of nearly 5 years (patient 2, 58 months, and patient 4, 57 months). However, any conclusions about the long-term complication rate are still likely premature. Nevertheless, up to this point the side effect profile of 3DCFR has been very mild.

One patient in this series (patient 10) underwent IMRT with an initial improvement in vision and no side effects during treatment. However, several months later she had a progressive decline in vision associated with slight radiographic increase in the size of her tumor. She also had decreased vision secondary to RT-induced edema that responded rapidly to corticosteroids. Her disease stabilized radiographically and clinically, with VA remaining the same as it was prior to RT. Additionally, an endocrinologist determined that she had radiation-induced hypothalamic dysfunction resulting in recrudescence of her menstrual periods and heat intolerance, but details of her workup were unavailable. After several years of further follow-up, there has been a slight radiographic decrease in the size of her tumor while her vision has remained stable.

One patient (patient 12) received SFR at another institution. She had visual and radiographic control of her tumor with a stable course without acute or late complications.

Comparison with other treatment modalities

Available treatment modalities for ONSM include observation, neurosurgical resection, medical therapy, and a variety of RT techniques, including SFR, IMRT, and 3DCFR in a single dose or, usually, in fractions. The relative value of these treatments has not been established by prospective randomized controlled trials, and the low incidence of ONSM makes it unlikely that such trials will be performed. The management of ONSM has been controversial, but recently this has begun to change with several reported series of successes with various forms of conformal and stereotactic fractionated RT. The various treatment modalities are evaluated and compared below.

Observation only

Several published case series contain patients with ONSM who were followed by observation (1, 3, 20, 24, 25, 58). Since ONSMs are benign and have no effect on mortality, observation was a reasonable option while the risk of vision loss from intervention was judged to be similar to that from continued growth of the tumor and as long as there is no threat of extension to the other optic nerve or intracranial structures. In general, presenting VA was a broad prognostic factor; patients with an initial VA of 20/50 or better tended to retain good VA for relatively long periods of follow-up, though some individuals experienced severe loss of vision.

In the review by Dutton (1) in 1992, 64 patients were followed with observation only, out of a total of 223 patients whose management and outcome were known. Vision remained stable in 14% and decreased in the remainder with no patients experiencing improvement. However, there is little detail about individual cases with which to base further conclusions.

In the 2002 analysis by Turbin *et al.* (20) comparing observation, radiation, surgery, and surgery and radiation, 13 patients were followed by observation only, which did not include those initially observed and later treated. Details on individual patients were not provided, but in the group analysis, the characteristics and outcomes for the observation group were not statistically significantly different from the other groups except that the outcomes were worse than for the radiation only group. None of the observation group showed any improvement in VA and 4 showed radiographic progression during the mean follow-up of 10.8 years.

In 2002, Egan and Lessell (25) published a report on 16 patients (mean age 50 years, range 26-74 years) who received a clinical and radiologic diagnosis of primary ONSM between 1973 and 1999 and, offered the choice of radiation treatment or observation, decided to be treated initially by observation only. These patients were followed for a mean of 6.2 years (range, 2-18 years) with one receiving surgery after his VA declined from 20/15 to NLP after 8 years and another receiving surgery after her VA declined from 20/20 to 20/30 after 7 years (the patient was NLP after surgery). Four patients had an initial VA of 20/200 or worse; of those, three had a decline in VA while one remained stable at 20/300. Of 11 patients with an initial VA of 20/30 or better, 6 retained a VA of 20/30 or better (with a follow-up of 5-20 years), while 5 had a decline of VA, including 3 who had marked loss of VA to 20/100 or worse. The remaining patient, with an initial VA of 20/40, also had a marked loss of VA to 20/100. Only 3 patients in the series experienced a slight improvement in VA, but all had initial VA of 20/30 or better. These 3 patients experienced a corresponding improvement in VF. It is unclear how frequently these

patients were followed with imaging or how they fared in comparison with the 25 patients with ONSM who were treated and excluded from the case series.

In a report published in 2003 by Saeed *et al.* (3) following 88 patients seen at two centers between 1976 and 1999 with a diagnosis of ONSM, 39 patients with 42 eyes were followed by observation only for a mean follow-up of 5.8 years. Of the 11 patients with an initial VA of 20/20, 9 maintained a stable VA of at least 20/25; the other 2 worsened to 20/50. Of the 19 patients with an initial VA between 20/25 and 20/50, 15 were unchanged, 3 worsened to 20/80, and 1 deteriorated to hand motions (HM). Two patients presented with a VA of CF or LP; 1 was stable while 1 became NLP. The remaining 8 eyes were NLP at presentation.

Landert *et al.* (58) reported in 2005 a series of 13 eyes with ONSM, 7 of which were treated with SFR (also reported in Baumert *et al.* (18)) and 6 of which were followed by observation (1 patient had bilateral ONSM; only the symptomatic eye was treated). Three patients refused RT despite progressive visual loss, while the other 3 had satisfactory and stable vision. Over a follow-up period of 16 to 118 months, 2 eyes remained stable at 20/16 while the other 4 (initially 20/20 to 20/100) had moderate to severe deterioration (to 20/70 to NLP). One patient had radiographic progression; she had severe visual loss from 20/20 to HM. A statistical comparison between this group and the RT group revealed a significantly better outcome for the treated group.

Overall, out of these 120 patients whose outcomes were reported, 44 (37%) remained stable through the period of follow-up while 76 (63%) experienced deteriorating vision. None of these patients had a spontaneous improvement in vision except for 3 patients in the report by Egan and Lessell who recorded a slight improvement from 20/25-20/30 to 20/15-20/20.

Medical therapy

Most data on the efficacy of medical therapy, specifically that directed at hormone receptors known to be expressed by meningiomas as well as hydroxyurea, have come from reports and trials on meningiomas other than ONSMs (discussed above). However, the evaluation of medical therapy for ONSM has the advantage that optic nerve function can be easily and sensitively assessed for evidence of tumor response, while the response of most meningiomas relies on radiographic visualization of macroscopic size changes.

To date, only one published case report exists describing the successful use of hydroxyurea in the treatment of ONSM. In 2003 Paus *et al.* (74) reported a patient with a radiologic diagnosis of ONSM who was treated only with 20 mg/kg/d oral hydroxyurea for 10 months and followed for a further 18 months. This dosage was the same as that used in trials of hydroxyurea for meningiomas other than ONSMs. Her VA improved from 20/400 to 20/25 and her VF was significantly improved after medical treatment, though there was no decrease in tumor size detected by MRI.

Hydroxyurea is generally well tolerated at the dose that has been used for meningioma (20 mg/kg/d orally); though reported side effects have included bone marrow suppression, skin rashes, elevated liver function tests, fatigue, bleeding gums, and constipation, these generally resolved with discontinuation of treatment (68-70). Given the relative safety of the drug and the particular sensitivity with which optic nerve function can be assessed clinically, it may be appropriate to offer hydroxyurea for ONSM where patients have refused RT and are not otherwise indicated for surgery.

Surgery

Since ONSM is a wholly benign tumor, the goals of surgery have been to prevent intracranial spread, to attempt to preserve vision, and to relieve uncomfortable proptosis in a blind eye. For preservation of vision, surgery has been largely supplanted by RT as excision often resulted in blindness due to disruption of the pial blood supply. Rarely there have been case reports of improved vision after surgical resection (20, 61, 100-102).

In the 1992 review by Dutton (1), 120 patients with primary ONSM were treated with surgery alone; 94% had postoperative visual loss, with 78% becoming NLP. Only 6% (7 cases) had stable or improved vision. In addition to poor visual outcomes, there was a recurrence rate of 25% for the 88 patients for whom data were given.

Saeed *et al.* (3) reported in 2003 a series of patients treated between 1976 and 1999 that included 47 who received surgery as primary management. Of the patients who underwent resection, only one patient who had a focal, anterior, superior intrasheath tumor had improvement of vision with no recurrence. All 4 patients who underwent partial excision of their intraorbital mass had recurrence and required secondary excision, though none of the 15 patients who had *en bloc* removal had recurrence. Decompression was performed on 10 patients; only 2 patients had stable or improved vision, while intracranial extension occurred in 2 others.

In 2002 Turbin *et al.* (20) compared statistically the outcomes of 64 patients. In this series there were 12 patients who were treated with surgery alone (4 biopsies or partial resections and 8 total resections). Seven of these patients developed radiographic progression during the follow-up period, which was a mean of 13.2 years. Compared with the patients treated with other modalities in this study, the patients who underwent surgery alone had a lower mean VA at diagnosis, but not statistically significantly so. Visual outcome was poor overall, with all but two patients ending up with a VA of 20/200 or worse at last follow-up, the median final VA being

NLP. The only patient who did not suffer a decline in VA experienced an improvement from CF to 20/25 after resection of a focal globular ONSM. Compared with the observation only group, there was no statistically significant difference in VA at last follow-up or in percentage change in VA ratio measure from diagnosis to last follow-up. However, since this surgery only group includes those patients initially observed, it is possible that disease progression during observation contributed to the poor final visual outcome of this group. Also, since it is unclear from the report how or why patients were assigned to each treatment group, it is possible that surgical intervention was favored for tumors that had a poorer visual prognosis anyway due to faster growth or more profound visual loss before treatment. Complications reported included vascular occlusion in 2, neovascular glaucoma in 2, CSF leak in 1, complete ophthalmoplegia in 1, 3rd nerve palsy in 1, and neurotrophic corneal exposure in 1 patient, for an overall complication rate of 66.7%.

Schick *et al.* (55) reported in 2004 a series of 73 patients who underwent surgery between 1991 and 2002 for ONSM. Ten also had RT after surgery. Of 34 patients with good initial VA (20/40 or better), 27 retained good VA at follow-up. Five of 10 patients with fair initial VA (between 20/40 and 20/200) were stable while one improved. Only one patient with poor initial VA improved. The follow-up period was 6 to 144 mos (mean 45.4 mos). Thirteen patients had recurrence of disease. Based on their ability to perform surgery without visual loss in a significant number of cases, the authors argue for a role for surgery in cases where the ONSM extends or threatens to extend intracranially or contralaterally, followed by RT to control residual tumor.

Roser *et al.* (57) reported in 2006 a series of 24 patients with primary ONSM at one center between 1980 and 2001, of whom 22 underwent surgery. The follow-up period was 2 to 280 months. Seven patients who had no useful vision underwent complete resection, and none had

recurrence during the follow-up period. Eight patients who underwent surgery had stable or improved vision for 36 to 96 months, though two later lost vision due to tumor progression. Both patients with improved post-operative vision had rapid visual deterioration prior to surgery. The authors argue for a role for surgery in the decompression of the optic nerve in cases of rapidly progressive visual loss because RT does not cause an acute decrease in tumor volume.

Overall, surgical excision, including decompression, has generally been unsuccessful in maintaining or improving vision except in infrequent cases, with patients overwhelmingly left with worse vision postoperatively. The complication rate is high, as is the recurrence rate except for *en bloc* resections. Decompression is also generally unsuccessful, and risks extradural recurrence. With the demonstration of successful visual and radiographic control using RT (see below), the role of surgery is increasingly limited. However, there may still be a role for surgery with or without RT in limited situations of intracranial extension or incipient intracranial extension, or in blind eyes with uncomfortable or painful proptosis.

Surgery and radiation

Kennerdell *et al.* (24) reported in 1988 a series of 4 patients with useful vision ranging from 20/25 to 20/40 who underwent surgery followed by radiation. No patient lost any vision and one patient improved after partial surgical excision. Two patients remained stable after radiation for 6 to 9 years of follow-up. One had VA decline after surgery that continued after radiation. The last patient had radiation only after VA loss 7 years after surgery; her VA stabilized after radiation.

In the report by Turbin *et al.* (20) in 2002, a group of 16 patients who received a combination of surgery (14 biopsies or partial resections and 2 total resections) and radiation. These patients, with a mean follow-up of 8.4 years, had a median decrease in VA of 98.1% that

was not significantly different from that of the observation or surgery only groups. Five patients in this group (31.3%) showed an improvement of at least two lines of Snellen acuity that remained stable through the last follow-up. Eight patients had radiographic progression of their tumors. It is unclear how this affected the decision to treat with radiation and surgery, or indeed how many patients received surgery after failure of RT versus how many may have received radiation for recurrence or as adjuvant after surgery. Complications reported included retinopathy or vascular occlusion in 2, glaucoma in 2, persistent iritis in 1, lymphoma in 1, recurrent hemorrhage in the tumor in 1, 3rd nerve palsy in 2, and MCA infarct and CSF leak in 1 for a rate of 62.5%.

In the current series, 1 patient (patient 13) received surgery followed by radiation. The patient lost all vision within 1 year postoperatively despite an attempt to spare the nerve. The tumor recurred 5 years after surgery despite a grossly total resection. After receiving SRS, there has been no further progression after 7 years. This experience is typical compared with those reported in the literature.

It appears that most of the benefit in cases treated by surgery and radiation is derived from the radiation rather than the surgery. Given the high rate of complications reported for surgery plus radiation, primary RT is a better option.

Radiation therapy

Conventional

Smith *et al.* (11) reported in 1981 the first series of patients with primary ONSM treated by primary RT. Five patients were treated with conventional fractionated RT, receiving 36 to 72.2 Gy in 1.8 to 2.0 Gy fractions. One patient was NLP before treatment; the other four had improvement in vision.

Sarkies (103) reported in 1987 two patients with bilateral ONSM who had their only seeing eye treated with conventional RT. One received 13.25 Gy in 4 fractions before treatment was terminated due to visual decline. The other received 40.00 Gy in 12 fractions with a temporary slight improvement in VF before further decline within 2 months. The large dose per fraction used or edema resulting from RT may account for the poor results in this series.

Kennerdell *et al.* (24) reported in 1988 that 6 of 6 patients who received primary conventional fractionated RT (50-55 Gy in 30-32 fractions) experienced stable or improved VA and VF with no late complications other than transient dry eye during 30 to 84 months of follow-up; one had radiographic tumor shrinkage while none had growth.

Ito *et al.* (76) reported in 1988 a series of patients with orbital meningiomas, of which 2 had primary ONSM treated by primary RT. These 2 received conventional RT with telecolbalt at total doses of 40 to 50 Gy, and both were improved afterward with a follow-up of 2 to 2.5 years, with one showing reduction in tumor size on CT.

Mondon *et al.* (75) reported in 1988 a patient with ONSM treated with 55.0 Gy of conventional RT with improvement in VA and VF but no change on CT imaging over the 2-year follow-up period.

Goh and Yeow (104) reported in 1994 three patients with ONSM, of whom one received external beam irradiation (details on the dosing and technique were not available) and experienced a subsequent improvement in VA.

The 2003 report by Saeed *et al.* (3) included 5 patients who received conventional fractionated RT at 50 to 55 Gy in 28 to 30 fractions. These patients had pre-treatment VA between 20/40 and 20/100 with progressive deterioration of VA and VF. All 5 experienced post-treatment improvements in their VA and/or VF. One patient experienced long-term complications, which were postradiation cataract and subsequent macular degeneration. No further tumor growth

was seen on imaging in all patients. However, follow-up was fairly short, with 4 patients being followed for 3 to 5 years and 1 for less than 1 year. Out of these 21 patients receiving conventional RT, improvement or stabilization was seen in 19 (90.5%) though differing protocols make the reports difficult to compare directly and little long-term follow-up data are available on complications and recurrence. Many of these patients received larger fractions (including the 2 patients who worsened after RT) or larger total doses than would be prescribed today given the existing data now available on radiation tolerance thresholds of the optic nerve and surrounding tissues.

The 2002 report by Turbin *et al.* (20) comparing aggregate outcomes of 64 patients treated by several methods with long-term follow-up included 18 who received radiation alone. These patients received 40 to 55 Gy of radiation, mostly by conventional multiport fractionated RT, a few by SFR, and one by gamma knife SRS. Unfortunately, no subgroup data was available as to which patients received which technique. Initial VA was not statistically significantly different from the other groups (observation, surgery, and surgery and radiation). However, this group did have a statistically significant difference in outcome compared with each of the other groups, experiencing better final VA (including the surgery and radiation group) and better percent change in ratio VA (except for the sugery and radiation group). Within the radiation alone group, the final VA was not significantly different from the initial VA. Eight patients (44.4%) showed at least two lines of stable improvement in VA through the last follow-up (median 8.3 years from treatment). Two patients also had radiographic progression of their tumor. It should be noted that the analysis compared initial VA at presentation and not VA just before treatment, so the effect of radiation would be underestimated in the analysis. Complications from RT included retinopathy or vascular occlusion in 4, persistent iritis in 1, and temporal lobe atrophy in 1 patient.

This amounted to a complication rate (33.3%) that was lower than that of the surgery alone (66.7%) or surgery and radiation (62.5%) groups.

Conformal and stereotactic

The primary conformal and stereotactic RT series to date are summarized in Table F, with a detailed listing in Table H. A comparison of outcomes between conformal and stereotactic techniques is in Table G.

In 1996, Lee *et al.* (80) reported one patient with primary ONSM who was treated with IMRT and immobilization with fixation screws attached to the vertex of the cranium. After receiving 50.40 Gy in 1.8-Gy fractions, the patient experienced an improvement in VF (her VA was 20/15) though only 1 week of follow-up was described.

Klink *et al.* (79) reported in 1998 a case of ONSM treated in 1995 by fractionated SRS, using 10 MV photons in 5 arcs to deliver 36 Gy in 6 fractions. The patient's VA and VF improved after treatment, and the radiographic appearance of the tumor remained stable over the 2-year follow-up period. The patient experienced periorbital edema and headache for several months after treatment that subsequently resolved.

Grant and Cain (105) reported in 1998 a case of ONSM treated by IMRT with 50 Gy in 25 fractions. The patient had improvement of vision and was stable during the 3-year follow-up period.

Fineman and Augsburger (46) reported in 1999 one patient with primary ONSM treated with SFR at a total dose of 54 Gy in 1.8 Gy fractions. The patient was clinically stable and suffered no complications during the 6-month follow-up period.

Augspurger *et al.* (106) reported in a 1999 abstract a series of 14 patients treated between 1994 and 1998 for ONSM using conformal IMRT with a dose of 49.3 to 50.4 Gy in 1.7 to 2.0 Gy

fractions. One patient had undergone subtotal resection and later became NLP despite RT. The follow-up period was 2 to 51 months (median 20 months). Vision improved objectively in 50% of patients and worsened in 14%. Radiographic regression was seen in 7% and progression was seen in none. Acute toxicity was seen but no late complications were reported other than blindness in the patient who had prior resection.

Tsao *et al.* (107) reported in a 1999 abstract a series of 15 patients treated between 1989 and 1997 for ONSM using 3DCFR with a dose of 50.4 to 54.0 Gy in 1.8 Gy fractions. The follow-up period was 11 to 102 months (median 32 months). Vision (VA and/or VF) was improved in 10 patients, none of whom showed radiographic progression. Two patients developed tumor progression on MRI. Two patients developed radiation-induced retinopathy likely related to a dose of 54.0 Gy delivered to the retina.

Moyer *et al.* (108) reported in 2000 one patient who received 3DCFR for ONSM in 28 1.8 Gy fractions for a total of 50.4 Gy using a six beam technique. This patient had a VA of 20/200 that improved to 20/40 one month after treatment. Her VF also improved with near-total resolution of her central scotoma. During the 24-month follow-up period, her VA improved further to 20/30 and her vision remained stable. Imaging showed a slight decrease in tumor size 8 months after treatment. No complications from RT were reported during the length of follow-up.

In a 2002 report, Liu *et al.* (84) reported a series of 5 patients who had ONSM treated by primary SFR, receiving 45 to 54 Gy in 1.8-Gy fractions with immobilization by dental plate. One patient had bilateral ONSM but only one eye was treated since the other was NLP and he refused craniotomy. These patients all had been experiencing progressive visual loss with VA prior to treatment ranging between 20/20 and 20/40. All patients had improved or stable vision within 3 months after treatment; 3 had an improved VA and 4 had improved VF. Complications included

postradiation nausea in 1 and transient postradiation periorbital edema that resolved. These patients were followed up for 1 to 7 years without evidence of long-term complications, and none had radiographic change in the size of the tumors.

Pitz *et al.* (98) reported in 2002 a series of 15 patients with ONSM seen between 1989 and 2000 with progressive loss of vision (these are the same patients also reported by Becker *et al.*(109) in 2002). These patients were treated by primary SFR with 6 MV photons in 3 to 6 non-coplanar fields, receiving 50.4 Gy in 26 fractions with a 5 mm margin and then an additional 3.6 Gy in 2 fractions with a 2 mm margin. Three underwent confirmatory biopsy prior to RT. These patients had pre-treatment VA of 20/16 to NLP. One patient had bilateral ONSM with NLP in one eye and preserved vision in the other. Of the 16 eyes, 12 had measurable vision at initiation of treatment. After a mean follow-up period of 37 months (range 12-71), 7 of those 12 had functional improvement (improvement in VA of two lines or more or improved VF of at least 8%) while the others remained stable. No increase in tumor size was seen radiologically in any patient after treatment. Complications acutely included local erythema in 5 and local alopecia in 11 patients that resolved; long-term complications included functional hyperprolactinemia in 1 and partial hypophyseal insufficiency in 1 patient.

The 2002 report by Andrews *et al.* (44) contained 30 patients with ONSM, 3 of whom had bilateral ONSM (33 eyes in total). Thirteen patients had prior surgery and 1 had a transsphenoidal biopsy before receiving RT; of the remaining 16 who had primary RT, 11 had useful vision (VA of at least CF) while 5 had only LP or NLP. The regimen used was SFR with immobilization by a dental plate attached to a head ring. The beams were delivered through cylindrical collimators using an average of 3 isocenters per case. Dose heterogeneity due to overlap between the radiation isocenters caused the median maximum dose to the optic chiasm and nerve to be 1.4x the prescription dose. The patients received 28 fractions of 1.8 Gy each with

immobilization by dental plate. For these 11 patients, initial VA ranged from 20/20 to 20/400, with 10 having VA of 20/50 or better. After RT, 1 patient had a marked improvement in VA from 20/400 to 20/70, 2 patients had improved VF, 2 patients experienced a slight decline in VA (20/25 to 20/40 and 20/20 to 20/50) with stable VF, and the others were clinically stable. No acute or late complications were reported for this group of patients, although within the entire group of 30 including those who received surgery prior to radiation, two lost vision, one developed optic neuritis that resolved with steroids, and one had orbital pain without optic neuritis that also resolved with steroids. This overall morbidity rate was thought to be due to the dose heterogeneity caused by limitations in the equipment used. The follow-up period for the entire group ranged from 9 to 284 weeks with a median of 89 weeks, but the actual follow-up duration was not specified for each patient.

In 2003, Narayan *et al.* (19) reported a series of 13 patients who were treated with primary 3DCFR between 1986 and 2001, using facemask immobilization and receiving 54 or 55.8 Gy in 1.8 to 2.0 Gy fractions using between 3 and 7 non-axial custom-shaped fields with 6 or 18 MV energy photons with a 1 cm margin. One other patient had undergone prior subtotal excision. Before treatment, 9 patients had VA of 20/50 or better, 2 were 20/100, and 2 were CF; all patients had VF abnormalities. Five patients experienced a clinically significant increase in VA (three lines or more of Snellen acuity), 1 improved initially before deteriorating to CF, 1 worsened after therapy and remained stable, and the remaining 6 had stable VA. Of the 11 patients who had initial VA of 20/100 or better, 9 were improved or stable. All patients in the series who had complete VF data experienced quantitative improvement (3 dB or better in mean deviation). One patient had radiographic shrinkage of her tumor that corresponded to her VA improvement; no size change was detected in the other patients. Acute complications reported included transient alopecia in most patients and mild corneal inflammation in 1 that resolved. Late complications included 1

patient with dry eye, 2 with iritis, 1 with grade 2 orbital pain, and 1 with grade 2 radiation retinopathy 4 years after treatment manifested by early microaneurysms; this last patient had a large anterior tumor and portions of her retina had received 54 Gy of radiation. The high overall complication rate (5 of 13, or 38%), similar to the 33% rate for conventional RT in the report by Turbin *et al.* (20), is likely related to the higher total doses of radiation used in this series.

In the 2003 report by Saeed *et al.* (3), 6 patients were treated by primary RT. One received SFR, at 45 Gy in 28 fractions. This patient had VA of 20/60 before treatment, and had stable vision and improved VF for 8 months afterward before developing a sudden focal (nerve fiber bundle) VF loss, thought to be caused by ischemia, but with retention of central vision. The patient was followed for only 1 year, during which no change in radiographic size was seen.

The 2004 report by Baumert *et al.* (18) describes 22 patients with ONSM who received primary SFR between 1996 and 2003 in four centers (1 other patient had undergone subtotal excision prior to RT). This report included 7 patients reported in 2005 by Landert *et al.* (58). Two patients had bilateral ONSM but only the symptomatic tumor site was treated in each. Twenty-one patients had useful vision prior to RT. All patients were given a SFR regimen of 45 to 54 Gy in 1.8 to 2.0 Gy fractions using 3 to 5 non-coplanar static fields with micro multi-leaf collimators to one isocenter; immobilization was achieved using a relocatable stereotactic frame as well as in most cases a customized bite block. They were followed up for 1 to 68 months (median 20 months). Improvement in VA (one line of Snellen acuity or better) was seen in 14 patients, of whom 6 had improved VF; 1 additional patient had improved VF with stable VA. Most patients who had improvement in vision had it within 1 to 3 months of treatment completion. The vision in 4 patients remained stable. One patient had progressive visual loss that continued after RT, and one patient (who was treated with 2.0 Gy fractions, though the total dose was not specified) developed radiation retinitis complicated by vitreous hemorrhage and cataract after 4 years of

stable vision. Acute complications included 1 patient with lid edema during RT that resolved with steroids, 1 patient with increased pain for a short time after RT, and local alopecia in all patients. Late complications were reported in 1 patient with increased headaches and the 1 patient who developed radiation retinitis as mentioned.

Richards *et al.* (81) reported in 2005 a series of 4 patients with ONSM who were treated with primary SFR between 1999 and 2002 at a single center and followed up for at least 18 months. All were given SFR, receiving 43.40 to 45 Gy in 25 to 27 fractions, using a frameless immobilization system with a bite block. All patients had experienced progressive decline in vision prior to treatment, with pre-RT VA from 20/20 to CF, and all showed signs of optic nerve dysfunction, defined as APD and/or decreased red saturation and/or decreased brightness saturation in the affected eye. Post-RT, all 4 patients had improved or stable VA from 20/15 to 20/40 with improvement in signs of optic nerve function. Three patients had an improvement in VF, but one developed a ring scotoma. No change in tumor size was detected on imaging during the period of follow-up. Complications reported were transient alopecia in one patient and radiologically evident cerebral punctuate small vessel fallout in the field of irradiation. However, the period of follow-up only ranged from 18 months to 4 years.

Comparing the current series to the published series, the rates of visual and radiographic control were similar. In this series, visual and radiographic control was achieved in 12 of 12 eyes (100%). Out of 99 eyes with useful vision (CF or better) who received conformal or stereotactic RT as primary therapy in the published literature, visual control was achieved in 92 (92.9%) and radiographic control was achieved in 97 (98.0%). Including the 12 eyes in this series, the overall visual control rate was 94.6% and the radiographic control rate was 98.2%. This is also comparable to the rate of visual control achieved by conventional RT (90.5%, $p = 0.14$, χ^2 test) in 21 eyes as noted above. Although a high rate of radiographic control of the tumor was achieved,

only 8 patients had any sign of radiographic regression; most (91.9%) had stabilization of radiographic appearance. This suggests that RT should be begun early as it does not appear to reverse the growth of ONSM even when there is a dramatic improvement in vision.

In the literature, there were 54 eyes with useful vision treated by primary RT using SFR, 29 eyes using 3DCFR, and 15 eyes using IMRT. The rate of visual control was 96.3% (52 of 54) for SFR and 86.2% (25 of 29) for 3DCFR ($p < 0.05$, χ^2 test). In this series, all (11 of 11) patients treated with 3DCFR achieved visual and radiographic control. This was not statistically significant from either sets of published data ($p = 0.5$, $p = 0.2$, χ^2 test) due to the small sample size. When combining the current SFR and 3DCFR series with the published data, there is still a statistically significant difference in visual control rate between SFR and 3DCFR (96.4% vs 89.7%, $p < 0.05$, χ^2 test). Thus it appears that the use of stereotaxis does provide an additional benefit above the use of three-dimensional conformal treatment planning. It is possible that this reflects an overall improvement in technique over time, as the control rate was 100% in the current series for 3DCFR.

Late complications reported for conformal or stereotactic RT in the literature included retinopathy in 4, iritis in 2, pituitary axis toxicity in 2, ischemic optic neuropathy in 1, dry eye in 1, orbital pain in 1, and mild brain toxicity in 1. In the current series there was one complication of mild dry eye syndrome and one of pituitary axis toxicity (giving a complication rate of 16.6%). The overall complication rate was 12.1% in the literature and 12.6% including this series. The overall rate was lower than the 33.3% reported by Turbin *et al.* (20) for patients mostly treated with conventional RT ($p < 0.001$, $p < 0.001$, χ^2 test). However, the complication rate was higher in the literature for 3DCFR (24.1%) than for SFR (9.3%, $p < 0.01$, χ^2 test). The complication rate was not significantly different between the current 3DCFR series (8.3%) and the reported 3DCFR series ($p = 0.2$). Again it appears that the use of stereotaxis does provide an additional benefit above the use of three-dimensional conformal treatment planning, and again this could reflect an

overall improvement in technique over time, as several of the 3DCFR series used higher total doses of radiation.

This current study confirms that while conformal and stereotactic techniques are at least as effective in treating ONSM as conventional RT, they appear to be safer in terms of late radiation toxicity. This can only be thoroughly evaluated, however, on prolonged follow-up. The current series demonstrates a 100% visual and radiographic control rate with a complication rate of only 8.3% for 3DCFR. However, this result is not statistically different from the 3DCFR and SFR outcomes in a review of the published data. The combined outcomes data from the literature and the current series indicate that SFR offers a benefit in both efficacy and safety over 3DCFR. Therefore, while 3DCFR is as effective and safer than conventional RT, it is less effective and produces more late complications than SFR. It is unknown whether there may be a confounding effect of improved techniques over time as dosages and experience vary between studies.

Dosimetry

Current dosing protocols, including that used in the current series, are designed to deliver the maximum dose possible to the tumor while remaining below the threshold for injury to nearby structures. As discussed above, the threshold total doses are 45 to 50 Gy for the retina (87, 88), 60 Gy for the optic nerve (89), 50 Gy for the pituitary gland (95), and 50 to 54 Gy for the brain (96, 97). Thus a prescribed dose of no greater than 50.4 Gy in 1.8 Gy daily fractions is generally recommended. The use of SFR reduces the dose absorbed by non-target tissues, allowing for a greater margin of safety around the threshold doses.

The dosimetry data for the current series are summarized in Table C. In all, 9 patients received 3DCFR at Yale, at a dose of 45.0 to 52.2 Gy in 25 to 29 fractions of 1.8 Gy each. This dose

is below the threshold for injury to the optic nerve. The highest maximum dose to the optic chiasm was 50.6 Gy, also below the threshold for optic nerve; the contralateral optic nerve received a maximum dose of 20.6 Gy. The highest maximum dose to the ipsilateral eye was 51.1 Gy, which is at the threshold for injury to the retina. Five patients received a calculated point dose of 50 Gy or higher to the ipsilateral eye, a dose at which there is an estimated risk of 22% of retinopathy (88). In the treatment of ONSM using SFR techniques, radiation retinopathy has been reported in 3 patients whose retinas had received 54.0 Gy (19, 107) and in 1 patient whose retina had received 48 Gy (110). One other patient developed retinopathy after treatment with 2.0-Gy fractions, but it was not stated what the total dose to the retina was (18). The highest maximum dose to the pituitary in this series was 48.5 Gy, which is below the anticipated threshold dose for iatrogenic injury. In the reported literature there have been 2 patients who developed endocrine complications after treatment of large ONSMs extending to the pituitary gland that required the dose distribution to include the sella turcica. The only patient in this series so far to have experienced a late complication was patient 1, who developed mild dry eye syndrome. Severe dry eye syndrome has been described to develop after 4 to 11 years with a threshold dose of 40 Gy to the lacrimal gland (91, 94). Though the overall rate of late complications is quite low, longer follow-up is necessary to ascertain the true complication rate of the treatment.

In a 2006 report Vagefi *et al.* (111) documented improvement in optic nerve function in all 4 patients who had formal neuro-ophthalmologic assessment during or immediately after RT out of a total of 35 patients treated for ONSM between 1990 and 2005, raising the question of whether some patients may derive benefit from lower doses of radiation than is currently prescribed. In the current series, several patients described subjective improvement during or immediately after treatment, but formal neuro-ophthalmologic testing was not performed until treatment was

complete. Thus, it is possible that some patients in the series could have benefited from lower doses but it is impossible to determine from the data available. Whether there are certain clinical or radiographic indicators that suggest a tumor that requires a lower dose is unknown.

Conclusions

The diagnosis of ONSM has improved with better imaging and increased awareness. Patients are diagnosed significantly sooner after the onset of symptoms than they had been previously. The clinical presentation has also become less severe (though not statistically significant except for color vision and proptosis) reflecting earlier diagnosis. Radiographic diagnosis remains pivotal in most cases, and investigation must include high spatial resolution MRI of the orbit with contrast enhancement and fat suppression. Radiography, however, can be misleading if the tumor is below the limit of imaging resolution, making it essential to maintain a strong suspicion of ONSM in the face of negative imaging when the clinical presentation is appropriate. Medical therapy has shown promise but has thus far been disappointing. Treating patients with 3DCFR at a dose of 50.4 Gy in 1.8-Gy fractions is highly effective in stopping visual loss and controlling the growth of tumor while maintaining a low rate of late complications. Outcomes in the current series for 3DCFR compared favorably (but without statistical significance) with those reported for 3DCFR and SFR. Compared with conventional RT, 3DCFR was found to be as effective in visual control while causing a lower rate of late complications. However, SFR techniques were superior to 3DCFR in visual control and rate of late complications. This suggests a benefit derived from the increased accuracy of stereotactic techniques. This could also reflect improvements in overall technique over time, as protocols varied between reports. It is not known if lower doses are effective in certain tumors that respond quickly to RT. Most patients, even those with dramatic visual improvement, do not have radiologically evident tumor

regression after therapy, suggesting that RT be offered early even in the absence of progressive visual loss. Longer follow-up will also be needed to fully evaluate the risk of complication and the durability of treatment response.

Table F. Summary of primary conformal and stereotactic radiotherapy series.

Author	Period	Method	Dose (Gy)	Eyes with useful vision	Stable or improved	Worse	Radiographic regression	Progression	Late complications	Follow-up
Lee *et al.*, 1996 (80)		IMRT	50.4 (28 x 1.8)	1	1	0	0	0	0	1 wk
Klink *et al.*, 1998 (79)	1995	Fract SRS	36 (6 x 6.0)	1	1	0	0	0	0	2 yrs
Grant and Cain, 1998 (105)		IMRT	50 (25 x 2.0)	1	1	0	0	0	0	3 yrs
Fineman and Ausburger, 1999 (46)	1997 (?)	SFR	54 (30 x 1.8)	1	1	0	0	0	0	6 mos
Augspurger *et al.*, 1999 (106) (abstract)	1994-1998	IMRT	49.3-50.4 (1.7-2.0 each)	13	12	1	1	0	0	2-51 mos (median 20)
Tsao *et al.*, 1999 (107) (abstract)	1989-1997	3DCFR	50.4-54.0	15	13	2	?	2	2 retinopathy	11-102 mos (median 32)
Moyer *et al.*, 2000 (108)	1996 (?)	3DCFR	50.4 (28 x 1.8)	1	1	0	1	0	0	2 yrs
Liu *et al.*, 2002 (84)	1994-2001	SFR	50.4 (28 x 1.8)	5	5	0	0	0	0	1-7 yrs (mean 3)
Pitz *et al.*, 2002 (98)	1989-2000	SFR	54 (28 F)	12	12	0	0	0	1 functional hyperprolactinemia, 1 partial hypophyseal insufficiency	12-49 mos (mean 32)
Andrews *et al.*, 2002 (44)	1996-2001	SFR	50.4-54.0	11	11	0	0	0	0	9-284 wks (median 89)*

Narayan *et al.*, 2003 (19)	1986-2001	3DCFR	53-55.8	13	11	2	1	0	2 iritis, 1 early radiation retinopathy, 1 dry eye, 1 orbital pain	8.9-86 mos (mean 51)
Saeed *et al.*, 2003 (3)	1976-1999	SFR	45 (28 x 1.6)	1	1†	0	0	0	1 ischemic optic neuropathy	1 yr
Baumert *et al.*, 2004 (18)	1996-2003	SFR	45-54	20	18	2	2	0	1 radiation retinitis and vitreal hemorrhage	1-68 mos (mean 22)
Richards *et al.*, 2005 (81)	1999-2002	SFR	43.40 (26 F)	4	4	0	0	0	1 cerebral punctate small vessel fallout	2-4 yrs (mean 2.5)
Current series, 2007	1998-2006	All patients	45.00-52.19	12	12‡	0	3	1	1 dry eye, 1 pituitary axis toxicity	7-124 mos (mean 47.4)
		3DCFR	45.00-52.19 (25-29 x 1.8)	10	10‡	0	2	0	1 dry eye	7-124 mos (mean 46.2)
		3DCFR, Yale only	45.00-52.19 (25-29 x 1.8)	9	9‡	0	2	0	1 dry eye	7-96 mos (mean 43.3)
		IMRT	45.00 (25 x 1.8)	1	1	0	1	1	1 pituitary axis toxicity	95 mos
		SFR	46.80 (26 x 1.8)	1	1	0	0	0	0	12 mos

Abbreviations: 3DCFR, three-dimensional conformal fractionated radiotherapy; F, fractions; Gy, Gray; IMRT, intensity-modulated radiotherapy; SFR, 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 x 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 due to pre-existing glaucoma.

Table G. Overall outcomes of primary conformal and stereotactic radiotherapy series, by technique.

Modality	Eyes with useful vision	Stable or improved	Worse	Radiographic regression	Progression	Late complications	Overall complication rate
Overall	99*	92 (92.9%)	7 (7.1%)	4 (4.0%)	2 (2.0%)	2 iritis, 4 retinopathy, 1 dry eye, 1 orbital pain, 1 ischemic optic neuropathy, 2 pituitary axis toxicity, 1 cerebral punctate small vessel fallout	12.1%
Overall (incl current series)	**111***	**105 (94.6%)**	**7 (6.3%)**	**7 (6.3%)**	**3 (2.7%)**	**2 iritis, 4 retinopathy, 2 dry eye, 1 orbital pain, 1 ischemic optic neuropathy, 3 pituitary axis toxicity, 1 cerebral punctate small vessel fallout**	**12.6%**
3DCFR	29	25 (86.2%)	4 (13.8%)	2 (6.9%)	2 (6.9%)	2 iritis, 3 retinopathy, 1 dry eye, 1 orbital pain	24.1%
3DCFR incl current series	**39**	**35 (89.7%)**	**4 (10.3%)**	**4 (10.3%)**	**2 (5.1%)**	**2 iritis, 3 retinopathy, 2 dry eye, 1 orbital pain**	**20.5%**
IMRT	15	14 (93.3%)	1 (6.7%)	1 (6.7%)	0	0	0%
IMRT incl current series	**16**	**15 (93.8%)**	**1 (6.3%)**	**2 (12.5%)**	**1 (6.3%)**	**1 pituitary axis toxicity**	**6.3%**
SFR	54	52 (96.3%)	2 (3.7%)	2 (3.7%)	0	1 ischemic optic neuropathy, 1 retinitis and vitreal hemorrhage , 2 pituitary axis toxicity, 1 cerebral punctate small vessel fallout	9.3%
SFR incl current series	**55**	**53 (96.4%)**	**2 (3.6%)**	**2 (3.6%)**	**0**	**1 ischemic optic neuropathy, 1 retinitis and vitreal hemorrhage , 2 pituitary axis toxicity, 1 cerebral punctate**	**9.1%**

						small vessel fallout	

Abbreviations: 3DCFR, three-dimensional conformal fractionated radiotherapy; IMRT, intensity-modulated radiotherapy; SFR, stereotactic fractionated radiotherapy; SRS, stereotactic radiosurgery.

*Overall figures include one patient who was treated by hypofractionated radiosurgery and does not appear in the subcategories below, which thus do not add up to the overall figures.

Table H. Outcomes of primary conformal and stereotactic radiotherapy series.

Author	Period	Patients	Initial VA	Pre-tx VA	Method	Dose (Gy)	Post-tx VA	VF	Size change	Follow-up	Complications
Lee *et al.*, 1996 (80)		n = 1 43 F		20/20	3DCFR	50.4 (28 x 1.8)	**20/15**	**Improved**		1 week	None
Klink *et al.*, 1998 (79)	1995	n = 1 40 F	20/25	20/300	Fract SRS	36 (6 x 6.0)	**20/200**	**Improved**	No	2 years	Transient periorbital edema and headache
Grant and Cain, 1998 (105)		n = 1			IMRT	50 (25 x 2.0)	**Improved**		No	3 years	None
Fineman and Ausburger, 1999 (46)	1997 (?)	n = 1 41 M		20/40	SFR	54 (30 x 1.8)	**20/40**	**Stable**		6 months	None
Augspurger *et al.*, 1999 (106) (abstract)	1994-1998	n = 13			IMRT	49.3-50.4 (1.7-2.0 each)	7 improved; 1 worse		1 regression; 0 progression	2 – 51 mos (median 20 mos)	2 acute transient toxicity; no late complications
Tsao *et al.*, 1999 (107) (abstract)	1989-1997	n = 15			3DCFR	50.4-54.0	**66.7% improved**		13.3% had progression	11 – 102 mos (median 32 mos)	2 retinopathy

Moyer *et al.*, 2000 (108)	1996 (?)	n = 1 35 F		20/200	3DCFR	50.4 (28 x 1.8)	**20/30**	**Improved**	**Smaller**	2 years	None
Liu *et al.*, 2002 (84)	1994-2001	63 F		20/40	SFR	50.4 (28 x 1.8)	**20/30**	**Improved**	No	3 years	For this series (individual details were not given): 1 postradiation nausea, 1 transient postradiation periorbital edema
		40 F		20/30	SFR	45 (25 x 1.8)	**20/30**	**Stable**	No	2 years	
		50 F		20/20	SFR	54 (30 x 1.8)	**20/15**	**Improved**	No	1 year	
		60 M		20/20	SFR	50.4 (28 x 1.8)	**20/20**	**Improved**	No	7 years	
		73 M		20/40	SFR	50.4 (28 x 1.8)	**20/30**	**Improved**	No	2 years	
Pitz *et al.*, 2002 (98)	1989-2000	64 F	20/50	20/30	SFR	54 (28 F)	**20/20**	**Improved**	No	43 mos	For this series (individual details were not given): 1 functional hyperprolactinemia, 1 partial hypophyseal insufficiency
		31 F	20/20	20/20	SFR	54 (28 F)	**20/16**	**Improved**	No	38 mos	
		67 F	20/20	20/20	SFR	54 (28 F)	**20/20**	**Improved**	No	46 mos	
		58 F	20/20	20/16	SFR	54 (28 F)	**20/20**	**Improved**	No	16 mos	

		42 F	20/25	20/25	SFR	54 (28 F)	**20/30**	**Improved**	No	49 mos	
		35 M	20/20	20/50	SFR	54 (28 F)	20/50	**Improved**	No	21 mos	
		13 M	CF	CF	SFR	54 (28 F)	**20/200**	**Stable**	No	37 mos	
		57 F	20/20	20/20	SFR	54 (28 F)	**20/25**	**Stable**	No	12 mos	
		44 F	20/30	20/60	SFR	54 (28 F)	20/100	**Stable**	No	22 mos	
		53 F	20/25	20/30	SFR	54 (28 F)	**20/25**	**Stable**	No	45 mos	
		29 F	20/16	20/16	SFR	54 (28 F)	**20/16**	**Stable**	No	32 mos	
		50 F	20/20	20/25	SFR	54 (28 F)	**20/25**	**Stable**	No	23 mos	
Andrews *et al.*, 2002 (44)	1996-2001	42 M	20/70		SFR	54	**20/70**	**Improved**	No	Individual details were not given; for the entire series including patients who had prior surgery and those without useful vision, the range was 9-284 wks and the median was 89 wks)	None
		62 M	20/25		SFR	50.4	20/40	**Stable**	No		None
		44 F	20/25		SFR	50.4	**20/20**	**Stable**	No		None
		41 F	20/20		SFR	50.4	**20/20**	**Stable**	No		None
		73 M	20/25		SFR	50.4	**20/30**	**Stable**	No		None
		31 M	20/20		SFR	52	**20/20**	**Stable**	No		None
		56 M	20/20		SFR	52	20/50	**Stable**	No		None
		76 F	20/40		SFR	50.4	**20/40**	**Stable**	No		None
		43 F	20/20		SFR	54	**20/20**	**Improved**	No		None

		46 F	20/400		SFR	54	**20/70**	**Stable**	No		None
		73 M	20/50		SFR	52	**20/40**	**Stable**	No		None
Narayan *et al.*, 2003 (19)	1986-2001	65 F		20/40	3DCFR	54	**20/40**	**Improved**	No	8.9 mos	None
		52 F		20/40	3DCFR	54	**20/40**	**Improved**	No	38.3 mos	Keratitis (acutely); dry eye (long-term)
		55 F		20/100	3DCFR	54	CF	**Worse**	No	48.3 mos	None
		34 F		20/100	3DCFR	54	**20/30**	**Improved**	No	69.9 mos	None
		50 F		20/15	3DCFR	54	**20/20**	**Stable**	No	39 mos	None
		43 F		20/50	3DCFR	54	**20/20**	**Improved**	**Smaller**	16.8 mos	None
		44 F		20/50	3DCFR	54	**20/25**	**Improved**	No	52.9 mos	Early radiation retinopathy
		65 F		CF	3DCFR	54	**20/200**	**Stable**	No	64.6 mos	Iritis
		26 F		20/30	3DCFR	53	20/70	**Stable**	No	60.7 mos	Orbital pain
		38 M		20/30	3DCFR	54	**20/25**	**Improved**	No	20.1 mos	None
		33 F		20/20	3DCFR	54	**20/25**	**Improved**	No	50.6 mos	None
		33 F		20/20	3DCFR	55.8	**20/20**	**Improved**	No	80.9 mos	Iritis
		65 F		CF	3DCFR	55.8	**20/70**	**Improved**	No	77.5 mos	None

Saeed *et al.*, 2003 (3)	1976-1999	34 F		20/60	SFR	45 (28 x 1.6)	**20/60**	**Improved**	No	1 year	Ischemic optic neuropathy
Baumert *et al.*, 2004 (18)	1996-2003				SFR		Worse	Worse	No	22 mos	None
					SFR		**Improved**	**Improved**	No	28 mos	None
					SFR		**Improved**	**Improved**	No	24 mos	None
					SFR		**Improved**	**Improved**	**Reduced contrast intensity**	52 mos	None
					SFR		**Improved**	**Stable**	No	28 mos	None
					SFR		**Improved**	**Improved**	No	23 mos	None
					SFR		**Improved**	**Stable**	No	40 mos	Transient lid edema
					SFR		**Improved**	**Stable**	No	5 mos	None
					SFR		**Improved**	**Improved**	No	44 mos	None
					SFR		**Improved**	**Stable**	No	20 mos	None
					SFR		Worse	Worse	No	68 mos	Radiation retinitis and vitreal hemorrhage 4 years later

					SFR		**Improved**		No	23 mos	None
					SFR		**Stable**	**Stable**	No	15 mos	None
					SFR		**Stable**	**Stable**	No	23 mos	None
					SFR			**Improved**	No	3 mos	None
					SFR		**Improved**	**Stable**	No	12 mos	None
					SFR		**Stable**	**Stable**	No	14 mos	None
					SFR		**Improved**		No	1 mo	None
					SFR		**Stable**	**Stable**	No	7 mos	None
					SFR		**Improved**	**Improved**	**Smaller**	4 mos	None
Richards *et al.*, 2005 (81)	1999-2002	F	20/17	20/25	SFR	43.40 (26 F)	**20/30**	**Improved**	No	2 years	For this series (individual details were not given): 1 transient alopecia, 1 radiologically evident cerebral punctate small vessel fallout
		F	20/15	20/20	SFR	45.00 (27 F)	**20/15**	**Improved**	No	2 years	
		27 M	20/200	CF	SFR	43.75 (25 F)	**20/30**	**Improved**	No	4 years	
		F	20/17	20/40	SFR	43.40 (26 F)	**20/40**	Ring scotoma	No	2 years	

Current series		1, 46 M	20/20	20/20	3DCFR	45.00 (25 x 1.8)	**20/15**	**Stable**	Slight decrease in enhancement	96 mos	Dry eye syndrome
		2, 16 F	20/80	20/200	3DCFR	52.19 (29 x 1.8)	**20/60**	**Stable**	No	58 mos	None
		3, 49 F	20/15	20/15	3DCFR	50.36 (28 x 1.8)	**20/20**	**Improved**	No	14.5 mos	None
		4, 56 M	20/20	20/20	3DCFR	50.30 (28 x 1.8)	**20/15**	**Improved***	Tumor no longer seen	57 mos	None
		5, 46 F	20/20	20/20	3DCFR	50.25 (28 x 1.8)	**20/20**	**Improved**	No	38 mos	None
		6, 51 F	20/15	20/15	3DCFR	50.34 (28 x 1.8)	**20/15**	**Improved**	No	30 mos	None
		7, 51 F	20/20	20/50	3DCFR	50.36 (28 x 1.8)	**20/40**	**Improved**	No	11 mos	None
		8, 58 F	20/20	20/20	3DCFR	50.41 (28 x 1.8)	**20/20**	**Improved**	No	26 mos	None
		9, 60 F	20/20	20/20	3DCFR	50.40 (28 x 1.8)	**20/25**	**Improved**	No	7 mos	None

		10, 47 F	20/70	20/70	IMRT	45.00 (25 x 1.8)	**20/30, later 20/60**	**Stable**	Enlargement, then stabilization, then decreased size	95 mos	Optic nerve swelling, treated by steroids, pituitary axis toxicity
		11, 36 F	20/200	20/200	3DCFR	50.40 (28 x 1.8)	**20/20**	**Improved**	No	124 mos	None
		12, 22 F	20/20	20/20	3DCFR	46.80 (26 x 1.8)	**20/20**	**Stable**	No	12 mos	None

Abbreviations: 3DCFR, three-dimensional conformal fractionated radiotherapy; CF, count fingers; IMRT, intensity-modulated radiotherapy; F, fractions; fract SRS, hypofractionated stereotactic radiosurgery; Gy, Gray; LP, light perception only; NLP, no light perception; SFR, stereotactic fractionated radiotherapy; SRS, stereotactic radiosurgery; VA, visual acuity; VF, visual field.

Only patients who were reported to have received primary radiotherapy (excluding biopsy) and had useful vision (defined as CF or better) are included. Dose is indicated in the form: total (fractions x dose/fraction). Boldface indicates stable or improved outcome.

*Patient 4 in the current series later had worsening of his VF due to progression of pre-existing glaucoma.

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