

Cancer Metastatic to the Orbit

The 2000 Robert M. Curts Lecture

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Purpose: To report the demographics and clinical features of a large series of patients with orbital metastasis.

Methods: Retrospective chart review on 100 consecutive patients and a literature review on orbital metastasis.

Results: Of 100 patients, the primary tumor site was breast in 53 (53%), prostate gland in 12 (12%), lung in 8 (8%), skin (melanoma) in 6 (6%), kidney in 5 (5%), gastrointestinal tract in 5 (5%), choroid (melanoma) in 2 (2%), parotid gland in 1 (1%), and adrenal gland (neuroblastoma) in 1 (1%). Of patients in whom a detailed history was available, there was no history of cancer at the time of presentation in 19%. In 10%, the primary tumor remained undetected despite systemic evaluation. There were 36 male patients and 64 female patients whose mean age at diagnosis was 62 years (median 60 years, range 5 to 91 years). Both the right and left orbits were affected equally, and 4 cases (4%) were bilateral. The most frequent clinical findings were limited ocular motility (54%), proptosis (50%), and palpable mass (43%). The diagnoses were established by history, systemic survey, imaging studies, and biopsy. Treatment included chemotherapy, hormone therapy, irradiation, surgical excision, or observation, depending on clinical circumstances. Among patients with sufficient follow-up, 95% died of metastasis, with overall mean survival of 15 months (median 15 months; range 3 to 96 months) after orbital diagnosis.

Conclusions: The most common primary cancers that metastasize to the orbit are breast, prostate gland, and lung cancer. In 19%, there is no history of cancer when the patient presents with ophthalmic symptoms and in 10% the primary site remains obscure despite systemic evaluation. The systemic prognosis is generally poor.

Most metastatic cancer to the ocular region occurs in the uveal tract, especially in the posterior part of the choroid.^{1,2}

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Metastasis to the soft tissues of the orbit is relatively uncommon, and most ophthalmologists and oncologists have had little or no experience with orbital metastasis. It is well known, however, that a patient with a history of cancer who has proptosis or globe displacement should be evaluated for orbital metastasis.³⁻⁴ Several authors have reported their experience with orbital metastasis.⁵⁻²⁹ The largest series was reported by Henderson and associates,²⁹ who described the combined experience of surgeons at the Mayo Clinic over 40 years (1948 to 1987). In this report, we describe our personal experience with 100 consecutive patients with cancer metastatic to the orbit and provide a literature review on this subject.

METHODS

The records of all patients diagnosed with metastases to the orbit at Wills Eye Hospital over a 23-year period were reviewed retrospectively. We initiated our survey as of July 1976 when the first such patient was diagnosed on the Ocular Oncology Service and completed the survey in October 1999 when a total 100 of consecutive patients with orbital metastasis had been accumulated. Of the 100 cases, 70 were evaluated by the senior author (J.A.S.) and his colleagues on the Oncology Service, and biopsy was performed in 30 cases by other physicians and submitted to the Pathology Department, where the specimens were reviewed by one of the authors (R.C.E.).

We used a computerized flowsheet to record and tabulate general data, tumor data, clinical findings, diagnostic techniques, treatment, and prognosis. General data included the patient's age, sex, race, history of cancer, and interval from diagnosis of the primary cancer to orbital metastasis. Tumor data included the location and type of the primary neoplasm, laterality (right orbit, left orbit, both orbits), and tumor size, configuration, location, and number as determined by computed tomography (CT) or magnetic resonance imaging (MRI) or surgical or pathologic observations. The presence of other ocular sites of metastasis was also recorded. Diagnostic methods used (history, ocular examination, imaging studies), treatment (observation, irradiation, chemotherapy, hormonal therapy), and patient outcome were also tabulated.

Only patients who had conclusive evidence of cancer metastatic to the orbit by hematogenous routes were included in this analysis. Cases of direct orbital invasion from adjacent structures and lymphomas and leukemias affecting the orbit were excluded.

RESULTS

General Data

Of 100 consecutive patients with cancer metastatic to the orbit, the diagnosis was established by surgical biopsy in 97 cases and fine needle aspiration biopsy (FNAB) in 3 cases. The primary site, type of tumor, and patient sex are shown in Table 1. Carcinoma of the breast accounted for 53 of the cases (53%), and all 53 occurred in female patients. Prostate cancer accounted for 12 (12%). Of the 8 patients with lung cancer metastatic to the orbit, 3 were men and 5 were women. All 6 cases of cutaneous melanoma and all 5 cases of renal neoplasms metastatic to the orbit occurred in male patients. There were 5 cases of metastasis from tumors of the gastrointestinal tract, which included 2 adenocarcinomas and 3

TABLE 1. Primary site and type of metastatic tumors to the orbit in 100 patients

Primary site	Tumor type	No. of patients	%	M	F
Breast	Carcinoma	53	53	0	53
Prostate gland	Carcinoma	12	12	12	0
Lung	Carcinoma	8	8	3	5
Skin (melanoma)	Melanoma	6	6	6	0
Kidney	Carcinoma (4) Sarcoma (1)	5	5	5	0
Alimentary tract	Carcinoma (2) Carcinoid (3)	5	5	3	2
Eye (choroid)	Melanoma	2	2	0	2
Parotid gland	Carcinoma	1	1	0	1
Adrenal	Neuroblastoma	1	1	1	0
Undetermined	...	7	7	5	2
Total		100	100	35	65

carcinoid tumors. Two of the carcinoid metastases occurred in men and 1 in a woman. There were 2 cases of choroidal melanoma metastatic to the contralateral orbit, both of which were in women. Both of these patients had prior enucleation for primary choroidal melanoma, and the orbital metastasis occurred in conjunction with widespread metastatic disease.

Primary Tumor Site and Patient Age

The relation between the site of the primary tumor and patient age at the time of diagnosis is shown in Table 2. The patient age ranged from 5 to 91 years, with a mean of 62 years. The only child was a 5-year-old boy with orbital metastasis from adrenal neuroblastoma. There were 6 patients (6%) between 20 and 39 years of age, 36 patients (36%) between 40 and 59 years of age, 53 patients (53%) between 60 and 79 years of age, and 4 patients (4%) older

TABLE 2. Relation between patient age and location of primary neoplasm

Primary site	0-19	20-39	40-59	60-79	>80	Total
	y	y	y	y	y	
Breast	0	5	20	28	0	53
Prostate	0	0	1	9	2	12
Lung	0	0	5	3	0	8
Skin (melanoma)	0	1	3	2	0	6
Kidney	0	0	2	3	0	5
Alimentary tract	0	0	1	3	1	5
Eye (choroid)	0	0	2	0	0	2
Parotid	0	0	1	0	0	1
Adrenal	1	0	0	0	0	1
Undetermined	0	0	1	5	1	7
Total	1	6	36	53	4	100

than 80 years of age. There were 64 female patients and 36 male patients, 89 whites, 10 blacks, and 1 Asian.

History of Primary Neoplasm

Of the 70 patients seen on the Oncology Service in whom a detailed history was available, 57 (81%) had a known primary neoplasm and 13 (19%) had no history of cancer when referred to us with orbital metastasis. Of those with a known primary neoplasm, orbital metastasis became evident at a mean of 71 months after the primary cancer was diagnosed (median, 55 months; range, 6 to 90 months) and 8 months after the first systemic metastases were detected (mean, 8 months; range, 0 to 12 months). Of the 13 patients with no history of previous cancer, the primary tumor was subsequently located in 6 cases. Three of these were in breast, one lung, 1 skin (melanoma), and 1 adrenal (neuroblastoma). In 7 cases (10%), the primary tumor remained obscure despite systemic evaluation. These tumors were generally classified histopathologically as poorly differentiated malignant neoplasms.

Laterality

The orbital metastasis affected the right orbit in 45 cases and the left eye in 43 cases; it was bilateral in 4 cases. In 8 cases from the Pathology Department files, the laterality was not available. Of the 4 cases with bilateral orbital metastasis, the primary tumor was breast cancer, prostate cancer, cutaneous melanoma, and choroidal melanoma in 1 case each.

Tumor Size and Location

Information on tumor size and location was available on 68 of the 70 patients evaluated clinically on the Oncology Service, based on clinical, radiologic, and/or surgical observations. The main component of the tumor was located in the anterior part of the orbit (posterior sclera to eyelids) in 41 cases and in the posterior half (posterior sclera to orbital apex) in 27. Further findings on CT and MRI are discussed subsequently.

Additional Ocular Metastases

Among the 70 patients with adequate clinical information, most of the orbital metastases were solitary. However, 5 patients had 2 metastatic foci in the affected orbit and 1 had 3 metastatic foci. In 15 (21%) patients there were ocular metastases in addition to the orbital metastases. These included 2 patients with metastases to the eyelid, 3 with metastases to the conjunctiva, and 9 patients with metastases to the choroid. In addition, 1

patient with a orbital metastasis from lung carcinoma primary also had simultaneous metastases to the choroid and conjunctiva.³⁰

Presenting Symptoms and Signs

Details of presenting symptoms and signs, available for the 70 patients seen clinically on the Oncology Service, are depicted in Table 3. Limited ocular motility was noted in 38 (54%), displacement of the globe or proptosis in 35 (50%), blepharoptosis in 34 (49%), palpable mass in 31 (43%), blurred or decreased vision was present in 16 (23%), pain in 12 (17%), visible mass or swelling in 12 (17%), enophthalmos in 8 (11%), and diplopia in 6 (9%). The enophthalmos was seen only with cases of scirrhous breast cancer metastatic to the orbit.

Diagnostic and Therapeutic Methods

It was not the purpose of this report to analyze in detail the diagnostic and therapeutic methods of patients with orbital metastasis. Furthermore, such assessment was very difficult because of the diversity of the cases and because many patients were ultimately treated elsewhere, thus limiting our ability to obtain follow-up information.

In general, the diagnosis was made in each instance by a thorough history, ocular examination, general physical assessment looking for a primary neoplasm and other metastases, orbital CT or MRI, and orbital open biopsy or FNAB. The extent to which each of these modalities was used depended on the overall clinical situation. We had access to CT or MRI studies in 64 of the 70 cases seen on the Oncology Service. Of these, 41 tumors (mostly breast and prostate primary sites) showed a diffuse configuration (Fig. 1). In 23 cases (mostly lung, kidney, skin melanoma, uveal melanoma, and carcinoma)

TABLE 3. Presenting symptoms and signs in 70 patients with orbital metastases

Symptom or sign*	No.	%
Limited ocular motility	38	54
Proptosis	35	50
Blepharoptosis	34	49
Palpable mass	31	43
Blurred vision	16	23
Pain	12	17
Visible lump	12	17
Enophthalmos	8	11
Diplopia	6	9

Data extracted from 70 patients seen specifically by the authors and in whom details of history and examination were available.

* Several patients had more than one complaint, explaining why numbers and percents add to more than the number of patients.



FIG. 1. Computed tomography of orbital metastasis from breast cancer. **A**, Axial image showing diffuse, infiltrative mass in orbit and along medial rectus muscle. **B**, Coronal image should diffuse tumor encircling globe.

tumors) the tumor was round to ovoid and well circumscribed (Fig. 2). Bone erosion was noted in 23 (39%) cases. It was seen in all 12 cases of metastatic prostate cancer (Fig. 3) and in several cases of breast cancer, lung cancer, and others. The 5-year-old child with metastatic neuroblastoma had extensive orbital bone involvement.

It was not possible to draw meaningful conclusions regarding the efficacy of different management methods because treatment varied widely and often consisted of more than one modality. Of the 70 patients on whom we had sufficient clinical data, approximately 50 were receiving some form of chemotherapy or hormonal therapy for known systemic metastases. After the diagnosis was established, 39 patients were treated additionally with



FIG. 2. Computed tomography of orbital metastasis from ileal carcinoid tumor. **A**, Axial image showing well-circumscribed, superior retrobulbar mass. **B**, Coronal cut showing location of mass in superior aspect of orbit. It is compressing superior rectus and levator muscles, obscuring clear view.

orbital irradiation, usually about 35–40 Gy to the affected orbit in divided doses over 3 to 5 weeks. In 18 cases, the orbital tumor was totally removed at the time of our biopsy, and no further orbital treatment was given. In 6 cases, the orbital tumor was managed by observation only, usually because the patient declined treatment or had near terminal disease. In 6 cases, treatment data could not be obtained. In the majority of cases, the local response to such palliative treatment was favorable and most patients remained free of major ocular complications.

Systemic Status and Prognosis

We attempted to obtain follow-up data on the 70 patients seen by our service (Table 4). One patient (<1%) with breast cancer was in remission with no active metastases 8 years after diagnosis and radiation treatment to the affected orbit. Three (4%) patients were living with active metastases. Fifty-two (75%) of the

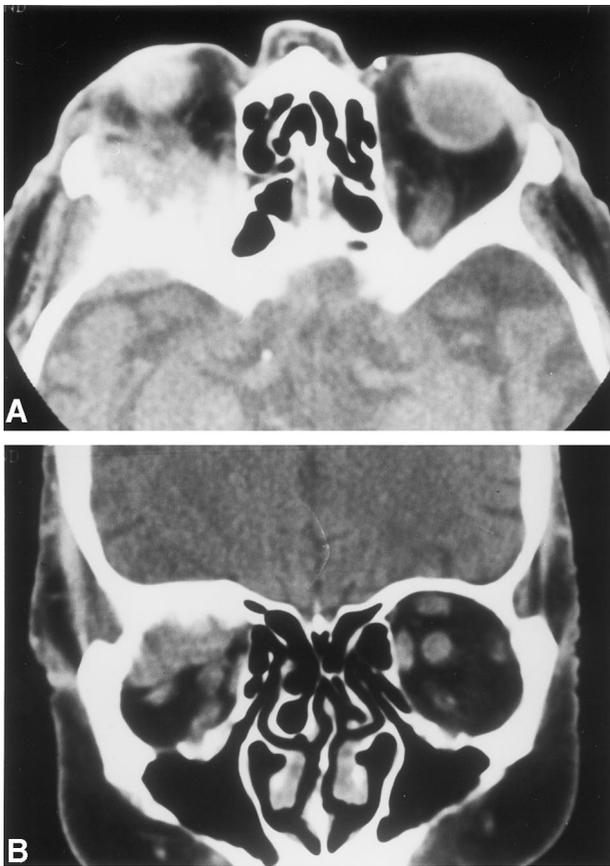


FIG. 3. Computed tomography of orbital metastasis from prostate cancer. **A**, Axial image showing diffuse, ill-defined mass is causing hyperostosis and erosion of bone. **B**, Coronal image showing bony thickening in orbital roof.

patients in this study were known to have died as a result of disseminated metastasis from the primary neoplasm. The mean time of death was 14 months after diagnosis of orbital metastasis (range, 2 to 46 months). Four (6%) patients had died of unrelated causes. In 10 (14%) patients we were unable to obtain specific details on the cause of death. However, because most of them had

TABLE 4. Systemic status of 70 patients with orbital metastases

Systemic status	No.	%
Alive with no active metastasis	1	<1
Alive with active metastases	3	4
Deceased from other causes	4	6
Deceased from metastases	52	75
Unknown but presumed dead from metastasis	10	14
Total	70	

systemic metastasis, we presume that they died of metastatic disease.

Overall, the mean survival time after the orbital diagnosis was 20 months. Patients with metastatic carcinoma had the longest mean survival (60 months) and patients with breast cancer had the second-longest mean survival (22 months) after diagnosis or orbital metastasis. Patients with lung cancer as the primary tumor had the shortest survival time (mean, 4 months) after orbital diagnosis.

DISCUSSION

The orbit is an unusual site for metastatic cancer. Metastasis to the orbit has ranged from 1% to 13% among reported series of all orbital tumors.⁵⁻¹⁵ Orbital metastasis is believed to occur in approximately 2% to 3% of patients with systemic cancer.^{16,17} Several authors have reported their experience with cancer metastatic to the orbit.¹⁸⁻²⁹ The largest prior series was reported by Henderson and associates,²⁹ in which they described 83 cases referred to the Mayo Clinic over a 40-year period. Since orbital metastasis is rather rare and unusual, a number of case reports or small series of specific tumor types have also been published.³⁰⁻⁸¹ Our series of 100 consecutive cases possibly represents the largest personal experience with orbital metastasis. A review of our personal experience and our review of the English-language literature has allowed us to make specific comments regarding the incidence, location, and types of tumors that metastasize to the orbit and to provide general guidelines about diagnosis and treatment of orbital metastasis.

Table 5, which is used as a reference point for subsequent comments, lists most of the larger series of orbital metastasis, including the present report. In our series, breast carcinoma accounted for the majority of cases, a finding consistent with other reports. The second most common primary cancer in our series, and in 2 other sizable series,^{23,24} was prostate carcinoma. In most other series, lung cancer was second and prostate cancer was third. In a few instances, the primary cancer was in the gastrointestinal tract, kidney, and skin (melanoma). Other less common primary cancers that are not specifically listed include carcinoma of the thyroid, liver, pancreas, adrenal gland (neuroblastoma) and salivary gland, choroidal melanoma, and several others. For the most part, tumors that metastasize to the orbit are the same as those that metastasize to the uveal tract.² The only exception is metastasis from prostate cancer, which accounts for approximately 12% of orbital metastasis and only 2% of metastasis to the uveal tract.¹

The relation between sex and type of primary tumor is

TABLE 5. Major reports on primary neoplasms for cancer metastatic to the orbit

First author	Year	No. of cases	Breast	Lung	Prostate	GI tract	Kidney	Skin, MM	Unknown	Other
Forrest ⁵	1949	4	3	0	0	1	0	0	0	0
Hart ⁶	1962	14	5	5	0	0	0	0	4	0
Moss ⁷	1962	3	1	0	0	0	0	0	2	0
Albert ¹⁶	1967	5	3	1	1	0	0	0	0	0
Silva ⁸	1968	7
Jensen ⁹	1970	8	3	0	0	1	0	1	0	3
Reese ¹⁰	1971	10
Font ¹¹	1976	28	8	4	1	1	0	0	10	4
Huchinson ¹⁸	1979	32
Bullock ¹⁹	1980	13	6	1
J Shields ^{13*}	1984	16	12	1	2	1
C Shields ^{22*}	1988	35	18	2	6	2	1	1	4	1
Goldberg ²³	1990	38	13	2	4	3	0	5	3	8
Tijl ²⁴	1992	34	20	1	5	0	2	0	3	1
Henderson ²⁹	1994	83	37	12	7	6	6	0	4	5
Gunalp ²⁶	1995	28	8	6	3	2	1	0	0	8
Seregard ¹⁵	1999	11	4	1	0	0	0	0	2	1
J Shields	2000	100	51	8	12	5	5	6	9	4
Totals		469	92	44	41	22	15	13	41	34

* Not included in the totals because these 2 reports comprised some of the earlier cases included in the current report. GI indicates gastrointestinal; MM, malignant melanoma.

also depicted in Table 1. Most metastatic cancer to the orbit occurs in women because of the tendency of breast cancer to metastasize to the orbit. It was of interest that of the 8 cases of lung cancer metastatic to the orbit, 5 occurred in women. All orbital metastases in our series from cutaneous melanoma and renal cell carcinoma occurred in men. A similar distribution of sex and type of primary tumor is also true for uveal metastases.¹

Most orbital metastases are carcinomas. Sarcomas and melanomas metastatic to the orbit are considerably less common. In our series, 91% were carcinomas or carcinoma tumors, a finding consistent with reported series. The 6 cases of cutaneous melanoma and the 2 cases of choroidal melanoma in our series may reflect referral bias because of our particular interest in melanoma. Our series included one unusual case of orbital metastasis from a malignant fibrous histiocytoma in the kidney. Most uveal metastases are also from primary carcinomas.¹

Orbital metastasis generally occurs in adulthood and is uncommon in childhood. Of our 100 orbital metastases, 93 occurred in patients 40 years of age or older. Adrenal neuroblastoma accounts for most orbital metastasis in children. It is possible that the single case of orbital metastasis from neuroblastoma in our series is deceptively low because more of such patients are seen in children's cancer centers after the primary tumor is known and the patient is undergoing treatment. Hence they would be less likely to be referred to an ophthalmologic hospital. Other childhood tumors that are well

known to metastasize to the orbit include Wilms tumor and Ewing sarcoma.^{3,4} These were not encountered in our series. Metastases to the uvea have a similar age distribution.

More than 90% of orbital metastases occur unilaterally. Clinically evident bilateral metastases were found in only 4% of our cases, a finding also consistent with other reports. In contrast, in our experience approximately 24% of uveal metastases are bilateral.² This discrepancy may reflect the fact that small metastases may be undetectable clinically and radiographically in the contralateral orbit, whereas small uveal metastases are readily seen with ophthalmoscopy.

The clinical manifestations of orbital metastases are well known.³⁻⁵ The findings in our series are consistent with other reports. The affected patient usually has a rather abrupt onset of blurred vision, diplopia, and pain and may have a visible lump beneath the eyelid. Examination may disclose proptosis, displacement of the globe, blepharoptosis, and a visible or palpable mass (Table 3). Such a rapid onset and severity of symptoms would be exceptional in cases of benign orbital tumors and lymphomas and should raise the possibility of orbital inflammatory pseudotumor or metastasis. Orbital metastasis should be the leading diagnostic consideration when the affected patient has a history of cancer. Most patients with a sizable orbital metastasis have proptosis of the affected eye. An interesting and paradoxical feature of some patients with orbital metastasis is enophthalmos of the affected eye. This occurred in 8 of our patients, all of

whom had metastatic scirrhous breast cancer to the orbit. The desmoplasia and fibrosis associated with that tumor causes contraction of the orbital contents and paradoxical enophthalmos.^{3,4,82,83}

In our series, the diagnosis was suggested by clinical history, clinical examination, and orbital imaging studies and confirmed by either open biopsy or FNAB. Our experience has allowed us to make generalizations about diagnostic approaches to orbital metastasis. The diagnosis of orbital metastasis should be suspected when a patient who has a history of cancer has the aforementioned symptoms and signs. If the patient has no history of cancer, such findings should prompt a systemic survey to detect a primary neoplasm and other sites of metastasis. A biopsy is necessary to confirm that the lesion is a metastatic tumor and not a simulating lesion such as idiopathic orbital inflammation ("orbital pseudotumor").

Orbital imaging studies, either MRI or CT, should be performed. Because most orbital metastases affect mainly the orbital soft tissues, MRI usually provides the best resolution of orbital metastasis. However, CT is more useful in cases of suspected prostate cancer metastasis because it provides better evaluation of bone. The pattern of tissue involvement disclosed by CT and MRI may suggest the primary neoplasm. For example, orbital metastasis from breast cancer tends to be diffuse and irregular, often growing along the rectus muscles and fascial planes. In contrast, orbital metastasis from carcinoid tumor, renal cell carcinoma, and melanoma tends to be more circumscribed, at least in the early stages. As such tumors enlarge, they can assume a more diffuse growth pattern. Almost all orbital metastases evaluated with MRI show some degree of enhancement with contrast agents.⁸⁴

The ultimate diagnosis of orbital metastasis is made by biopsy and histopathologic examination of the tissue. In many cases, the location of the tumor is sufficiently anterior in the orbit to permit an open incisional biopsy through either a conjunctival or cutaneous approach. If the tumor is well circumscribed and amenable to complete removal, then it should be treated by complete excisional biopsy. When the tumor is located deep within the orbit and when the patient is known to have a primary cancer, FNAB may be justified.^{85,86} This should be performed by an experienced orbital surgeon, often using MRI or CT guidance.

The treatment in our cases varied. As indicated above, many patients were treated elsewhere by various physicians. Hence it was not possible in this study to analyze and compare methods of treatment. Some well-circumscribed tumors were completely removed, and no additional ocular treatment was recommended. In other in-

stances, the orbital metastasis appeared to be controlled by the chemotherapy or hormonal therapy that was being used for systemic metastasis. For tumors that were not controlled by chemotherapy or hormonal therapy, orbital irradiation with a dose of 35 to 40 Gy was used with satisfactory results in most cases. Before irradiation, it is generally appropriate to obtain a biopsy for confirmation of the diagnosis. If the patient has known widespread metastasis and the orbital tumor is not readily accessible to biopsy, then irradiation without a biopsy may sometimes be justifiable.

In general, orbital metastasis is associated with rather poor systemic prognosis. Most reported series are small and data on prognosis are limited. We were able to obtain adequate follow-up on 60 the 70 patients who were evaluated clinically on the Oncology Service (Table 4). Patients with metastatic carcinoid tumor and breast cancer had the longest survival, with a mean of 60 months and 22 months, respectively, after diagnosis of orbital metastasis. Patients with orbital metastasis from lung cancer had the least favorable prognosis, with a mean survival of 4 months. However, patients with bronchial carcinoid tumors had a more favorable prognosis.

In summary, we have reported our experience with 100 consecutive patients with orbital metastasis seen in the Oncology Service and Pathology Department of a major eye hospital. Breast, lung, and prostate cancers account for the majority of orbital metastasis, but a number of other tumors can metastasize to the orbit. Orbital metastasis is predominantly a condition of adulthood and is usually unilateral. The diagnosis can be suggested by history, ocular evaluation, systemic evaluation, and orbital imaging studies and confirmed by open biopsy or FNAB. The management involves treatment of associated systemic malignancy with chemotherapy or hormone therapy, and orbital irradiation. The tumor is usually controlled locally, but the systemic prognosis is usually poor.

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