Orbital Metastasis with Enophthalmos: A Review of the Literature

David M. Reifler
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David M. Reifler, MD*

Orbital metastasis is associated with enophthalmos in up to one third of all cases. After analyzing the clinical and pathologic features in 25 reported cases of enophthalmic orbital metastasis, the condition was found to almost exclusively affect females, usually in the 60 to 70 age group. The right orbit was the most commonly affected. The primary lesion was located in the breast in 19 (76%) cases and in the abdomen in 6 (24%) cases. In one third of the cases, the manifestations of the orbital metastasis were recognized before diagnosing the primary lesion. The most common presenting features were diplopia with ophthalmoplegia, ptosis, and decreased vision. Enophthalmos was usually less than 6 mm.

The clinical findings of enophthalmos, ophthalmoplegia, blepharoptosis, and a resistance to ocular retropulsion strongly suggest the presence of an orbital metastasis, even in patients without a previous history of cancer. Following a thorough systemic evaluation, an open orbital biopsy should be performed, if possible, to confirm the pathologic diagnosis. Special histologic techniques and laboratory studies may be valuable in directing further palliative therapy.

Metastasis of adenocarcinoma to the orbit is generally manifested by diplopia and blepharoptosis, followed by the development of pain, swelling, and exophthalmos (1). Henderson (2) has emphasized the clinical syndrome of the scirrhous types of metastatic carcinoma. While the initial orbit symptoms are similar to those of other adenocarcinomas, the diffusely infiltrating tumor may lead to a progressively immobilized globe with enophthalmos rather than exophthalmos.

Less than 2% of all orbital tumors are associated with enophthalmos. Henderson (2) found 6 (1.2%) cases among the Mayo Clinic series of 465 orbital tumors, while Ossoinig (3) recorded 3 (1.8%) cases among 170 orbital tumors. The percentage of tumors with enophthalmos in these two series increased significantly to 19% and 33%, respectively, when the tabulations considered only the tumors that were metastatic to the orbit. This higher incidence is probably related to breast carcinoma being the most common primary site of orbital metastases, with about 20% to 25% of these orbital breast metastases developing enophthalmos (1,2).

Although orbital metastasis with enophthalmos is decidedly more rare than metastasis with exophthalmos, the recognition of this unique syndrome is of great diagnostic importance. This paper reviews the literature concerning enophthalmic orbital metastasis.

Number of Cases

Twenty-four cases of enophthalmic orbital metastasis have been reported in the literature (2-14). In another case, the clinical presentation and special histochemical findings have been described (15). A summary of these 25 cases is listed in Table I. Among those reported, Cases 3,8,11,12, and 20 were mentioned in passing as part of the discussions that emphasized other allied aspects of either primary or metastatic orbital tumors. Of the two cases mentioned by Ferry (8), one (Case 7) had been previously reported by Sachs and O'Grady (7). This same case was subsequently included by Font and Ferry (1) in their classic article.

Although based on a few reported cases, a relatively widespread appreciation exists concerning the unusual behavior of metastatic scirrhous carcinoma in the orbit. As this syndrome has become somewhat more understood, many cases undoubtedly have gone unreported. Ossoinig (3) has reported three cases of enophthalmic orbital metastasis and has since seen an additional three cases, two of which arose from primaries in the breast and one that originated in the abdomen (Ossoinig, personal communication, July 9, 1985). These latter three cases and others whose documentation could not be reviewed were not included in this study.
Lateralization

The majority of enophthalmic orbital metastases have shown involvement of the right orbit. Of 21 unilateral cases in which the location of metastasis was specified, 16 (76%) involved the right orbit, and 5 (24%) involved the left orbit. These findings are in contrast to orbital metastasis in general, as various authors have noted involvement of both sides with about equal frequency (1,16) or even a left-sided predominance (17-19). The apparent right-sided preponderance of enophthalmic orbital metastases is therefore strikingly paradoxical. The left orbit was formerly believed to experience more metastases, since the left common carotid artery arises directly from the aorta (17-20).

Bilateral involvement occurs in about 25% of the cases with metastatic neoplasms to the eye and adnexa (21). However, only 1 (4%) of the 25 cases reviewed showed bilateral enophthalmic orbital metastases (1). (Except for the bilateral involvement, the clinical features in this case were similar in other respects to unilateral cases as will be described.) In the series considering all forms of orbital metastasis, the incidence of bilateral metastases was found to be approximately 7% to 9% (1,2) at the initial presentation. Henderson (2) observed that this rate virtually doubled as extended follow-up of patients with unilateral metastases disclosed subsequent contralateral involvement.

Because the initial symptoms are rather undramatic in scirrhous orbital metastases, whether there may be an occult involvement of the contralateral orbit is questionable. Sensitive noninvasive studies such as computed tomographic (CT) scanning and ultrasonography have failed to demonstrate contralateral involvement in such cases. This provides further evidence for the rarity of bilateral orbital metastases with enophthalmos.

Site of the Primary Tumor

The orbital metastasis arose from carcinoma of the breast in 19 (76%) of the 25 cases reviewed. Breast carcinoma involved the right side in two cases, the left side in four cases, and apparently both sides in two cases. The side of the breast involvement was not stated in 11 cases. In the remaining 6 (24%) cases, the carcinoma originated in the abdomen (Table I). Some authors have emphasized only linitis plastica of the stomach as an abdominal source of orbital metastasis with enophthalmos (12). In this series, however, three cases involved carcinomas arising from the stomach while other primary sites were documented (3,14), including one from the colon (Case 5), one from the pancreas (Case 24), and one that was not further specified (Case 6).

![Age distribution of 19 cases with enophthalmic orbital metastasis.](image)

Fig 1
Orbital Metastasis with Enophthalmos

Table I
Summary of Reported Cases of Orbital Metastasis Associated with Enophthalmos

<table>
<thead>
<tr>
<th>Case</th>
<th>Author/Year</th>
<th>Age/Sex</th>
<th>Orbit with Metastasis</th>
<th>Location of Primary</th>
<th>Amount of Enophthalmos (mm)</th>
<th>Ptosis</th>
<th>Ophthalmoplegia</th>
<th>Interval from Diagnosis of Primary to Diagnosis of Metastasis</th>
<th>Decreased Vision</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lawson, 1910</td>
<td>*/F</td>
<td>R</td>
<td>Breast (R)</td>
<td>*</td>
<td>Present</td>
<td>Present</td>
<td>+ 6 y</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>2</td>
<td>Biro, 1941</td>
<td>41/F</td>
<td>R</td>
<td>Breast (R,L)</td>
<td>3</td>
<td>Present</td>
<td>Present</td>
<td>+ 1 y</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>3</td>
<td>Hoyt, 1966</td>
<td>*/F</td>
<td>R</td>
<td>Breast†</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Unspecified</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>4</td>
<td>Ossoinig, 1969</td>
<td>78/F</td>
<td>R</td>
<td>Breast†</td>
<td>5</td>
<td>Present</td>
<td>Present</td>
<td>+ 2 y</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>5</td>
<td>Ossoinig, 1969</td>
<td>62/F</td>
<td>R</td>
<td>Colon</td>
<td>11</td>
<td>Present</td>
<td>Present</td>
<td>+ 18 mo</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>6</td>
<td>Ossoinig, 1969</td>
<td>56/F</td>
<td>L</td>
<td>Abdomen</td>
<td>4</td>
<td>*</td>
<td>Present</td>
<td>+ 6 y</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>7</td>
<td>Sachs, 1971</td>
<td>47/F</td>
<td>R</td>
<td>Breast (R)</td>
<td>4</td>
<td>Present</td>
<td>Present</td>
<td>Unspecified</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>8</td>
<td>Ferry, 1973</td>
<td>*/F</td>
<td>*</td>
<td>Breast†</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Metastasis first</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>9</td>
<td>Henderson, 1973</td>
<td>68/F</td>
<td>R</td>
<td>Breast†</td>
<td>2</td>
<td>Present</td>
<td>Present</td>
<td>+ 4 y</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>10</td>
<td>Henderson, 1973</td>
<td>45/F</td>
<td>R</td>
<td>Breast†</td>
<td>5</td>
<td>Present</td>
<td>Present</td>
<td>Unspecified</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>11</td>
<td>Henderson, 1973</td>
<td>*/F</td>
<td>*</td>
<td>Breast†</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Unspecified</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>12</td>
<td>Henderson, 1973</td>
<td>*/F</td>
<td>*</td>
<td>Breast†</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Unspecified</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>13</td>
<td>Henderson, 1973</td>
<td>60/F</td>
<td>R,L</td>
<td>Stomach</td>
<td>*</td>
<td>Present</td>
<td>Present</td>
<td>Metastasis first</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>14</td>
<td>Henderson, 1973</td>
<td>63/F</td>
<td>R</td>
<td>Stomach</td>
<td>*</td>
<td>*</td>
<td>Present</td>
<td>+ 6 mo</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>15</td>
<td>Manor, 1974</td>
<td>72/F</td>
<td>R</td>
<td>Breast (L)</td>
<td>3</td>
<td>*</td>
<td>*</td>
<td>Metastasis first</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>16</td>
<td>Radnot, 1975</td>
<td>50/F</td>
<td>R</td>
<td>Breast (R,L)</td>
<td>1</td>
<td>Present</td>
<td>Present</td>
<td>+ 5 y</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>17</td>
<td>Barroche, 1979</td>
<td>55/F</td>
<td>R</td>
<td>Breast (L)</td>
<td>4</td>
<td>Absent</td>
<td>Present</td>
<td>Metastasis first</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>18</td>
<td>Larmande, 1979</td>
<td>51/F</td>
<td>R</td>
<td>Stomach</td>
<td>10</td>
<td>Present</td>
<td>Present</td>
<td>Metastasis first</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>19</td>
<td>Larmande, 1979</td>
<td>68/F</td>
<td>R</td>
<td>Breast (L)</td>
<td>4</td>
<td>*</td>
<td>Present</td>
<td>+ 1 y</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>20</td>
<td>Hesselink</td>
<td>*</td>
<td>L</td>
<td>Breast†</td>
<td>2</td>
<td>*</td>
<td>*</td>
<td>Unspecified</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>21</td>
<td>Cline, 1984</td>
<td>65/F</td>
<td>R</td>
<td>Breast†</td>
<td>4</td>
<td>Present</td>
<td>Present</td>
<td>+ 51 mo</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>22</td>
<td>Cline, 1984</td>
<td>53/F</td>
<td>R</td>
<td>Breast†</td>
<td>3</td>
<td>*</td>
<td>Present</td>
<td>+ about 5 y</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>23</td>
<td>Cline, 1984</td>
<td>58/F</td>
<td>L</td>
<td>Breast†</td>
<td>2</td>
<td>*</td>
<td>Present</td>
<td>+ about 5 y</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>24</td>
<td>Cline, 1984</td>
<td>77/M</td>
<td>L</td>
<td>Abdomen</td>
<td>5</td>
<td>*</td>
<td>Present</td>
<td>Unspecified</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>25</td>
<td>Reifler, 1985</td>
<td>62/F</td>
<td>L</td>
<td>Breast (L)</td>
<td>2</td>
<td>Present</td>
<td>Present</td>
<td>Metastasis first</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

* unknown
† side not indicated

Age and Sex

The age of the patient was included in 19 of the 25 cases reviewed. The average age was 59.5 years with a range of 41 to 78 years (Table I). Over two-thirds of these cases occurred in the 60 to 70 age group with a peak occurrence in the early seventies (Fig 1).

Because of the preponderance of breast carcinoma as the source of enophthalmic metastasis, this condition was found to affect females almost exclusively (Table I). Although breast carcinoma is known to occur in males, and though an instance of ocular metastasis from breast carcinoma in a male has been reported (22), any documentation of men who suffered an orbital metastasis from a primary in the breast is unknown. Only one instance (Case 24) of enophthalmic orbital metastasis has been reported in a male (14), and though the source of the primary was not known, a carcinoma involving the pancreas was strongly suspected.

Temporal Relationship: Diagnosis of Primary Versus Metastatic Lesions

Information regarding the temporal relationship between the time of the respective manifestations and/or diagnoses of the primary and metastatic lesions was available in 18 of the 25 cases reviewed (Table II). In 12 (66.7%) of these 18 cases, the manifestations of orbital metastasis occurred between six months and six years following the diagnosis of the primary carcinoma, with an average interval of about 3.5 years. In the remaining 6 (33.3%) cases, the manifestations of the orbital metastasis were recognized before diagnosing the primary lesion.
Table II
Temporally Relationship Between Presentation of Primary and Metastatic Lesions in Orbital Metastases Associated with Enophthalmos: Analysis by Site of Primary Lesion

<table>
<thead>
<tr>
<th>Presentation of Lesions</th>
<th>Primary in Breast</th>
<th>Primary in Abdomen</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antecedent or simultaneous presentation of</td>
<td>3 (15.8%)</td>
<td>5 (50.0%)</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsequent presentation of orbital metastasis</td>
<td>11 (57.9%)</td>
<td>1 (16.7%)</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Unspecified interval</td>
<td>5 (26.3%)</td>
<td>2 (33.3%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Total number of cases</td>
<td>19 (100.0%)</td>
<td>6 (100.0%)</td>
<td>25 (100%)</td>
</tr>
</tbody>
</table>

The phenomenon of orbital metastasis as the presenting manifestation of a carcinoma has been emphasized in the literature reviewed (2,3,11,12). Orbital metastasis may also comprise the first evidence of disseminated malignancy in patients with a previous history of carcinomas. Because the initial opthalmic manifestations of orbital metastasis with enophthalmos may be subtle and a history of carcinoma remote or even absent, the proper diagnosis represents a diagnostic challenge. Nevertheless, the ophthalmologist is certainly in a unique position to properly commence an evaluation of such patients, who may greatly benefit from subsequent palliative therapy.

Among the cases reviewed, the tendency for an antecedent or simultaneous presentation of orbital metastasis was much more evident in carcinomas arising in the abdomen than those arising in the breast. The three instances (Cases 9, 17, and 25) of orbital metastasis occurring from breast carcinoma before the diagnosis of the primary tumor was unusual. In contrast, only once instance (Case 6) presented a well-documented abdominal carcinoma in which the primary tumor was diagnosed before manifestations of the orbital metastasis (3). Even in this case, the patient was apparently not aware that diffuse scirrhous abdominal carcinoma had been diagnosed at the time of a cholecystectomy, 18 months before ophthalmic presentation (Ossoinig, personal communication, July 9, 1985).

**Signs and Symptoms**

The amount of enophthalmos was recorded in 19 of the cases reviewed. In all but two cases, the enophthalmos measured less than 6 mm but ranged from 1 mm to as much as 11 mm (Table I). The enophthalmos was most commonly in the range of 3 mm to 4 mm (Fig 2). The two instances (Cases 5 and 18) of profound metastatic enophthalmos (11 mm and 10 mm) both arose from abdominal primaries (colon and stomach, respectively).

![Fig 2](#)

*Amount of enophthalmos in 19 cases of enophthalmos-producing orbital metastasis.*
Fig 3

A 61-year-old woman with enophthalmos and ophthalmoplegia caused by infiltrating lobular breast carcinoma metastatic to orbit: (A) attempted upward gaze, (B) right gaze, (C) primary position, (D) left gaze, and (E) downward gaze. Note also blepharoptosis and lack of lid movement.
The most common presenting features of enophthalmic orbital metastasis were diplopia and a limitation of ocular motility (Fig 3). These features were present in virtually all of the sufficiently detailed reports. The first symptom usually to be noticed by the patient was diplopia, a feature that is common with orbital metastases in general but one that often appears much later in cases of primary orbital tumors (20). However, in contrast to orbital metastases in general, most of the enophthalmic metastases seemed to have a more insidious onset and gradually progressive course. The diplopia is surprisingly well tolerated in many cases of enophthalmic metastasis (Ossoinig, personal communication, July 9, 1985). When the eyes remain aligned in the primary position (eg, Case 7), patients may be unaware of diplopia until it is brought to their attention (7). The mechanics of the restricted ocular motility are well documented by Lancaster projection testing (11,12).

Sachs and O'Grady (7) emphasized the similarities of physical findings between patients with essential facial hemiatrophy (Parry-Romberg syndrome) and enophthalmic orbital metastasis. The former condition is also associated with enophthalmos and restricted ocular motility. For this reason, an erroneous diagnosis of Parry-Romberg syndrome is rarely made in cases of orbital metastasis. However, essential facial hemiatrophy is characterized by a more regional atrophy of facial tissue including skin, subcutaneous fat, and connective tissue, bone, and muscle. The diagnosis of "early" essential facial hemiatrophy should be viewed with suspicion when based solely on orbital findings.

In the cases described herein, ptosis was frequently seen and usually in greater amount than could be accounted for by the enophthalmos alone (Fig 3). The movements of the lid and the blinking mechanisms tend to be severely impaired, probably because of scirrhous infiltration surrounding the levator. Relative corneal hypesthesia may occur and, combined with a mechanical dysfunction of the lid movement, leads to further corneal decompensation. Despite extensive infiltration that virtually encases the deeper orbital structures, the skin remains remarkably supple and normal in appearance without ulceration.

A profound resistance to attempted retropulsion of the globe, when seen in conjunction with enophthalmos, is an important diagnostic sign. Replacing compliant fat with a dense fibrous stroma results in an orbit that feels "rock hard." However, because of the diffuse scirrhous infiltration, a discrete mass sometimes cannot be palpated. The findings of enophthalmos, ophthalmoplegia, and resistance to retropulsion of the globe should strongly suggest a scirrhous carcinoma metastatic to the orbit even when there is no previous history of a primary tumor.

Localized pain has been emphasized as a prominent feature of orbital metastasis (1,2). However, in many cases of enophthalmic orbital metastasis, pain was either absent or minimal (3). This may be due in part to the absence of a sudden, dramatic onset of pain and a lack of acute inflammatory edema. Conjunctival hyperemia and chemosis is frequently noted, but this may be related to exposure as well as elevated venous pressure.

Decreased vision was noted frequently among the cases reviewed. A number of factors probably contributed to visual decline including keratopathy, hypermetropia (3), glaucoma (9), choroidal metastasis (14), and papilledema (6). Concurrent orbital and ocular involvement has been observed in occasional cases of metastatic carcinoma (8,19,23). One (4%) of the cases of orbital metastasis with enophthalmos (Case 21) had an associated intraocular metastasis on the same side (14).

**Diagnostic Studies**

**Radiology**

Plain radiographs are typically normal in cases of orbital metastasis associated with enophthalmos. Cases of scirrhous orbital carcinoma are typically not associated with destruction of the orbital bones. Apparently, the one case (Case 15) that showed an extensive destruction of bone was not a scirrhous carcinoma. The enophthalmos in this case was probably due to the bone destruction itself. While minimal bone destruction was noted in other cases (13), it probably was insufficient to account for the enophthalmos.

In general, about 68% of orbital metastases are associated with aggressive bone destruction, with a large number of these tumors showing direct intracranial extension (23). With the exception of the few cases noted previously, the orbital metastases in this series seemed to behave differently in this respect.

**Computed tomography**

Reproductions and descriptions of orbital CT scans were included in some of the more recent reports of orbital metastasis with enophthalmos (Cases 17,20,21, and 25). The amount of enophthalmos can easily be estimated from axial projections, although both axial and coronal views are recommended to accurately assess the character, extent, and anatomic relationships of the metastatic tumor. Evidence of local infiltration involving both the intraconal and extracanal compartments as well as extracanal muscle could be discerned. In one case (Case 25), enhancement of the lesion and the optic nerve following intravenous contrast injection was misinterpreted by the radiologist as representing optic glioma or meningioma (Reifler, unpublished data, January 17, 1985). Actually, the optic disc enhancement was probably due to papilledema.

**Other radiographic studies**

Carotid arteriography and orbital venography may be
normal in cases of orbital metastasis with enophthalmos (11). Because of the sensitivity of CT scanning and orbital ultrasonography, these studies are probably unnecessary except in unusual circumstances.

Ultrasonography
The A-scan and B-scan ultrasonographic findings of enophthalmic orbital metastasis have also been reported (3). The lack of an acoustic interface between the tumor and adjacent orbital tissue correlates well with the histological absence of encapsulation, although the pattern of the adjacent orbital fat may be irregular. In the densest areas of infiltration, there is a remarkable lack of internal reflectivity, resulting in an acoustically "empty" or "lucent" zone on the B-scan. Apparently, the relatively dense desmoplastic reaction is a remarkable lack of internal reflectivity, resulting in an acoustically "empty" or "lucent" zone on the B-scan. Apparently, the relatively dense desmoplastic reaction results in a lack of acoustic interfaces.

Fluorescein angiography
In cases of orbital metastasis, ancillary studies of the ocular fundus can be helpful sometimes in characterizing associated pathology of the choroid, retina, and optic disc. In particular, choroidal metastasis (24), striae, and papilledema (6) can be documented by fundus photography and fluorescein angiography.

Electromyography
No particular electromyographic abnormalities were noted in one case of orbital metastasis with enophthalmos where this study was performed (11).

Carcinoembryonic antigen
In the past, the serial measurement of serum carcinoembryonic antigen (CEA) in cases of orbital metastasis has been emphasized (25,26). However, serum CEA levels have no specificity and little diagnostic value in the evaluation of orbital metastases. Serum CEA levels were within a normal range in the one case of enophthalmic orbital metastasis where this study was performed (Case 25).

Biopsy
Even in patients with presumed orbital metastasis and a previous history of carcinoma, an attempt should be made to obtain an orbital specimen for cytologic or histopathologic diagnosis. This is to assure the implementation of an appropriate treatment regimen by consulting medical oncologists and radiation therapists. The histopathology of enophthalmos-producing metastases usually reveals infiltration with a dense fibrous stroma, and it may be difficult to distinguish between an abdominal and mammary source. In one of the cases (Case 18) reported by Larmande and Rossazza (12), an orbital metastasis arising from a primary in the stomach occurred in a patient with a previous history of breast carcinoma. An orbital biopsy confirmed the presence of scirrhous carcinoma that was presumed to be a metastasis from the breast. The gastric carcinoma went undiagnosed for another year until abdominal complications ultimately led to the patient’s death.

An orbital biopsy may be easy to perform, particularly if there is a palpable, anteriorly situated component of the lesion. Metastatic tumors that are located posteriorly are technically a more difficult biopsy, especially if the tumors are located medially. Because the orbit is typically noncompliant in cases of scirrhous metastasis, access to the medial orbital region may require removal of the lateral wall for adequate exposure.

A negative fine-needle aspiration biopsy is a characteristic of tumors with a predominantly fibrous matrix where intercellular cohesion is strong and cellularity is diminished (27). Fine-needle aspiration biopsy may therefore be nondiagnostic in cases of orbital metastasis with enophthalmos (15). For debilitated patients or those refusing major surgery, a large bore-needle biopsy (16- to 18-gauge) may be considered to obtain a cylinder of tissue that is readily processed by paraffin embedding rather than cytologic techniques (28).

Assays for hormone receptors
Bullock and Yanes (25) have described the usefulness of steroid-hormone receptor assays in patients with breast carcinoma metastatic to the orbit. In women with metastatic breast carcinoma, the rate of objective response to endocrine therapy is much improved when the cancerous tissues contain estrogen receptors (29). In one case of orbital metastasis with enophthalmos (Case 25), steroid-hormone receptors were documented using this technique as well as with fluorescent histochemical techniques. Because of the low yield of needle aspiration biopsy in cases of scirrhous tumors and the potential value of special techniques requiring an adequate tissue specimen, an open orbital biopsy seems the best way to harvest tissue in suspected cases of orbital metastasis with enophthalmos.

Pathologic Findings
Histopathology
The histologic features of orbital metastasis are generally typical of scirrhous carcinoma. The degree of cellular differentiation varies between cases. The orbital fat shows infiltration of small carcinoma cells occurring in small nests or a single file distribution. A proliferation of fibrous tissue occurs adjacent to the sheets and nests of the infiltrating cancer cells. The interrelationships between the neoplastic infiltration, the decrease in the volume of orbital fat, and the fibrous proliferation remain to be elucidated. The clinicopathologic correlations between these destructive processes and findings such as enophthalmos and ophthalmoplegia also remain to be defined.
In cases of orbital metastasis, special histologic stains such as mucicarmine, alcian blue, and periodic acid-Schiff can further characterize the biochemical composition of cytoplasmic organelles and thus may be used to accurately predict the site of the primary neoplasm (1). The diagnosis of a mucus-secreting adenocarcinoma can easily be confirmed by these staining techniques. Documentation of further characterize the biochemical composition of cytoplasmic organelles and thus may be used to accurately predict the site of the primary neoplasm (1). The diagnosis of a mucus-secreting adenocarcinoma can easily be confirmed by these staining techniques. Documentation of steroid-hormone receptors in orbital metastases may be accomplished with quantitative assays, fluorescence microscopy, or immunoenzyme techniques (30). The increasing availability of clinically useful tissue-specific antibody-conjugated reagents has proven valuable in the study of some orbital metastases (31). However, immunoperoxidase techniques have not yet been applied to the study of enophthalmic orbital metastasis.

**Electron microscopy**
The electron microscopic findings were presented in only one of the cases reviewed (Case 16). Groups of tumor cells were found embedded among collagen fibers, correlating with the light microscopic findings of abundant scirrhous connective tissue. The tumor cells were spindle-shaped and poorly differentiated, but with scanning electron microscopy they often assumed a club-like appearance and had clustered in small groups.

**Treatment**
Palliative treatment should be sought for patients with biopsy-proven orbital metastasis. In addition to the management of ocular problems such as corneal exposure, various modes of treatment include localized radiation therapy, systemic chemotherapy, and endocrinologic therapy in some cases. Radiation therapy may cause a temporary increase in periorbital inflammation that quickly subsides after treatment has ended. Antiestrogenic agents such as tamoxifen citrate are particularly efficacious when estrogen receptors have been detected in primary and metastatic tumor specimens. Systemic therapy can also have a beneficial effect on other sites of metastasis. Palliative treatment was successful in several of the cases in improving the lid function and reducing the amount of enophthalmos.

**Prognosis**
In the cases reviewed, the data were not sufficient to generate meaningful mortality statistics. In many of the cases, follow-up data either was not given or covered only short periods of time. However, with palliative therapy, several patients did well for over one year while others experienced the complications of diffuse metastatic carcinoma within a few months. In cases of metastatic carcinoma to the orbit in general, the median survival has been reported to be about 16 months from the time of surgery (8). Whether the survival rate in cases of enophthalmic orbital metastasis would be any different is unknown.

**Etiology of Ophthalmoplegia and Enophthalmos**
Many theories have been proposed to explain the etiology of ophthalmoplegia and enophthalmos in cases of orbital metastasis. It has been well recognized that ophthalmoplegia can be produced by discrete orbital carcinomatous metastasis in the extraocular muscles and motor nerves (32). Ptosis and ophthalmoplegia associated with extraocular muscle infiltration may also be seen in cases of primary orbital lymphoproliferative disorders (33). Various diseases associated with infiltration involving extraocular muscles have been observed to produce an acquired orbital retraction syndrome (34). However, the retraction of the globe is present only with attempted versions within the field of action opposite the involved muscle. Acquired orbital retraction syndrome due to infiltrative orbital disease also has been described in cases associated only with exophthalmos. Since ophthalmoplegia occurs so early in the course of scirrhous orbital metastasis, perhaps subtle retraction with attempted eye movements might be observed early in such patients. However, by the time enophthalmos develops, replacement of the orbital tissues is usually quite extensive, and noncompliance within the orbit probably would prevent such retractions from occurring.

Orbital neoplastic infiltration alone does not explain the phenomenon of enophthalmos. In general, three mechanisms alone or in combination can lead to enophthalmos: structural abnormality, fat atrophy, and traction. Various conditions that may be associated with enophthalmos have been reviewed by Cline and Rootman (14) and are summarized in Table III. Sachs and O'Grady (7) postulated that normal orbital fat is replaced by a tumor that has a relatively

<table>
<thead>
<tr>
<th>Table III</th>
<th>Conditions Associated with Enophthalmos (after Cline and Rootman [14])</th>
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<tbody>
<tr>
<td>Structural abnormalities</td>
<td>Orbital asymmetry</td>
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<td></td>
<td>Maxillary hypoplasia</td>
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<td></td>
<td>Microphthalmos</td>
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<td>Destruction of the orbital bones (sinusitis, neoplasia)</td>
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<td>Trauma</td>
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<td></td>
<td>Absence of sphenoid wing as in neurofibromatosis</td>
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<tr>
<td>Orbital fat atrophy</td>
<td>Orbital varix</td>
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<tr>
<td></td>
<td>Scleroderma</td>
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<td></td>
<td>Following irradiation</td>
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<td>Following orbital hemorrhage</td>
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<td></td>
<td>Lipodystrophy</td>
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<td>Repeated self-inflicted pressure</td>
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<tr>
<td>Traction</td>
<td>Nystagmus retractor</td>
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<tr>
<td></td>
<td>Following surgical shortening of an extraocular muscle</td>
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<tr>
<td></td>
<td>Following injection of succinylocholine (transient)</td>
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</table>
smaller volume and that maturation of the collagen matrix is associated with contracture in a manner similar to that seen in maturing scar tissue. Henderson (2) emphasized this proposed mechanism of contracture causing the muscles, nerves, and surrounding soft tissues to become "so entwined and infiltrated by the scirrhous tumor that the helpless eye soon is immobilized and pulled posteriorly."

As previously mentioned, one report (Case 15) was given by Manor (9) in which the enophthalmos was produced by extensive bone destruction. This case did not seem to follow the clinical picture of scirrhous carcinoma and therefore was probably unique among the cases reviewed. As Clíne and Rootman (14) noted, the various causes of enophthalmos may occur alone or in combination with one another. Further studies may substantiate the proposed mechanisms producing ophthalmoplegia and enophthalmos in cases of orbital metastasis. As Barroche et al (11) said: "Whilst the pathogenesis of the ophthalmoplegia is evident, that of the enophthalmos is purely conjectural."

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References