Survey of 520 Eyes with Uveal Metastases

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Objective: The purpose of this investigation is to report the clinical features of patients with uveal metastases seen at a major ocular oncology center.

Design/Participants: A retrospective chart review was performed on all patients with uveal metastases evaluated at an ocular oncology outpatient facility over a 20-year period.

Main Outcome Measure: To assess the systemic and ophthalmic features of uveal metastases.

Results: A total of 950 uveal metastases were diagnosed in 520 eyes of 420 consecutive patients. Of the 950 metastatic foci, the uveal involvement included iris in 90 (9%), ciliary body in 22 (2%), and choroid in 838 (88%). The total number of uveal metastases per eye was 1 (71%) in 370 eyes, 2 (12%) in 63 eyes, and 3 or more (17%) in 87 eyes. The mean number of uveal metastases per eye was two (median, one).

Iris metastases presented most often as a yellow-to-white solitary nodule in the inferior quadrant. Ciliary body metastases typically presented as a solitary, sessile, or dome-shaped yellow mass in the inferior quadrant, but were difficult to visualize directly. The choroidal metastases typically were yellow in color, plateau shaped, and associated with subretinal fluid. In the 479 eyes with choroidal metastases, the epicenter of the main tumor was found in the macular area in 59 eyes (12%), between the macula and equator in 383 eyes (80%), and anterior to the equator in 37 eyes (8%). The mean size of the main (largest) choroidal tumor in each eye was 9 mm in base and 3 mm in thickness.

At the time of ocular diagnosis, 278 patients (66%) reported a history of a primary cancer and 142 patients (34%) had no history of a cancer. Subsequent evaluation of these 142 patients after the ocular diagnosis of uveal metastasis showed a primary tumor in the lung in 50 patients (35%), breast in 10 (7%), others in 9 (6%), and no primary site was found in 73 patients (51%). Nearly half of the patients with no known primary site eventually died of diffuse metastatic disease.

In the entire group of 420 patients, the uveal metastasis came from a primary cancer of the breast in 196 (47%), lung in 90 (21%), gastrointestinal tract in 18 (4%), kidney in 9 (2%), skin in 9 (2%), prostate in 9 (2%), and other cancers in 16 (4%). In 73 cases (17%), the primary site was never established despite systemic evaluation by medical oncologists.

Conclusions: Iris, ciliary body, and choroidal metastases have typical clinical features that should suggest the diagnosis. The choroid is the most common site for uveal metastases, and the tumors occur most often in the posterior pole of the eye with an average of two tumors per eye. Approximately one third of patients have no history of primary cancer at the time of ocular diagnosis. Breast and lung cancers represent more than two thirds of the primary tumor sites. *Ophthalmology 1997;104:1265–1276*

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Historically, metastatic tumors to the eye were believed to be rare. A classic ophthalmic textbook in 1966 stated that few surgeons had observed more than one case of ocular metastases.[1] Later, it was realized that ocular metastases were more common, and over the past 30 years, there have been several reports on the incidence and prognosis of patients with metastatic tumors to the eye.[2–10] Albert et al[3] found in a clinical report of 213 patients with known systemic cancer and known metastases that 2% had choroidal metastases. Bloch and Gartner[5] reported

that 8% of eyes in 230 patients with autopsy-proven carcinomas had histologically confirmed uveal metastatic foci. More recently, Nelson et al[8] found in an autopsy study that 4% of patients dying of carcinoma had ocular metastases. They estimated that in the year 1983, 22,000 patients who died of cancer had ocular metastatic disease.[8] We have learned from these and other reports that ocular metastases are not uncommon. It is anticipated that as the life expectancy of patients with cancer increases, the number of patients in whom uveal metastases will develop who will require ophthalmic care will rise accordingly.

Most prior reports on uveal metastases came from pathology laboratories or from general cancer centers where patients had known primary cancers or metastatic disease or both, and the eyes subsequently were examined. These studies have focused on the source of the primary tumor, general clinical features of the tumor (derived from autopsy or pathology reports in some instances), and the histopathologic features of the tumors.[2–6,8] Ocular metastases on file at the Armed Forces Institute of Pathology have been reviewed by Hart in 1962[2] and Ferry and Font[6] in 1974. These and other pathology-based studies have added greatly to our understanding of uveal metastases.[2–6,8,10]

Conversely, there are relatively few comprehensive reports on the clinical features of uveal metastases from an ophthalmologic point of view. In 1979, Stephens and Shields[7] reviewed 70 cases of uveal metastases and provided general details on the clinical findings of these tumors. Others have focused on the features of uveal metastases from specific primary sites such as breast,[11–13] prostate,[14] skin,[15–17] and carcinoid tumors.[18] In 1987, Freedman and Folk[9] reported on the ophthalmic clinical aspects of metastatic tumors to the choroid in 61 patients, and they addressed specifically the factors affecting the median survival time after ocular diagnosis. Later, we summarized in a textbook our experience with diagnostic techniques and management of uveal metastases.[19] In this report, we provide our personal observations of a large group of consecutive patients with uveal metastases as seen in an outpatient ophthalmology facility over a 20-year period. We believe that our comprehensive clinical study is an accurate and practical representation of uveal metastases from an ophthalmic standpoint and provides important information on a special subset of patients, those who present with no history of cancer.

Patients and Methods

The charts of all patients from the Ocular Oncology Service at Wills Eye Hospital with the clinical diagnosis of metastatic tumor to the ocular structures who were evaluated between January 1, 1974, and December 31, 1994, were reviewed. Those patients with a metastatic tumor to the uvea were selected for further analysis and comprise the group included in this report. The criteria for the clinical diagnosis of uveal metastasis have been published.[19] All patients with lymphoproliferative disorders such as lymphoma, leukemia, and myeloma were excluded.

The data collected included information on the primary cancer as well as the metastatic focus in the eye. The primary cancer information included primary tumor organ location (e.g., breast, lung, gastrointestinal tract, kidney, others, unknown), primary cancer type (e.g., carcinoma, sarcoma, melanoma, carcinoid, others, unknown), and initial primary cancer treatment (e.g., external beam radiation therapy, chemotherapy, resection, hormone therapy, observation). The systemic status at the time of ocular diagnosis was recorded and included information on systemic metastasis (e.g., present, absent), number and location of sites of systemic metastasis, and treatment of systemic metastasis.

The patient's age at the time of ocular diagnosis, gender, race, and symptoms (e.g., blurred vision, flashes and floaters, pain) were recorded. The involved eye (right, left), laterality (unilateral, bilateral), visual acuity, and intraocular pressure were noted. An evaluation for evidence of additional metastatic foci in the eyelid, orbit, conjunctiva, retina, and optic disc was made. The anatomic location of the uveal metastasis (iris, ciliary body, choroid), number of metastases at each location, and meridional location of the epicenter of the tumor (superior, nasal, inferior, temporal, macula [choroid only]) were recorded. In the choroid, the epicenter of the largest metastasis was analyzed for anteroposterior location (macula [≤3 mm from foveola], between macula and equator, between equator and ora serrata), basal dimension (mm), thickness (mm), distance from the optic nerve and foveola (mm), morphology (plateau, dome, mushroom), and color (yellow, brown, orange). Initial management of the uveal metastases (external beam radiation therapy, chemotherapy, resection, hormone therapy, plaque radiation therapy, observation) was noted. The local tumor response to treatment was not included in this article and will be the subject of other analyses.[20,21]

Results

There were a total of 950 uveal metastases in 520 eyes of 420 patients (Table 1). The uveal involvement was unilateral in 320 patients and bilateral in 100 patients. The right eye was affected in 249 eyes (48%) and the left in 271 (52%). Of the 420 patients, 380 (90%) were white, 35 (8%) were black, 4 (1%) were Hispanic, and 1 (<1%) was Asian. There were 137 male patients (33%) and 283 female patients (67%). The mean age at ocular diagnosis was 58 years (median, 58 years; range, 10–85 years).

Primary Cancer

The primary cancer location after systemic evaluation was found to be the breast in 196 patients (47%), lung in 90 (21%), gastrointestinal tract in 18 (4%), kidney in 9 (2%), skin (melanoma) in 9 (2%), prostate in 9 (2%), others in 16 (4%), and unknown primary in 73 (17%) in the total of 420 patients (Fig 1). The group classified as *others* included cancer of the uterus in one patient, contralateral uvea (melanoma) in three, thyroid in two, pancreas in three, bladder in one, ovary in two, bile duct in one, testes in one, bone in one, and adrenal gland in one patient. Unilateral uveal involvement was found in 320 patients and was from cancer of the breast in 132 patients (41%), lung in 72 (22%), gastrointestinal tract in 17 (5%), kidney

Table 1. Uveal Metastases Related to Site of Primary Cancer in 520 Eyes of 420 Patients

	Primary Site of Tumor							
	Breast	*Lung*	*GI*	*Kidney*	*Skin*	*Prostate*	*Others*	*Unknown*
Eyes (n = 520)	260	108	19	10	11	11	20	81
Patients (n = 420)	196	90	18	9	9	9	16	73
Age* (yrs) (n = 420)	56	57	60	65	50	67	57	64
Race (n = 420)								
White	175	80	17	9	9	8	15	67
Black	17	10	1	0	0	0	1	5
Other	4	0	0	0	0	1	0	1
Sex (n = 420)								
Male	2	55	13	8	5	9	5	40
Female	194	35	5	1	4	0	11	33
Laterality (n = 420)								
Unilateral	132	72	17	8	7	7	12	65
Bilateral	64	18	1	1	2	2	4	8
Symptoms (n = 520)								
None	28	12	4	1	1	3	2	8
Blurred vision	192	68	14	5	4	7	12	59
Flashes, floaters	35	14	0	2	2	0	6	6
Pain	5	14	1	2	4	1	0	8
Other ocular metastases								
Eyelid	1	0	0	0	1	0	1	0
Orbit	2	1	0	1	0	1	0	2
Conjunctiva	2	1	0	0	2	0	1	2
Retina	2	1	0	0	0	0	0	2
Optic disc	10	1	1	0	0	0	2	10
Location uveal metastases								
Iris (n = 43)	17	8	2	1	4	1	2	8
Ciliary body (n = 21)	4	2	2	1	3	1	1	7
Choroid (n = 479)	252	98	18	8	5	10	17	71
No.* of uveal metastases/ location								
Iris	2	1	1	2	1	1	7	1
Ciliary body	1	1	1	1	1	1	1	1
Choroid	2	1	1	1	2	1	1	2
Choroidal metastasis (largest tumor)								
Base*	8	9	9	8	7	9	10	8
Thickness*	2	3	4	4	1	3	2	3
mm to foveola*	5	5	4	8	5	6	6	5
mm to optic nerve*	6	5	5	7	5	6	5	5
Color (n = 479)								
Yellow	249	90	17	5	0	9	12	66
Brown/gray	2	1†	1¶	0	5	0	5§	3‖
Orange	1	7‡	0	3	0	1	0	2
Shape (n = 479)								
Plateau	197	55	7	1	3	5	12	45
Dome	55	43	11	7	2	5	5	24
Mushroom	0	0	0	0	0	0	0	2¶
Subretinal fluid (SRF)	168	79	13	7	4	9	16	56
If SRF present, % retina elevated	20	24	12	17	15	27	29	21

GI = gastrointestinal.

* Mean.

† In these cases a very thick tumor (>9 mm thick) induced a gray-brown color.

‡ Six of the seven orange tumors were metastatic from the lung.

§ Three of the five brown tumors were metastatic uveal melanoma from one choroid to the other choroid. The other two tumors were metastatic ovarian carcinoma and they assumed a light brown-gray color.

‖ Two of these cases were believed to be metastatic cutaneous melanoma to the uvea but the primary tumor site was not evident. The third case was brown-gray related to the overlying homogeneously dark retinal pigment epithelium.

¶ These two cases were very large tumors (>12 mm thick).

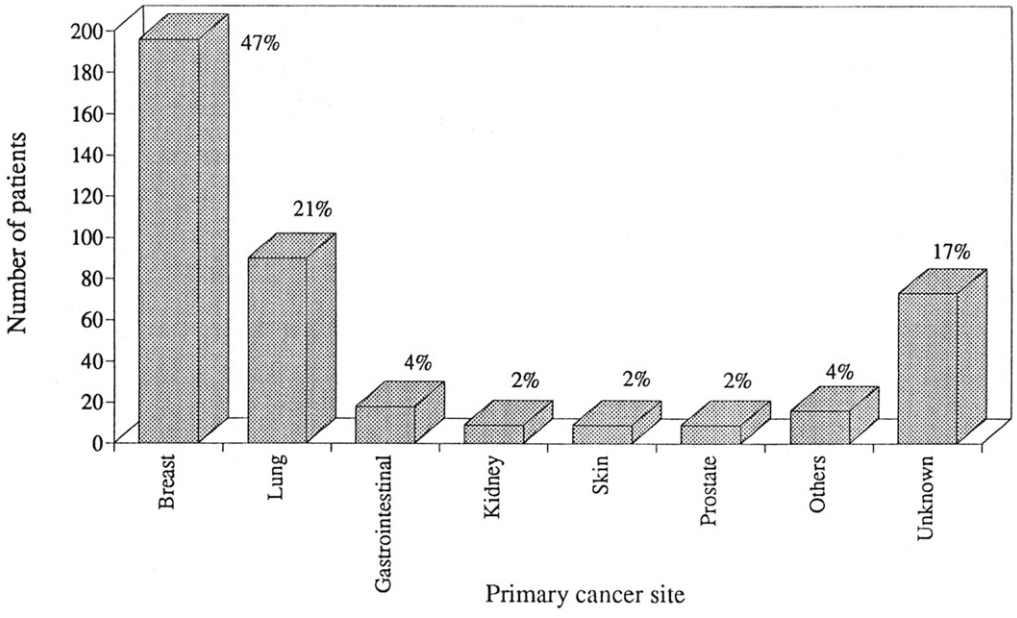

Figure 1. Location of primary cancer in 420 patients with uveal metastases.

in 8 (2%), skin in 7 (2%), prostate in 7 (2%), others in 12 (4%), and unknown primary cancer in 65 patients (20%) (Fig 2). Bilateral uveal involvement was found in 100 patients and was from primary cancer of breast in 64 patients (64%), lung in 18 (18%), gastrointestinal tract in 1 (1%), kidney in 1 (1%), skin in 2 (2%), prostate in 2 (2%), others in 4 (4%), and unknown primary cancer in 8 patients (8%) (Fig 3). The primary cancer types included carcinoma in 346 patients (82%), sarcoma in 1 (Ewing sarcoma) (<1%), melanoma (cutaneous, uveal, and undetermined) in 13 (3%), carcinoid in 5 (1%), and unknown in 55 patients (13%) (Fig 4).

The primary cancer site for the 137 male patients was breast in 2 (1%), lung in 55 (40%), gastrointestinal in 13 (9%), kidney in 8 (6%), skin in 5 (4%), prostate in 9 (6%), others in 5 (4%), and unknown in 40 patients (29%). The primary cancer site for the 283 female patients was breast in 194 (68%), lung in 35 (12%), gastrointestinal in 5 (2%), kidney in 1 (<1%), skin in 4 (1%), prostate in 0 (0%), others in 11 (4%), and unknown in 33 patients (12%).

At the time of ocular diagnosis, 278 patients (66%) reported a history of a primary cancer, and 142 patients (34%) had no history of cancer. Of the 142 patients with no prior cancer, the primary site was discovered after complete oncologic evaluation in 69 patients (49%), and the primary site remained unknown in 73 patients (51%). Those primary cancers discovered after the uveal metastasis included cancer of the breast in 10 patients (7%), lung

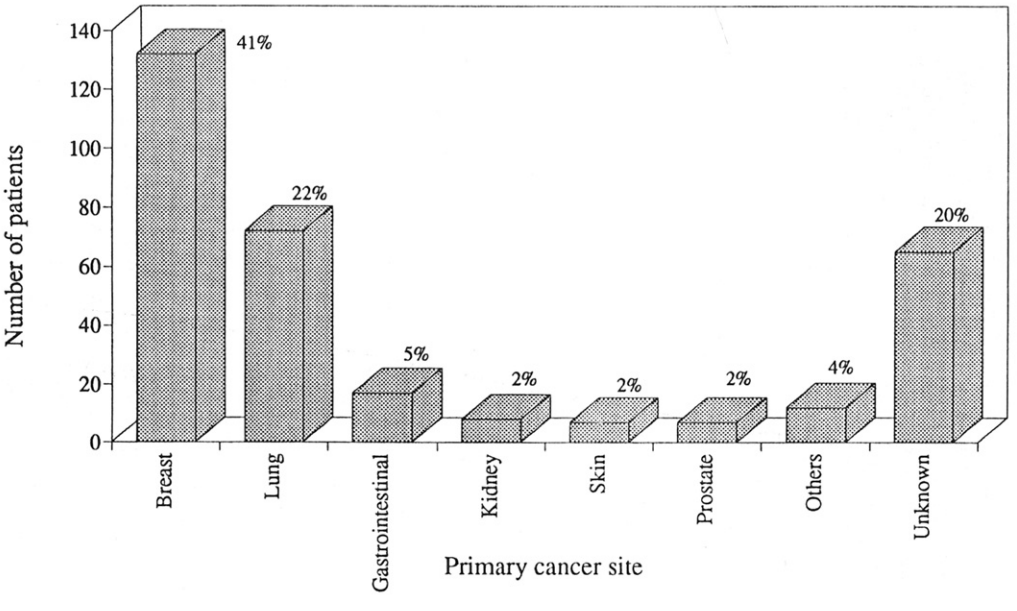

Figure 2. Location of primary cancer in 320 patients with unilateral uveal metastases.

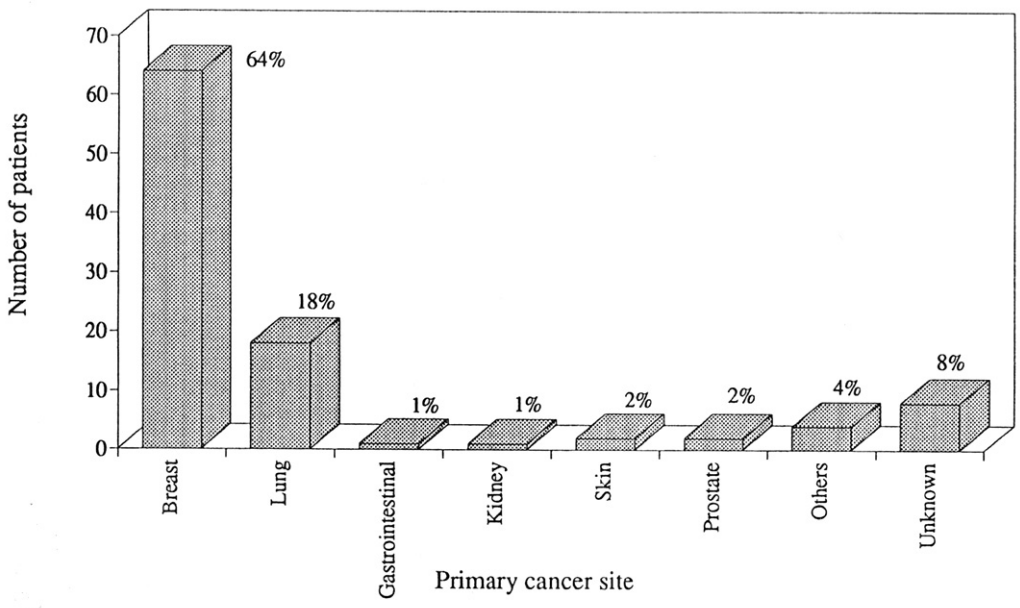

Figure 3. Location of primary cancer in 100 patients with bilateral uveal metastases.

in 50 (35%), gastrointestinal in 2 (1%), skin (melanoma) in 1 (<1%), prostate in 2 (1%), eye (uveal melanoma) in 1 (<1%), pancreas in 1 (<1%), thyroid in 1 (<1%), and bile duct in 1 patient (<1%) (Fig 5). The 142 patients with no prior cancer included 75 male (53%) and 67 female (47%) patients. After systemic evaluation, the male patients proved to have primary cancer of the breast in 0 case, lung in 29, gastrointestinal tract in 1, skin (melanoma) in 1, prostate in 2, pancreas in 1, and no detectable primary cancer in 41 patients. The female patients proved to have primary cancer of the breast in 10 patients, lung in 21, gastrointestinal tract in 1, thyroid in 1, bile duct in 1, contralateral uveal melanoma in 1, and no detectable primary cancer in 32 patients.

The 73 patients with no known primary cancer eventually died of diffuse metastatic disease in 33 cases (45%), died of other unrelated causes in 12 cases (16%), remained alive but with other systemic metastatic foci in 2 cases (3%), and remained alive and well without other metastases in 10 cases (14%). In 16 cases (22%), follow-up was unavailable.

At the time of ocular diagnosis, systemic metastases were under active treatment in 54 patients (13%), whereas in 366 patients (87%), there was no active treatment, either because of control of the systemic metastatic disease or lack of knowledge or presence of systemic metastases. During the course of the patient's ocular evaluation, there were 295 patients (70%) found to have systemic metastases elsewhere and 125 (30%) without systemic metastases (Fig 6). Of the 295 patients with systemic metastases, the initial site of systemic metastasis elsewhere was lung in 58 patients (20%), bone in 40 (14%), liver in 34 (12%), brain in 30 (10%), skin in 4 (1%), soft tissue in 9 (3%), disseminated in 113 (38%), and unknown in 7 patients (2%).

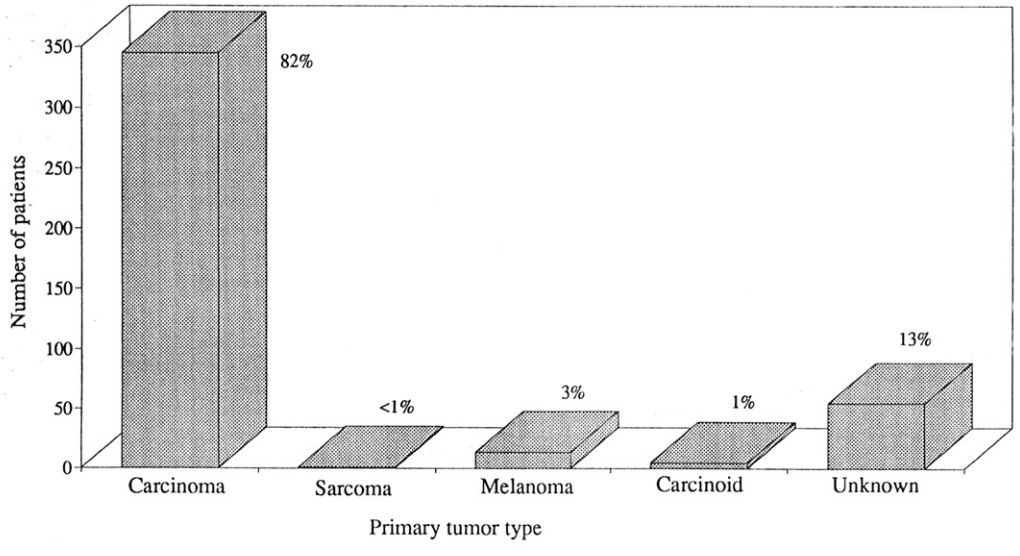

Figure 4. Type of primary tumor in 420 patients with uveal metastases.

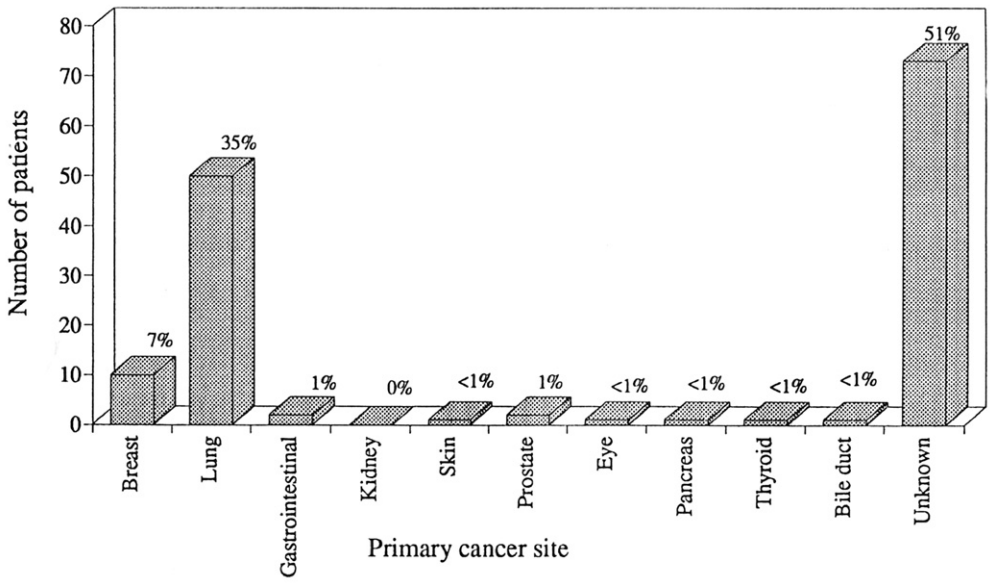

Figure 5. Eventual primary cancer site in 142 patients who presented with a uveal metastasis and no history of cancer.

Ocular Findings

The main ocular symptom at diagnosis included blurred vision in 361 eyes (70%), flashes and floaters in 65 (12%), pain in 35 (7%), and no symptoms in 59 eyes (11%). Visual acuity in the affected eye was 6/6 in 67 eyes (13%), 6/7.5 in 30 (6%), 6/9 in 35 (7%), 6/12 in 27 (5%), 6/15 in 26 (5%), 6/18 in 23 (4%), 6/21 in 27 (5%), 6/24 in 20 (4%), 6/30 in 30 (6%), 6/60 in 61 (12%), 6/120 in 41 (8%), count fingers in 86 (16%), hand motions in 28 (5%), light perception in 16 (3%), and no light perception in 3 eyes (1%) (Fig 7). The intraocular pressure was elevated to greater than 22 mmHg in 21 eyes (4%) and less than or equal to 22 mmHg in 499 eyes (96%).

In addition to the uveal metastases, metastatic foci were found in other ocular sites, including the eyelids in 3 eyes (<1%), orbit in 7 (<1%), conjunctiva in 8 (<1%), retina in 5 (<1%), and optic disc in 24 eyes (5%). Regarding specific location of the uveal metastasis, the tumor was located in the iris in 43 eyes, ciliary body in 21 eyes, and choroid in 479 eyes (total is greater than 520 because of multiple locations in some eyes). Of the 950 metastatic tumors to the uvea, the location of the individual lesion was iris in 90 tumors (9%), ciliary body in 22 (2%), and choroid in 838 tumors (88%) (Fig 8).

Iris Metastases. Of the 43 eyes with iris metastasis, 32 eyes showed 1 focus, 5 eyes had 2 metastatic foci, and in 6 patients more than 2 foci were found. The maximum number of iris metastases in an eye was 12. The iris metastases assumed a white or yellow color (Fig 9) in all cases except those that originated from skin melanoma, which were brown, and lung carcinoid tumor and renal cell carcinoma, which were orange. The iris metastases

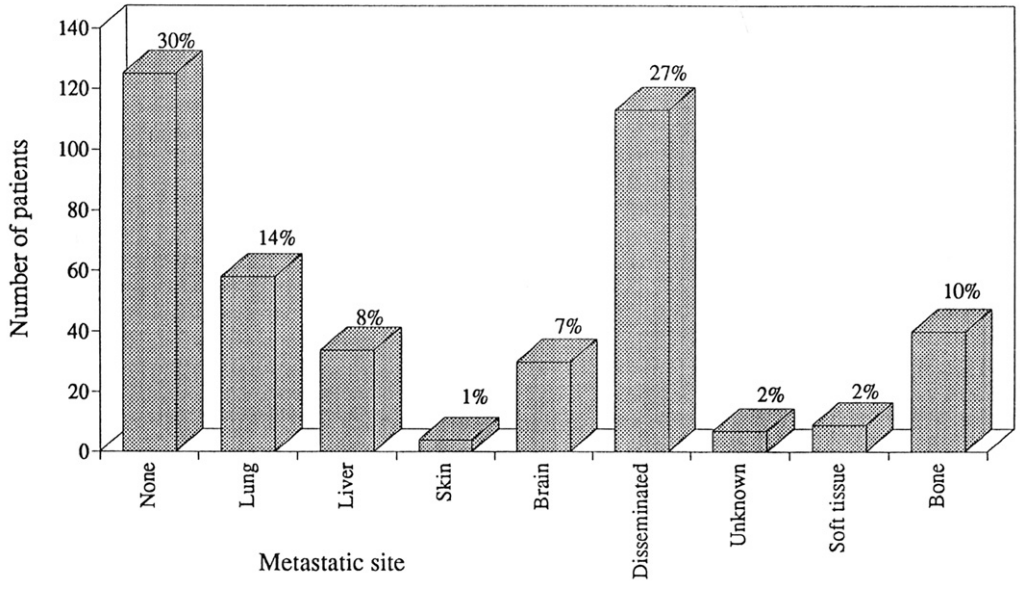

Figure 6. Initial systemic metastatic site before the ocular diagnosis in 420 patients with uveal metastases.

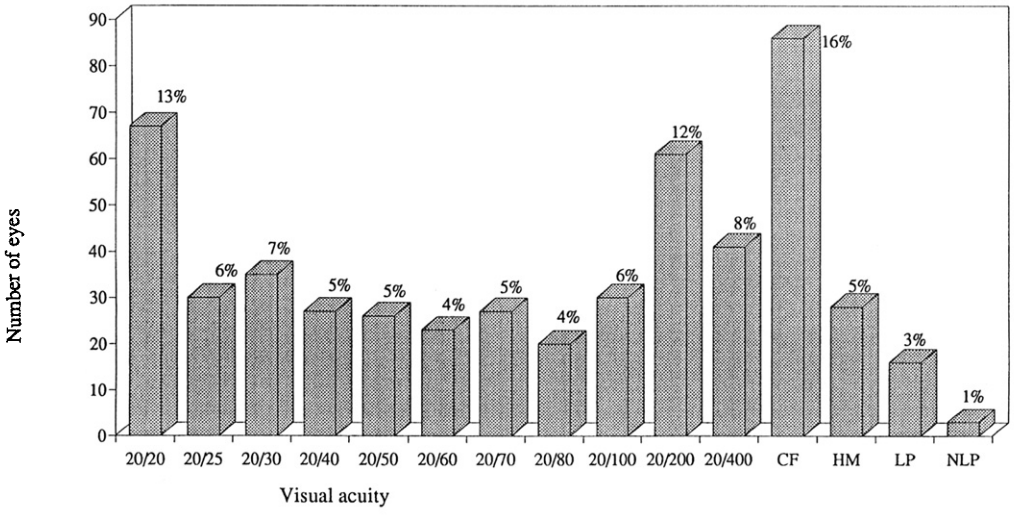

Figure 7. Visual acuity at the time of diagnosis of uveal metastases in 520 eyes.

originated from cancer of the breast in 17 eyes, lung in 8, gastrointestinal tract in 2, kidney in 1, skin (melanoma) in 4, prostate in 1, adrenal gland in 1, bone in 1, and unknown primary site in 8 eyes.

The iris tumors were located in the superior quadrant of the iris in 7 eyes (16%), nasal in 9 (21%), inferior in 18 (42%), lateral in 6 (14%), and diffuse in all quadrants in 3 eyes (7%) (Fig 10). The anteroposterior location of the tumor on the iris leaf was at the pupillary margin in 7 eyes (16%), midzone in 20 (46%), iris periphery in 8 (19%), anterior chamber angle in 7 (16%), and diffuse over the meridian in 1 eye (2%) (Fig 11). The iris metastasis was managed initially with systemic chemotherapy in 1 case (2%), external beam radiation therapy in 16 (37%), plaque radiation therapy in 4 (9%), local resection in 7 (16%), observation in 3 (7%), combination therapy (combination of two or more of the following methods: chemotherapy, radiation therapy, hormone therapy, resection) in 12 cases (28%).

Ciliary Body Metastases. Of the 21 eyes with ciliary body metastases, 20 had 1 metastatic ciliary body focus and 1 eye had 2 foci. These tumors appeared as a yellow sessile or dome-shaped mass in the ciliary body region, but often were difficult to visualize directly. The ciliary body metastases originated from cancer of the breast in four eyes, lung in two, gastrointestinal tract in two, kidney in one, skin (melanoma) in three, prostate in one, adrenal gland in one, and unknown primary site in seven eyes.

The location of the largest metastasis was superior in three (14%), nasal in four (19%), inferior in ten (48%), lateral in three (14%), and diffuse in one eye (5%) (Fig 12). The treatment for the ciliary body metastasis was external beam radiation therapy in eight eyes (38%), plaque radiation therapy in two (10%), resection in six (28%), and combination therapy (combination of two or more of the following methods: chemotherapy, radiation therapy, hormone therapy, resection) in five eyes (24%).

Choroidal Metastases. Of the 479 eyes with choroidal metastases, 344 eyes had 1 focus, 55 had 2 foci, 26 had 3 foci, 21 had 4 foci, 13 had 5 foci, 10 had 6 foci, and 9 had more than 6 foci with a maximum number of 13 metastatic choroidal foci in 1 eye. The median number of choroidal metastases per eye was 1 and the mean was 1.6 tumors. Choroidal metastases generally appeared as a creamy yellow subretinal mass, often with a secondary retinal detachment.

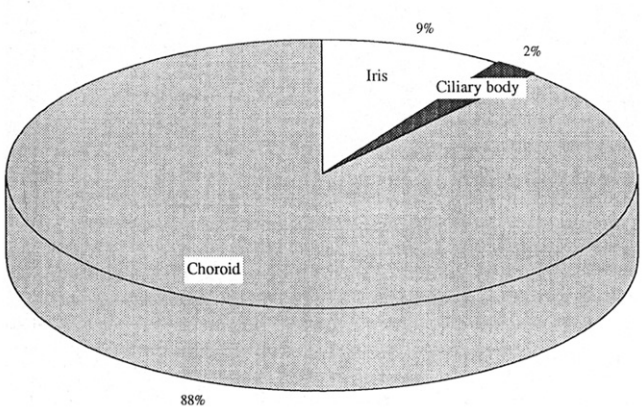

Figure 8. Anatomic location of 950 consecutive uveal metastases.

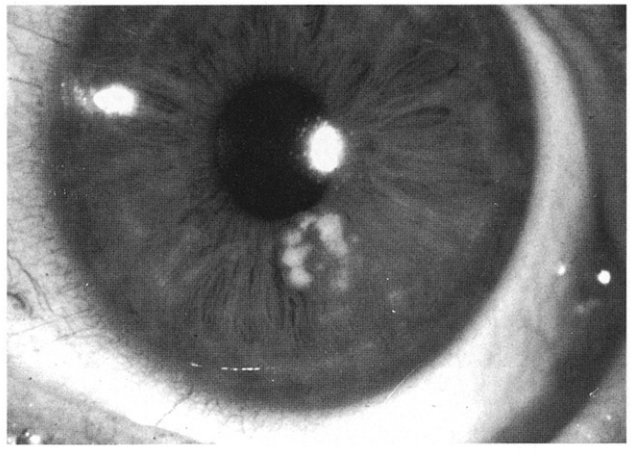

Figure 9. Iris metastasis. The small fluffy avascular metastasis on the iris originated from breast cancer.

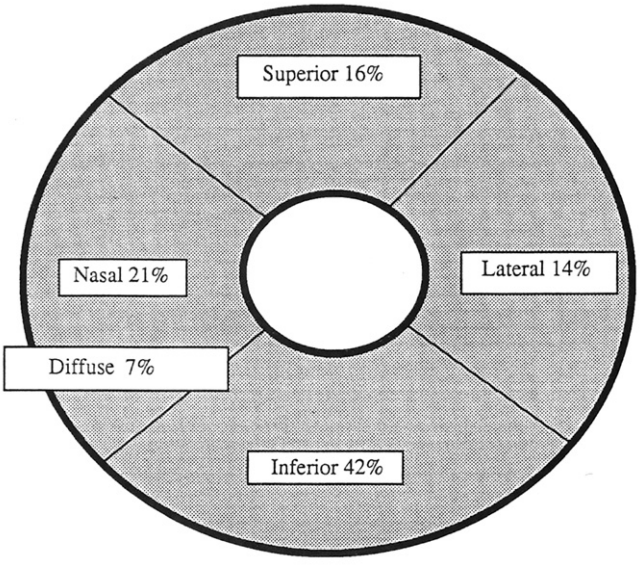

Figure 10. Radial distribution of iris metastases in 43 eyes.

Associated features of subretinal fluid was observed in 352 eyes (73%) and retinal pigment epithelial alterations in 277 eyes (57%). The choroidal metastases originated from cancer of the breast in 252 eyes, lung in 98, gastrointestinal tract in 18, kidney in 8, skin (melanoma) in 5, prostate in 10, and other sites including uterus, opposite choroid (melanoma), thyroid, bone, adrenal gland, pancreas, bile duct, ovary, and testis. The primary site of the choroidal metastasis was unknown in 71 eyes, even after systemic evaluation by a general oncologist.

When considering the largest metastatic choroidal tumor, the radial location was superior in 103 eyes (22%), nasal in 67 (14%), inferior in 83 (17%), lateral in 167 (35%), and within the region of the macula in 59 eyes (12%) (Fig 13). The anteroposterior location of the epicenter of the mass was between the equator and ora serrata in 38 eyes (8%), between the equator and macula in 382 (80%), and within the macula in 59 eyes (12%) (Figs 14, 15). The mean base measurement of the largest metastatic focus was 9 mm (median, 8 mm) and mean thickness was 3 mm (median, 2 mm). These tumors were a mean of 5 mm to the optic nerve (median, 5 mm) and foveola (median, 4 mm). The tumor surface configuration was dome in 152 (32%), mushroom in 2 (<1%), and plateau in 325 (68%) (Table 1). The tumor was judged to be a yellow color in 448 cases (94%), brown–gray in 17 (4%), and orange in 14 cases (3%). The choroidal metastases were treated with chemotherapy in 40 eyes (8%), external beam radiation therapy in 188 (39%), plaque radiation therapy in 35 (7%), hormone therapy in 5 (1%), resection in 28 (6%), observation in 66 (14%), and combination methods (combination of 2 or more of the following methods: chemotherapy, radiation therapy, hormone therapy, resection) in 117 eyes (24%).

Discussion

Historically, metastatic tumors to the uvea were believed to be relatively rare,[1] but several important studies in the 1950s through 1970s showed that uveal metastasis actually represents the most common uveal malignancy, being more common than primary uveal melanoma.[2–6] These studies were from various centers and were based on autopsy, pathology, or general cancer center data.

Bloch and Gartner[5] reported on 28 patients at autopsy with ocular metastases from carcinomas and the distribution of ocular involvement included choroid in 57%, ciliary body in 14%, iris in 7%, retina in 14%, sclera in 11%, optic nerve in 21%, orbit in 14%, and extraocular muscle in 4%. When considering the primary tumor source in these 28 autopsies, breast and lung cancer represented the majority (43%).[5]

Others have evaluated ocular metastases from a pathology laboratory. In 227 eyes evaluated at the Armed Forces Institute of Pathology with carcinoma metastatic to the eye or orbit, the site of ocular involvement was choroid in 76%, iris–ciliary body in 43%, and orbit in 23%, but many of these sites overlapped with others.[6] The primary tumor site was breast in 39%, lung in 29%, kidney in 4%, testis in 3%, and others in approximately 1% or less.[6] In 18% of patients, the primary tumor site was undetermined.[6]

Still others have evaluated patients with ocular metastases as they were detected at a general cancer center, and this group included exclusively patients with known cancers and metastases.[3] Breast and lung cancers represented the most common source of metastases in this select group.[3]

These studies have provided an excellent overview of ocular metastatic disease. They represent a selected population of patients with cancer who either came to office evaluation with known cancer and known systemic metastatic disease or came to biopsy, enucleation, or autopsy. These reports portray perhaps a more advanced stage of ocular metastases. We have chosen to evaluate ocular metastatic disease from an ophthalmologic standpoint, as

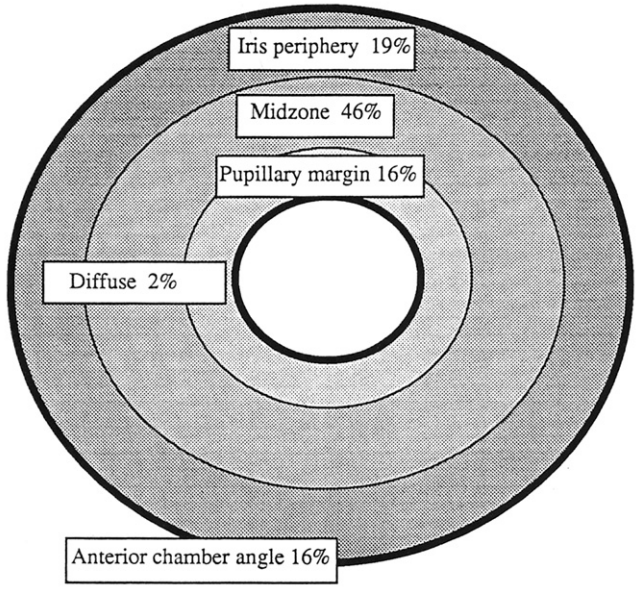

Figure 11. Anteroposterior distribution of iris metastases in 43 eyes.

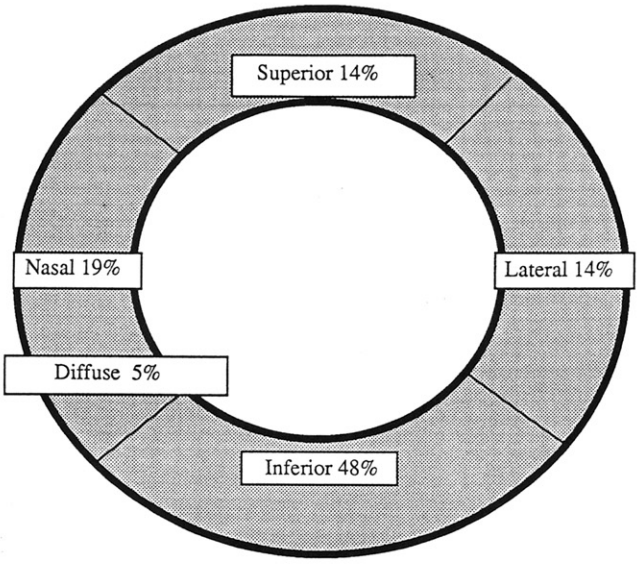

Figure 12. Radial distribution of ciliary body metastases in 21 eyes.

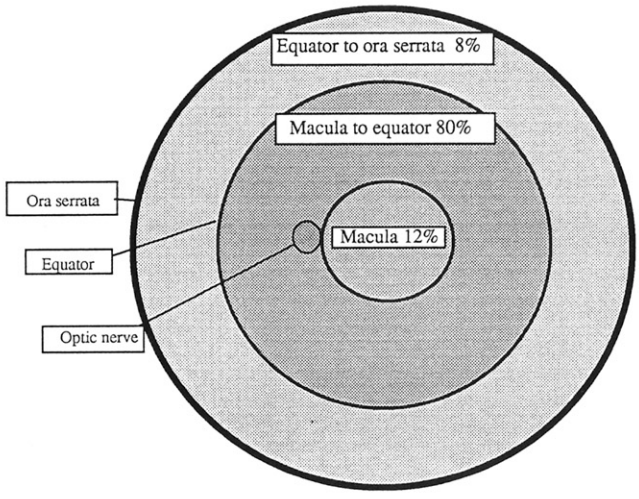

Figure 14. Anteroposterior distribution of largest choroidal metastasis in 479 eyes.

the patient with known or unknown cancer presents to the ophthalmologist for routine evaluation or for symptomatic reasons. Although our series has referral bias, it does reflect the situation as seen by the general ophthalmologist or retina specialist and may be quite informative to the clinician, especially when there is no history of cancer.

From our results, a minority of patients with uveal metastases (11% of affected eyes) were without symptoms at the time the patient presented to the ophthalmologist. Only 26% of eyes had 20/30 visual acuity or better. The most common presenting symptom was blurred vision, and when visual acuity was affected, the visual acuity usually was decreased to the range of 20/200 to count fingers, as seen in 36% of patients. Other presenting symptoms included flashes and floaters in 12% and pain in 7%. The flashes and floaters typically were related to the presence of subretinal fluid, but the cause of the pain was more difficult to determine. It was found to be related either to glaucoma or less measurable sources such as tumor necrosis, inflammation, or microscopic scleral involvement. The symptom of pain is rarely found with other uveal malignancies.[19]

Similar to prior studies,[3,6,7] the choroid was the most common site of uveal involvement by metastatic disease in our study, representing 836 (88%) of the 950 metastatic foci. Ferry and Font[6] speculated that the posterior uveal distribution of metastases was related to the abundant supply of posterior ciliary arteries to the choroid, especially the posterior choroid. The numerous posterior ciliary vessels allow a greater flow of tumor emboli to the posterior uvea as compared to the fewer anterior ciliary vessels supplying the anterior uvea. This was reflected in our results as iris and ciliary body involvement was much less common than choroidal involvement, representing only 9% and 2% of the 950 metastatic tumors, respectively. Interestingly, nearly half of the iris and ciliary

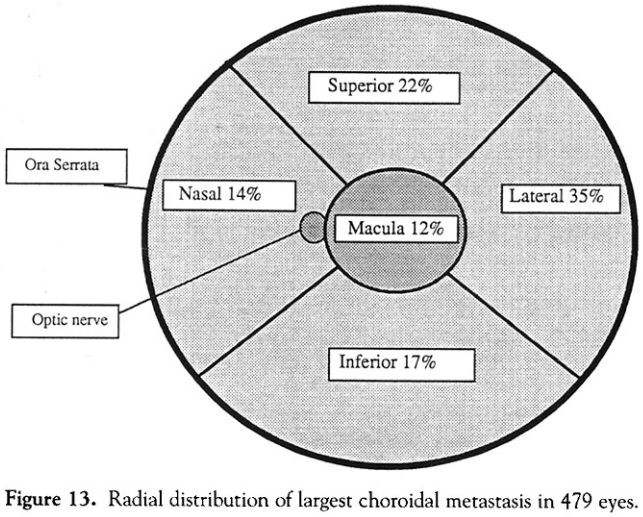

Figure 13. Radial distribution of largest choroidal metastasis in 479 eyes.

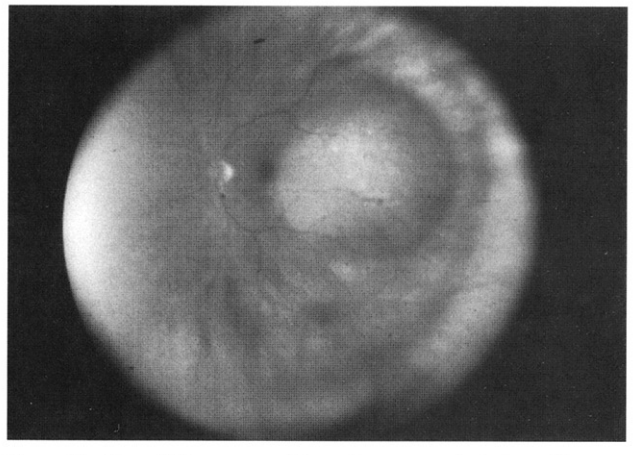

Figure 15. Choroidal metastasis. The well-circumscribed choroidal metastasis in the posterior pole of the eye was discovered in a patient with no known cancer. Subsequent systemic evaluation showed a primary breast cancer.

body metastatic foci involved the inferior quadrant of the eye, and many of the ciliary body metastases were contiguous with iris metastases. In contrast, the most common location of metastatic foci within the choroid was in the superior and lateral quadrants in the postequatorial region.

The clinical features of iris metastases have been well described,[22] and ciliary body metastases from a clinical standpoint are exquisitely rare, so the focus of this discussion will be on choroidal metastases. It is well known that choroidal metastases generally assume a yellow color when viewed through the ophthalmoscope.[23] Our results confirmed this belief, and we found that 95% of the metastatic tumors were judged to be yellow in color. Other tumor hues such as brown and orange were observed in rare cases. Brown-colored uveal metastases usually represented metastatic melanoma (from both cutaneous and contralateral choroidal sources); however, very large tumors originating in the breast, lung, and gastrointestinal tract occasionally assumed a light brown color.[24] Orange-colored choroidal metastases were found most often with metastases from bronchial carcinoid tumors and renal cell carcinoma.[18] In addition, it is recognized that orange-colored choroidal tumors also may represent choroidal hemangioma, posterior scleritis, or metastases from thyroid cancer.[18,23] The orange color should be differentiated from clumped orange pigment commonly visualized over active choroidal melanoma.[23] Clumped *orange* pigment overlying choroidal metastasis appears as a geographic, irregular accumulation of golden brown pigment beneath the retina and appears ophthalmoscopically different from the homogeneous orange uveal hue of certain uveal metastases.[19]

At the initial diagnosis, most choroidal metastases were plateau or dome shaped and measured approximately 3 mm in thickness. Flatter tumors were observed with metastases from cutaneous melanoma and breast cancer (Table 1). Thicker tumors generally were observed with metastases originating from the gastrointestinal tract, kidney, lung, and prostate. The only two metastatic foci to assume a mushroomed appearance were extremely large metastases measuring more than 12 mm in thickness. A mushroom or collar button shape to a uveal tumor strongly suggests a primary uveal melanoma and not a metastatic tumor, whereas an amelanotic plateau-shaped lesion strongly suggests a choroidal metastasis. Some metastatic tumors developed ophthalmoscopically visible individual nodules or clones of tumor cells on the apex of the tumor, under Bruch membrane, and this should not be interpreted as a break in Bruch membrane or mushroom-shaped choroidal metastasis.

A choroidal metastatic focus does not always warrant direct ocular treatment, especially when considering the patient's systemic status.[7,19,25] In our series, treatment was delivered in 86% of patients with uveal metastases, and observation was recommended in 14% of patients. Treatment was prescribed if the metastasis appeared active and was threatening the vision or the globe. If the patient was receiving systemic treatment such as chemotherapy or hormone therapy, then this was continued as treatment for the eye and the eye was monitored for treatment response. External beam radiation therapy[21] or plaque radiation therapy[26] was recommended if the uveal metastasis continued to grow or if visually symptomatic subretinal fluid increased while the patient received systemic chemotherapy or hormone therapy. When realizing that the mean life expectancy of a patient with a uveal metastasis has been reported to be approximately 9 to 10 months,[7,9] there is an argument to provide the minimal ocular treatment necessary to preserve the globe or vision or both. We have found that plaque radiation therapy is effective for chemotherapy-resistant solitary choroidal metastases, and the radiation therapy can be delivered over a short period of 3 days or less so that it occupies only a small percentage of the patient's remaining days.[26]

It has been recognized that breast and lung cancers account for most metastatic tumors to the choroid,[2–9] and our current study confirmed this finding. It is curious that genitourinary and gastrointestinal tumors rarely metastasize to the uvea. Of an estimated 1,130,000 new cases of cancer in the United States in 1992, 168,000 (15%) were in lung, 156,000 (14%) were in colon–rectum, 181,000 (16%) were in breast, and 132,000 (12%) were in prostate.[27] Of the approximately 520,000 cancer-related deaths in 1992, 146,000 (28%) were from lung cancer, 58,300 (11%) were from colorectal, 46,300 (9%) were from breast, and 34,000 (6%) were from prostate cancer.[27] Prostatic cancer represents 12% of all cancers and 6% of all cancer deaths, but only 2% of all uveal metastases, and colorectal cancer represents 14% of all cancers, 11% of cancer-related deaths, but only 4% of uveal metastases. These two cancers are under-represented regarding uveal metastatic disease. Conversely, breast and lung cancers are over-represented because they account for 16% and 15% of all new cancers, respectively, and 47% and 21% of all uveal metastases, respectively. This discrepancy has been recognized in other autopsy and pathology studies.[6,8] The biologic factors responsible for cultivating metastatic tumor cells generally are unknown but may be related to patient resistance, tissue factors promoting growth, and other determinants.[6]

Are there any clinical features of a choroidal metastasis that may suggest one or another primary site? In some instances, the primary tumor site can be suspected based on a constellation of findings. We found that metastatic breast cancer was the most common choroidal metastasis and was almost always found in women. It had the strongest tendency to occur as a multifocal and bilateral tumor, and 33% of all patients with metastases from breast cancer had bilateral involvement. In fact, of all patients with bilateral metastases, 64% were from breast cancer and 18% were from lung cancer. Breast cancer metastases showed a tendency toward flatter tumors measuring a mean thickness of only 2 mm in the largest tumor focus.

Lung cancer metastatic to the uvea was the second most common primary site. These tumors more often were unifocal and unilateral than breast cancer metastases. Although the number of patients was relatively small, 13% presented with pain as the main symptom as compared to only 2% pain with breast cancer metastases and 5% pain with other uveal metastases excluding lung. The most outstanding feature of lung metastases to the uvea

was the likelihood of the uveal tumor to present before the discovery of the lung cancer. Of all patients who presented with a uveal metastasis and no prior cancer, lung cancer was found to be the originating site most often, representing 35% of these cases, whereas breast cancer represented 7% and all other cancers individually accounted for 1% or less.

Gastrointestinal and kidney cancers were uncommon, but an important clinical feature was their tendency to be thicker than the other metastases. In fact, the mean thickness of metastatic gastrointestinal or kidney cancers was 4 mm, approximately double the thickness of breast cancer metastasis.

Skin melanoma metastatic to the uvea was more easily recognizable than other metastatic foci as it usually assumed a brown color, unlike the typical yellow color of other metastases.[17] Furthermore, metastatic skin melanoma occurred in the youngest age group of white patients. These tumors tended to be multifocal and flat, measuring a mean thickness of 1 mm.

From our data, we can give recommendations regarding patient evaluation when a patient presents with a suspected choroidal metastasis and no history of cancer. One must first realize that approximately 50% of these patients will not have a primary site detected despite systemic evaluation by medical oncologists, and many ultimately die of disseminated metastatic disease with the primary site remaining unknown. In our study, 45% of these patients died of diffuse metastatic disease and the primary site remained unknown. Of the remaining 50% in which a primary site is found, lung and breast represent the primary site of cancer in 86%. Other remote sites can be investigated as necessary. Ultrasonography, computed tomography, or magnetic resonance imaging will not likely differentiate various metastatic tumors in the eye.[24,28] Fine needle aspiration biopsy[29] of the uveal tumor may be helpful in establishing the diagnosis and determining the primary site using immunohistochemical techniques.

We recognize that there are limitations and a degree of bias in our study. The patient population in this report was from a center of ocular oncology, and many of the patients may have been a diagnostic challenge for the referring physician. This could have biased our series toward healthier patients with no history of cancer or even those patients with a solitary tumor or less advanced disease. In addition, the healthier patient with uveal metastatic disease also may have biased our decisions regarding treatment. We tend to treat with focal methods such as radiation therapy if the patient has no detectable systemic disease, whereas we prefer to use systemic chemotherapy, hormone therapy, or observation in those patients with uveal metastases who are systemically ill with cancer. Another bias of our study concerns the patients with unknown cancer. We suspect that the number of patients with unknown primary cancer despite systemic evaluation may be over-represented as some patients were referred to us specifically for fine needle aspiration biopsy of a uveal tumor in an otherwise healthy patient. Many of these cases were clinically diagnosed based on classic features without the need for pathologic confirmation, whereas others had fine needle biopsy confirmation. The follow-up of these patients supports the ophthalmoscopic suspicion in that nearly half of the group with unknown primary cancer died of diffuse metastatic disease, but we realize that it is possible that the clinical diagnosis in the others who remained healthy may not have been accurate.

In summary, we report our experience with a large group of patients with uveal metastases. We have described the general clinical and ocular features of this disease. The ophthalmologist should be familiar with these features as he or she may be the first physician to recognize that the patient has a systemic cancer.

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