Management of Ocular Metastasis
William Small, Jr, MD

Treatment for intraocular metastases can prevent or postpone visual loss and maintain quality of life.

**Background:** Intraocular metastasis is a significant clinical problem in patients with metastatic cancer. The frequency of intraocular metastasis in all patients dying of cancer is approximately 12%, but in breast cancer patients, the frequency can be as high as 37%.

**Methods:** A review of pertinent literature and the author’s experience are used to describe the epidemiology, diagnosis, and management of metastatic tumors of the eye.

**Results:** Intraocular metastases occur frequently and are diagnosed by ophthalmologic examination. Radiotherapy remains the cornerstone of therapy and allows the majority of patients to maintain useful vision for the remainder of their lives.

**Conclusions:** The recognition and treatment of intraocular metastasis are important clinical oncologic issues. With proper management, patients with ocular metastasis can maintain vision and thus maximize quality of life.

**Introduction**

Historically, metastatic carcinoma to the eye, particularly to the choroid, was considered a rare event. Perls reported the first case of choroidal metastasis in 1872, and Lemoine and McLeod reported only 230 cases in the literature in their 1936 review. In a survey of 8,712 patients with malignancies, Godtfredsen reported only six patients (0.07%) with choroidal metastasis. Over the last 30 years, however, a number of reports have appeared noting a much higher incidence of metastatic disease to the eye. Bloch and Gartner performed postmortem examinations on 230 patients who died of systemic carcinoma and found 28 patients (12%) with metastatic tumor in the eye and/or orbit. Given the incidence and consequence (ie, blindness) associated with an untreated ocular metastasis, all oncologists should be familiar with this entity. This report reviews the incidence, diagnosis, and management of ocular metastasis.

**Epidemiology**

The frequency of choroidal metastasis in patients with cancer is estimated to be approximately 2% to 7%. If all intraocular metastases are considered, this number rises to approximately 12%. Intraocular metastasis is now considered the most common malignancy of the eye. The frequency of ocular metastasis varies significantly among primary sites. Table 1 reviews the percentage of patients dying of cancer or with generalized malignancy who on examination were found to have ocular metastasis. Table 2 reviews the primary sites in patients who have been diagnosed with ocular metastasis during life. Ocular metastasis, and particularly choroidal metastasis, can precede the diagnosis of the primary malignancy. In a study by Ferry and Font, 46% of the patients had tumor-related symptoms that preceded the detection of the primary neoplasm. In a study by Shields et al, 34% of patients had no history of cancer at the time of ocular diagnosis. In both the Ferry study and the Shields study, lung cancer was the most common primary tumor detected in patients with no neoplasm at the time of ocular diagnosis (35% and 41%, respectively, in these studies). There was also a significant percentage of patients in whom no primary tumor was ever detected (51% and 39%, respectively, of the patients without a primary tumor at presentation).

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Bloch and Gartner (%)</th>
<th>Nelson et al (%)</th>
<th>Eliassi-Rad et al (%)</th>
<th>Albert (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>37%</td>
<td>9.7%</td>
<td>8.3%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Lung</td>
<td>6%</td>
<td>6.7%</td>
<td>6.1%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>3%</td>
<td>4.2%</td>
<td>0.0%</td>
<td>–</td>
</tr>
<tr>
<td>Prostate</td>
<td>11%</td>
<td>0.0%</td>
<td>4.2%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Uterus/cervix</td>
<td>25%</td>
<td>–</td>
<td>5.0%</td>
<td>–</td>
</tr>
<tr>
<td>Skin</td>
<td>–</td>
<td>2.0%</td>
<td>14.3%</td>
<td>–</td>
</tr>
<tr>
<td>Thyroid</td>
<td>11%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kidney</td>
<td>11%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Leukemia</td>
<td>–</td>
<td>28.8%</td>
<td>34.8%</td>
<td>–</td>
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<tr>
<td>Lymphoma</td>
<td>–</td>
<td>6.7%</td>
<td>23.3%</td>
<td>–</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>–</td>
<td>–</td>
<td>29.0%</td>
<td>–</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>–</td>
<td>0.0%</td>
<td>16.0%</td>
<td>–</td>
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</tbody>
</table>
As seen in Table 2, breast and lung cancers are the most commonly detected malignancies to metastasize to the eye. Mewis and Young\textsuperscript{12} analyzed 250 patients with known breast carcinoma. At the time of evaluation, 152 patients were referred secondary to ocular symptoms, and 98 were asymptomatic. In the asymptomatic group, nine patients (9.2\%) were found to have metastatic disease. Taken as a whole, ocular metastasis is a major clinical oncologic problem. Eliassi-Rad et al\textsuperscript{6} estimated that in 1993, 66,262 (12.6\%) of 526,000 patients who died of their cancer would have ocular metastasis.

<table>
<thead>
<tr>
<th>Patients Who Present With Ocular Metastases: Primary Sites</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Breast</td>
</tr>
<tr>
<td>Lung</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Kidney</td>
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<tr>
<td>Prostate</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Cutaneous melanoma</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

\(=\) = not stated.

\(*\) = includes four cases of orbital metastasis

Pathogenesis/Site of Intraocular Metastasis

While any portion of the eye can be involved by metastatic disease, the most common tissue involved is the highly vascular choroid.\textsuperscript{4-12} There is no good explanation as to why the eye, particularly the choroid, is a common site for metastasis. Ferry and Font\textsuperscript{9} speculated that the distribution of tumors within the choroid may be related to its vascularity characteristics. Also, as previously noted, there are significant differences between primary tumors and their incidence of ocular metastasis. The reasons for these differences are also unexplained, but Ferry and Font suggest that the high incidence of breast cancer metastasis may be related to the longer life expectancy of breast cancer patients with metastasis, thus providing a longer time for intraocular metastasis to develop.

Shields et al\textsuperscript{11} surveyed 420 consecutive patients with uveal metastases. The tumors were unilateral in 320 patients and bilateral in 100 patients. This proportion of bilateral cases is considerably more than the 4.4\% noted by Ferry and Font. The study by Mewis and Young\textsuperscript{12} of breast cancer patients noted a 31\% incidence of bilaterality. In both the Ferry study and the Mewis study, the incidence of subsequent bilaterality was notable (17.6\% and 15\%, respectively). There seems to be no predilection for metastasis to preferentially affect the right or left eye.\textsuperscript{6,11}

In each affected eye, more than one metastasis may be noted. Shields et al\textsuperscript{11} reported multiple foci in 20\% of patients with choroidal metastasis. The mean number of uveal metastasis noted per eye was 2.0, and the maximum number noted was 13.

Presentation, Diagnosis, and Workup

The majority of symptomatic patients note a decreased visual acuity at the time of presentation.\textsuperscript{9-11} Other presenting signs or symptoms include diplopia, photophobia, ptosis, blepharitis, metamorphopsia, pain, flashes and floaters, mass lesion, uveitis, exophthalmos, secondary glaucoma, and detached retina.\textsuperscript{9,11}

The presence of metastatic disease to the eye is obviously high in the differential diagnosis of ocular lesions when a primary cancer is present elsewhere. Other conditions can be mistaken for metastatic disease;\textsuperscript{13} therefore, a careful evaluation is necessary for a correct diagnosis. The differential diagnosis includes amelanotic nevus, amelanotic melanoma, choroidal hemangioma, posterior scleritis, choroidal osteoma, retinitis, hemorrhage, choroiditis, rhegmatogenous retinal detachment, reactive lymphoid hyperplasia, lymphoma, Harada’s disease, uveal effusion syndrome, and central serous chorioretinopathy.\textsuperscript{8,13}

The diagnosis of ocular metastases is based primarily on clinical findings supplemented by imaging studies. The choroidal metastases usually appear as solid, flat, plaque-like, mottled, yellow-brown lesions.\textsuperscript{14} Figs 1-3 are fundus photographs from patients with metastatic tumor to the choroid. A number of ancillary ophthalmologic procedures can assist in the diagnosis of metastatic tumors. These procedures include ultrasonography, fluorescein angiography, computed tomography/magnetic resonance imaging, fine-needle aspiration, or wedge biopsy.\textsuperscript{8} On B-scan ultrasound, metastatic tumors tend to be acoustically solid convex masses with a lower silhouette, ie, lower height-to-base ratios than malignant melanoma.\textsuperscript{15} A-scan ultrasound shows moderate internal reflectivity compared with melanoma, which is usually low. Fluorescein angiography of metastatic choroidal tumors has some diagnostic value. The most common angiographic finding in metastatic choroidal tumors noted by David and Robertson\textsuperscript{16} was fluorescence that appeared in the early arteriolar or arteriovenous phase with progressive and more intense staining in the late phase.
Occasionally, biopsies of intraocular lesions are needed to ascertain the diagnosis. Fine-needle aspiration or, more rarely, a wedge biopsy can be obtained. Computed tomography and magnetic resonance imaging have a limited role in the diagnosis of ocular metastasis. Nevertheless, brain imaging is useful before initiation of radiotherapy to assist in treatment planning. This is especially important when treating patients with breast cancer. Mewis and Young reported that 22% of patients diagnosed with choroidal metastasis had a concurrent diagnosis of central nervous system metastasis. An additional 19% of patients had a subsequent diagnosis. When concurrent brain metastasis is diagnosed, the radiation technique is usually altered to include the entire cranial contents.

Management

A number of options are available for the therapy of ocular metastasis, including observation, chemotherapy, photocoagulation, cryosurgery, surgical resection, or radiotherapy. The specific therapy chosen for a patient is an individualized process that considers the clinical condition of the patient. For example, a patient with an asymptomatic metastasis who is near death probably does not require therapy. On the other hand, a symptomatic patient with controlled systemic disease should receive therapy to prevent further deterioration in vision. The most commonly applied treatment is external-beam radiotherapy.

Radiotherapy

Mewis and Young listed four indications for the use of external-beam radiotherapy in the treatment of metastatic breast carcinomas to the eye: (1) secondary retinal detachment, (2) decrease in visual acuity, (3) threat to decrease visual acuity, and (4) rapidly enlarging tumor. Using these criteria, 52 of 66 affected eyes with follow-up data available underwent irradiation. The visual acuity of these patients remained stable in 67.3%, improved in 26.9%, and deteriorated in only two eyes. One eye did not have a posttreatment visual acuity evaluation. Treatment consisted of 25 to 30 Gy with a lateral portal in 10 fractions.

Numerous publications document the ability of external-beam radiotherapy to successfully treat ocular metastasis effectively. Response rates in these series ranged from 33% to 89%, with the majority in the 80% range. In most of these studies, vision either improved or stabilized in a high percentage of patients.

Rudoler et al recently reported a multivariate analysis of 188 patients treated with external-beam radiotherapy for choroidal metastasis. The median total dose of radiotherapy was 36 Gy with a range of 30 to 40 Gy in 2 to 3 Gy fractions. The treated volumes include the unilateral posterior globe in 33% of patients, bilateral
posterior globes in 22%, the entire globe in 30%, and the whole brain plus the posterior globes in 15%. Following radiotherapy, 57% of all eyes had improved visual function or were able to maintain at least navigational vision. Of 47 eyes that were legally blind before radiotherapy, 21% improved to excellent vision and 15% to navigational vision at last follow-up. Ninety-three percent of patients remained free of clinically evident recurrent disease at last follow-up, with a 98% rate of globe preservation. Four patients were enucleated after radiotherapy for intractable pain from glaucoma.

Fig 4 is a fundoscopic photograph of a patient following external-beam radiation with a good clinical and fundoscopic response. The pretreatment fundoscopic picture is depicted in Fig 3.

**Target Volume, Techniques, and Dose Prescription of Radiotherapy**

In general, most authors have directed the radiation beam to include only the affected eye(s). Tkocz et al chose to irradiate both the affected eye and the nonaffected eye because of the relatively frequent development of bilateral disease. Obviously, if both eyes are affected, both should be targeted with radiotherapy. When synchronous brain metastases are present, the entire cranium should be targeted and both posterior globes included in the target volume. Also, if a decision for radiation is made, treatment should be initiated as soon as possible.

Multiple techniques have been described for treating unilateral metastasis. The majority of ocular metastases are located in the posterior uveal tract, allowing the use of lens-sparing techniques. Brady et al used either a wedge pair technique or direct lateral fields. The direct lateral field, commonly with a one-half beam technique and/or posterior angling to avoid the other lens, is the most commonly used posterior globe irradiation technique. Other techniques include a direct anterior/posterior field, a precision lateral technique with a vacuum eye immobilization, and a direct oblique field. I usually prefer a direct lateral field, angled posteriorly with half-beam blocking to avoid divergence (Fig 5).

The majority of authors deliver a prescribed dose of 30 to 40 Gy in fractions of 2 to 3 Gy. The dose is generally prescribed, in direct lateral fields, to a depth of 3 cm or an isodose curve to include the target volume. Although most authors do not describe the prescription point. In general, 30 to 40 Gy in 10 to 20 fractions could be considered a standard course of radiotherapy. For patients with a long life expectancy (ie, breast cancer patients with controlled systemic disease), a higher total dose with lower dose per fraction can be considered.

**Other Forms of Radiotherapy**
Shields et al. used plaque radiotherapy in the management of uveal metastasis in 36 patients -- as primary therapy in 27 patients and as therapy for recurrence in nine patients. A mean dose of 68.8 Gy was delivered to the tumor apex. Ninety-four percent of patients had regression of tumor, and five of six patients previously treated with external-beam radiotherapy were salvaged. Anteby et al. reported a patient with metastatic thyroid carcinoma who responded to systemic I therapy.

Chemotherapy

The use of chemotherapy to treat choroidal metastasis is not widely reported in the medical literature. Letson et al. described six patients with choroidal metastasis treated with chemotherapy. The tumor regressed in all of these patients. This experience, coupled with a description of regression of choroidal metastases from a bronchial carcinoid, suggests that the choroid may not always be considered a chemotherapy "sanctuary site." In very select patients with asymptomatic tumors not fitting the indications for external-beam radiation described by Mewis and Young, chemotherapy can be cautiously used as management for choroidal metastasis if the primary tumor type is likely to respond to a specific chemotherapeutic regimen. Close ophthalmologic follow-up is obviously extremely important if radiotherapy is not used in the initial management.

Survival and Follow-up

In general, survival is limited after the diagnosis of ocular metastasis. Ferry and Font noted a median survival of 7.4 months. Other authors have noted similar median survival rates of 5 to 20 months. Breast cancer patients tend to survive longer; Merrill et al. noted a 32-month median survival.

Follow-up is dictated by the clinical situation and the original treatment. In patients who initially are not irradiated, relatively frequent ophthalmologic evaluations should be obtained to allow initiation of radiotherapy at the earliest sign of disease progression.

Sequeae of Radiotherapy

With current techniques and dosages, complications of radiotherapy (both acute and long-term) are uncommon. Parsons et al. analyzed radiation retinopathy after external-beam radiotherapy for patients who were treated primarily for head and neck tumors. They noted no radiation retinopathy at doses below 45 Gy, a dose that is generally higher than that given for metastatic disease.

Rudoler et al. analyzed factors predisposing to long-term sequelae after therapy with external-beam radiotherapy for choroidal metastasis. Of 136 eyes, 28 (12%) developed one or more serious complications, including cataracts (14.5%), radiation retinopathy (2.5%), optic neuropathy (2.1%), exposure keratopathy (2.1%), and neovascularization of the iris (1.7%). Two patients developed narrow-angle glaucoma (0.8%), one of whom required enucleation. This rate of serious complication, ie, radiation retinopathy, is higher than that seen by Parsons et al. and is higher than expected. This cannot be completely explained by fractionation or other factors since one patient developed radiation retinopathy six months after receiving 10 Gy in 5 fractions.

Conclusions

Intraocular metastasis is a significant and under-recognized clinical problem for the practicing ophthalmologist and oncologist. The overall frequency of ocular metastasis in patients dying of cancer is approximately 12%, but it can be as high as 37% in patients with breast cancer. The diagnosis generally can be made by careful ophthalmologic examination. Radiotherapy is the cornerstone of management and will allow the majority of patients to maintain useful vision.

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References


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