Saudi Journal of Ophthalmology (2019) 33, 229–237

Original Article

Uveal metastasis in 1111 patients: Interval to metastasis and overall survival based on timing of primary cancer diagnosis

R. Joel Welch; Kunal Malik; Eileen L. Mayro; Jennifer H. Newman; Stephanie E. Honig; Su Mae Ang; Evan B. Selzer; Luis A. Acaba-Berrocal; Mark P. McGarrey; Alexander E. Graf; Sean P. Considine; Jerry A. Shields; Carol L. Shields *

Abstract

Purpose: To evaluate interval between primary cancer diagnosis and uveal metastasis and assess survival outcomes based on whether the primary cancer was diagnosed before or after uveal metastasis.
Methods: In this retrospective analysis, all patients with uveal metastasis evaluated on the Ocular Oncology Service, Wills Eye Hospital, Philadelphia, PA, USA between February 1, 1974 and June 1, 2017 were included. Features and outcomes based on timing of primary cancer diagnosis, whether before or after diagnosis of uveal metastasis, were assessed.
Results: A total of 2214 uveal metastases were diagnosed in 1310 eyes of 1111 consecutive patients. Primary cancer was known prior to uveal metastasis in 742 patients (67%) and not known in 369 (33%). Of those not known, the primary cancer was later found in 192 patients (17%) and never found in 177 patients (16%). For those with known primary cancer, mean interval from primary cancer diagnosis to uveal metastasis was 5.2 years with differences in primary sites of gastrointestinal (2.1 years, $p = 0.003$), lung (2.2 years, $p < 0.001$), breast (6.5 years, $p < 0.001$), and thyroid (13 years, $p < 0.001$). By Kaplan-Meier analysis, the 5-year overall survival showed no difference between patients with primary cancer found before (28%) vs after (20%) vs never found (33%), relative to uveal metastasis.
Conclusion: Of 1111 patients with uveal metastasis, early-onset uveal metastases were found with lung and gastrointestinal tract cancers, whereas late-onset metastases were found with breast and thyroid cancers. Overall survival did not vary on whether the primary tumor was diagnosed before, after, or never found, relative to uveal metastasis.

Keywords: Eye, Uvea, Metastasis, Breast cancer, Lung cancer

https://doi.org/10.1016/j.sjopt.2019.07.006

Introduction

Uveal metastasis most often originates from primary sites in the breast, lung, kidney, or gastrointestinal (GI) tract, with clinical features and outcomes varying depending on the source.[1–16] In a comprehensive single-center analysis of 1111 patients with uveal metastasis, patient survival was significantly worse with tumors originating in the lung, GI tract, and pancreas compared to those originating in the breast and carcinoid tumors of the lung.[1] For patients with uveal metastasis, regardless of primary site, overall prognosis was poor with 5-year survival estimate of 23%.[1]

A previous analysis of 950 uveal metastases in 520 eyes of 420 patients disclosed that 278 patients (66%) had known primary cancer at ocular presentation whereas 142 (34%) had no knowledge of pre-existing malignancy.[2] Of those without

Received 25 January 2019; accepted 8 July 2019; available online 25 July 2019.

The Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, United States

* Corresponding author at: Ocular Oncology Service, Suite 1440, Wills Eye Hospital, 840 Walnut Street, Philadelphia, PA 19107, United States.
e-mail address: carolshields@gmail.com (C.L. Shields).

Peer review under responsibility of Saudi Ophthalmological Society, King Saud University

Production and hosting by Elsevier

Access this article online:
www.saudiophthaljournal.com
www.sciencedirect.com

pre-existing cancer, the primary site was eventually detected in 69 patients (49%) and included cancers of the lung (35%), breast (7%), GI (1%), and others (6%).[2] Lacking in previous publications is a robust comparison on demographics, clinical features, and survival outcomes based on discovery of the primary cancer, whether before or after the uveal metastasis.[1,5] Herein, we explore patient demographics, primary cancer type, interval between primary cancer diagnosis and uveal metastasis, and overall survival based on whether the primary cancer was diagnosed before, after, or never found in relation to the uveal metastasis.

Methods

Patients with uveal metastasis evaluated between January 1, 1974, and June 1, 2017 at the Ocular Oncology Service at Wills Eye Hospital, Philadelphia, PA were included. Patients with lymphoproliferative disorders such as lymphoma, leukemia, and myeloma were excluded. This analysis adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Wills Eye Hospital.

Data included patient demographics, primary cancer site, uveal metastasis clinical features, and survival outcome. Demographic data included patient age at the time of ocular diagnosis, sex, and race. Primary cancer information included site of primary malignancy (breast, lung, kidney, gastrointestinal tract, skin, prostate, thyroid, pancreas, others, unknown), date of primary cancer diagnosis, and interval between primary cancer diagnosis and uveal metastasis. Follow up interval and overall survival data were collected.

Clinical features included patient symptoms, involved eye (right, left), laterality (unilateral, bilateral), visual acuity, and intraocular pressure. The total number of metastases per eye, anatomic location of the uveal metastases (iris, ciliary body, choroid), tumor basal dimension (mm), thickness (mm), and color (yellow, orange, brown, other) were recorded. All tumors were counted; however, if multiple metastatic tumors were present in an eye, detailed data were recorded for only the largest tumor per uveal tissue (iris, ciliary body, choroid). In iris metastases, presence of hyphema was recorded. In the choroid, distance to foveola and optic nerve (mm), presence of subretinal fluid, and acoustic quality (dense, hollow) were recorded.

All data were tabulated on Microsoft Excel 2016 and comparative analyses were performed regarding demographics, primary cancer site, tumors features and outcomes based on timing of primary cancer as before, after, or never found, relative to the uveal metastasis. Measures of central tendencies (mean, median, range) were obtained using built in functions. Independent two-sample *t*-test and analysis of variance (ANOVA) test were used to assess statistical significance between continuous data while Fisher's exact test or chi-squared test were used for categorical data. Five-year Kaplan-Meier survival analysis was performed using Microsoft Excel 2016 by grouping censored and death data into half-month intervals and comparative analysis was performed based on timing of primary cancer as before, after, or never found, relative to the uveal metastasis. Log-rank test was used to assess statistical significance among Kaplan-Meier data and hazard ratios with 95% confidence intervals were calculated. A *P*-value less than 0.05 was considered statistically significant for all tests.

Results:

A total of 2214 uveal metastases were diagnosed in 1310 eyes of 1111 consecutive patients. Patient demographics, tumor laterality, and primary cancer site are listed in Table 1, stratified by timing of primary cancer diagnosis, whether before, after, or never found, relative to uveal metastasis detection. A comparison of cohorts (primary cancer known vs not known before uveal metastasis) revealed significant differences in mean patient age (59 vs 61 years, $p = 0.04$), patient sex (71% female vs 51% female, $p < 0.001$), bilateral tumors (21% vs 11%, $p < 0.001$), and primary site of breast (52% vs 7%, $p < 0.001$), lung (21% vs 38% $p < 0.001$), kidney (6% vs < 1%, $p < 0.001$), gastrointestinal (GI) (5% vs 2%, $p = 0.02$), cutaneous melanoma (3% vs < 1%, $p < 0.001$),

Table 1. Uveal metastasis based on timing of primary cancer diagnosis in 1111 patients. Demographics and primary cancer type.

Feature	Timing of primary tumor diagnosis		
	Primary tumor diagnosed before uveal metastasis [n = 742 patients]	Primary tumor diagnosed after uveal metastasis or never found [n = 369 patients]	*P* value[a]
Age mean, years [median, range]	59 [60, 17–94]	61 [62, 10–93]	**0.04**[b]
Race, no. (%)			
White	659 (89)	323 (88)	0.55
Black	49 (7)	26 (7)	0.80
Asian	13 (2)	3 (1)	0.29
Indian			
Middle Eastern	0 (0)	2 (<1)	0.11
Hispanic	6 (<1)	6 (2)	0.23
Other	15 (2)	9 (2)	0.67
Sex, no. (%)			**<0.001**
Male	216 (29)	180 (49)	
Female	526 (71)	189 (51)	
Laterality, no. (%)			**<0.001**
Unilateral	583 (79)	329 (89)	
Bilateral	159 (21)	40 (11)	
Primary Site, no. (%)			
Breast	392 (52)	24 (7)	**<0.001**
Lung	155 (21)	140 (38)	**<0.001**
Kidney	44 (6)	2 (<1)	**<0.001**
GI	34 (5)	6 (2)	**0.02**
Cutaneous melanoma	26 (3)	1 (<1)	**<0.001**
Lung Carcinoid	16 (2)	8 (2)	>0.99
Prostate	21 (3)	2 (<1)	**0.01**
Thyroid	14 (2)	1 (<1)	**0.03**
Pancreas	5 (1)	3 (1)	0.73
Others	35 (5)	5 (1)	**0.003**
Unknown	0 (0)	177 (48)	**<0.001**

GI = gastrointestinal; no. = number.

Others include larynx (n = 6), carcinoid (small intestine, appendix, colon, pancreas, testicle) (n = 6), bladder (n = 4), contralateral choroidal melanoma (n = 3), uterus (n = 3), leiomyoma/leiomyosarcoma (n = 3), salivary gland (n = 2), testicle (n = 2), bone (Ewing sarcoma) (n = 2), liver (n = 1), biliary tract (n = 1), scalp (adenocarcinoma) (n = 1), cervix (n = 1), seminal vesicle (n = 1), ovary (n = 1), myxofibrosarcoma (n = 1), trachea (n = 1), and adenoid cystic carcinoma (n = 1). Bold values indicate significant values at $P < 0.05$.

[a] Fisher's exact test.

[b] Independent sample t-test.

prostate (3% vs < 1%, p = 0.01), thyroid (2% vs < 1%, p = 0.03), other cancers as a single group (5% vs 1%, p < 0.001), and unknown site [no primary found] (0% vs 48%, p < 0.001). The primary cancer group classified as *others* is addressed in the footnotes of Table 1. A flow-diagram was created to demonstrate the percentages of patients whose primary cancer was diagnosed before, after, or never found in relation to uveal metastasis, including a breakdown of primary cancer site for all uveal metastasis. (Fig. 1).

Primary cancer was diagnosed before uveal metastasis in 94% of patients with breast cancer, statistically similar to patients with primary cancers of the kidney (96%, p > 0.99), skin melanoma (96%, p > 0.99), prostate (91%, p = 0.6), thyroid (93%, p = 0.6), and others (88%, p = 0.2). Compared to breast cancer, primary cancer was less often diagnosed before uveal metastasis in patients with cancer arising in the lung (53%, p < 0.001), lung carcinoid tumor (67%, p < 0.001), GI tract (85%, p = 0.04), and pancreas (63%, p = 0.01). (Fig. 2).

For those with known primary cancer before uveal metastasis, the interval from primary cancer diagnosis to uveal metastasis is listed in Table 2. Overall, the mean interval from primary cancer diagnosis to uveal metastasis was 5.2 years, similar for all races, but with differences per young age [21–40 years] (3.7 years, p = 0.02), older age [≥81 years] (9.6 years, p < 0.001), female sex (5.9 years, p < 0.001), and those with primary sites of GI (2.1 years, p = 0.003), lung (2.2 years, p < 0.001), breast (6.5 years, p < 0.001), and thyroid (13 years, p < 0.001).

For those with no known primary cancer before uveal metastasis, the findings are listed in Table 3. There was no difference in interval from ocular diagnosis to establishment of primary cancer site when stratified by demographics or primary tumor site. The mean interval to finding the primary cancer for breast (1.7 months) and lung (1.8 months) cancers was non-significantly shorter than GI cancer (2.5 months) and lung carcinoid (8.6 months).

The ophthalmic features of uveal metastasis based on primary site discovered before, after, or never found are listed in Table 4. When comparing cohorts (primary cancer found before vs after uveal metastasis), differences were seen in number of metastasis per eye (1.9 vs 1.4, p < 0.001), choroidal tumor basal diameter (9.2 vs 10.7 mm, p < 0.001), choroidal tumor thickness (2.9 vs 3.9 mm, p < 0.001), and subretinal fluid presence (69% vs 82%, p < 0.001).

Kaplan-Meier (KM) survival estimates based on timing of primary site discovered before, after, or never found are listed in Table 5. There was no significant difference in overall KM survival or mean survival when groups were compared by timing of primary cancer diagnosis. (Fig. 3) There was no survival difference for the group whose primary cancer was never found. (Fig. 4) For males and females, there was no difference in survival based on timing of primary cancer diagnosis. Similarly, for both breast and lung cancer, overall and mean survival did not change based on timing of primary cancer diagnosis.

Discussion

In prior reports on uveal metastasis, 66–71% of patients presented with knowledge of their primary cancer,[2,6] similar to 67% of patients in this study. However, in this analysis, we found important information regarding knowledge of underlying cancer by primary site. When considering the two most common primary cancer sites, breast and lung cancer, with uveal metastasis, there was a significant difference in that 94% of patients with breast cancer admitted knowledge of primary cancer compared to only 53% of those with lung

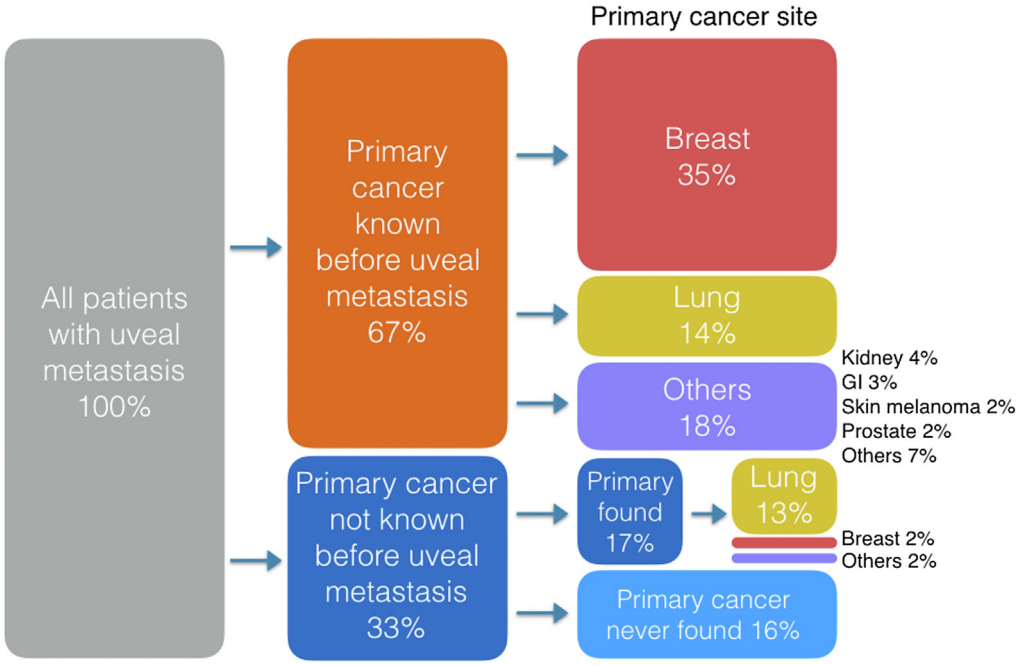

Fig. 1. Flow-diagram of uveal metastasis in 1111 patients demonstrating percentage with known or unknown primary cancer at time of uveal metastasis. Primary cancer site for all 1111 patients is seen on the right side of the diagram. The group labeled ''others'' includes kidney, GI, skin melanoma, prostate, thyroid, pancreas, lung carcinoid, and those mentioned in the footnote of Table 1.

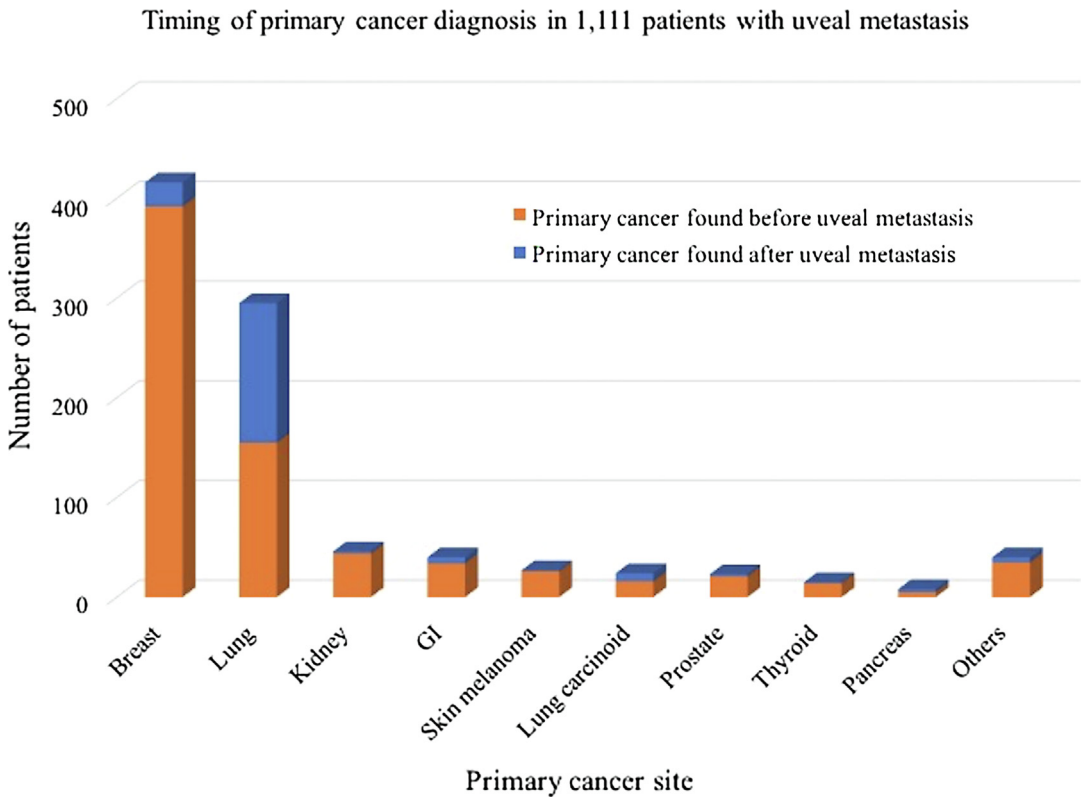

Fig. 2. Stacked column chart demonstrating timing of primary cancer diagnosis in 1111 patients based on whether the primary cancer was found before or after uveal metastasis.

cancer ($p < 0.001$). Other studies on uveal metastasis have reported similar findings and these numbers mirror what has been reported in a large national database regarding the stage of breast and lung cancers at diagnosis.[2–4,17] In >500,000 patients diagnosed with either breast or lung cancer, just 5% of patients with breast cancer presented with distant metastasis while 55% of those with lung cancer presented with distant metastasis.[17] Other primary cancer sites that frequently present with distant metastasis include ovary (62%), pancreas (53%), and stomach (33%), and uveal metastasis from these cancers is relatively rare.[1,17] The lack of an effective screening tool for lung cancer and its asymptomatic nature are likely responsible for the number of patients with lung cancer that present at an advanced stage.[18]

The interval from primary cancer diagnosis to uveal metastasis was longer in older individuals (≥81 years). No other study on uveal metastasis has demonstrated significance by age for this metric, however, a thorough discussion of metastasis by age from this database was reported earlier.[16] Regarding breast cancer specifically, the mean interval from cancer diagnosis to uveal metastatic disease in prior reports ranged from 3.4 to 5.4 years.[3,6] For lung cancer, mean interval between lung cancer diagnosis and uveal metastasis has been reported as 0.8 to 2.6 years.[4,6] This analysis supports these findings as mean interval between primary cancer diagnosis and uveal metastasis was 6.5 years for breast cancer ($P < 0.001$) and significantly shorter at 2.2 years for lung cancer ($P < 0.001$). Gastrointestinal cancers had a significantly shorter mean interval (2.1 years, $P < 0.001$) while thyroid cancers (13 years, $P < 0.001$) had a relatively longer mean interval. No large series on uveal metastasis due to thyroid cancers exists; however, a survey by Besic and Luznik[19] of 22 published cases from multiple centers reported mean interval from diagnosis of thyroid cancer to choroidal metastasis at 10.4 years, similar to our findings. The more favorable life prognosis with thyroid cancer (20-year survival rate > 90%) possibly allows for such late recurrence/metastasis compared to cancers with poorer life prognosis, like lung cancer (20-year survival rate < 10%).[17] Further analysis of relatively late-onset metastases, as seen with thyroid cancer, may increase understanding of the angiogenic, immunologic, and cellular models of cancer dormancy.[20] Historically, renal cell carcinoma and cutaneous melanoma have demonstrated late-onset metastasis[21]; however, the mean interval to uveal metastasis for these cancers was 4.6 years and 4.9 years, respectively, similar to the overall mean of 5.2 years.

Of patients presenting with knowledge of their primary cancer diagnosis, 71% were female in this study compared to 78% females in a prior large analysis.[2] The predominance of breast cancer in those presenting with known primary cancer is likely responsible for the female majority. This could also explain the high rate of multifocality, bilaterality, smaller choroidal tumor thickness, and less frequent association with subretinal fluid, compared to those presenting with no known primary cancer as prior reports have focused on the tendency for bilateral, multifocal, and flatter tumors in breast cancer metastasis compared to other primary cancer sites.[2,7] Although there was a female majority in patients with known primary cancer, the sex ratio in those presenting with no known cancer diagnosis was nearly even, 51% females and 49% males. This is consistent with 48% females and 52% males reported previously.[2]

Table 2. Interval (years) between primary cancer diagnosis and uveal metastasis in 742 patients with known primary cancer, based on demographics and primary cancer site.

Feature	Interval between primary cancer diagnosis and uveal metastasis, mean years [median, range]	*P* value[a]
All (n = 742 pts.)	5.2 [3.0, 0.1–42]	–
Age		**0.001**[b]
0–20 years (n = 2 pts.)	1.1 [1.1, 1.0–1.2]	0.35
21–40 years (n = 54 pts.)	3.7 [2.1, 0.1–17]	**0.02**
41–60 years (n = 326 pts.)	4.8 [3.3, 0.1–37]	0.49
61–80 years (n = 332 pts.)	5.5 [2.9, 0.1–42]	0.15
≥81 years (n = 28 pts.)	9.6 [7.9, 0.3–36]	**<0.001**
Race		0.10[b]
White (n = 659 pts.)	5.2 [3.1, 0.1–42]	
Black (n = 49 pts.)	3.9 [1.9, 0.1–23]	
Asian (n = 13 pts.)	9.2 [7.2, 0.2–32]	
Hispanic (n = 6 pts.)	7.1 [6.4, 0.2–14]	
Other (n = 15 pts.)	3.7 [1.4, 0.3–16]	
Sex		**<0.001**
Male (n = 216 pts.)	3.4 [1.5, 0.1–42]	
Female (n = 526 pts.)	5.9 [3.9, 0.1–36]	
Laterality		0.55
Unilateral (n = 583 pts.)	5.2 [3.0, 0.1–42]	
Bilateral (n = 159 pts.)	4.9 [3.3, 0.1–37]	
Primary Site		**<0.001**[b]
Breast (n = 392 pts.)	6.5 [4.8, 0.1–36]	**<0.001**
Lung (n = 155 pts.)	2.2 [0.8, 0.1–24]	**<0.001**
Kidney (n = 44 pts.)	4.6 [2.7, 0.1–24]	0.50
GI (n = 34 pts.)	2.1 [1.1, 0.1–7.6]	**0.003**
Cutaneous melanoma	4.9 [3.2, 0.2–22]	0.83
(n = 26 pts.)	6.0 [4.5, 0.1–15]	0.60
Lung Carcinoid (n = 16 pts.)	5.4 [2.8, 0.1–42]	0.87
Prostate (n = 21 pts.)	13 [11, 0.1–37]	**<0.001**
Thyroid (n = 14 pts.)	4.6 [4.3, 0.1–11]	0.84
Pancreas (n = 5 pts.)	4.6 [2.3, 0.1–33]	0.58
Others (n = 35 pts.)		

GI = gastrointestinal; pts. = patients.
Others are mentioned in footnote of Table 1.
Bold values indicate significant values at $P < 0.05$.
[a] Independent sample t-test (for age, t-test between category versus all other ages; for primary site, t-test between primary site and all other sites combined).
[b] Single factor analysis of variance (ANOVA).

Table 3. Interval (months) between uveal metastasis diagnosis and identification of primary cancer in 192 patients with no known primary cancer at presentation based on demographics and primary cancer site.

Feature	Interval between uveal metastasis diagnosis and identification of primary cancer site, mean months [median, range]	*P* values[a]
All (n = 192 pts.)	2.1 [0.5, 0–88]	–
Age		$P = 0.30$
0–20 years (n = 1 pts.)	0.13	
21–40 years (n = 10 pts.)	5.9 [2.9, 0.1–26]	
41–60 years (n = 77 pts.)	3.1 [0.5, 0–88]	
61–80 years (n = 95 pts.)	1.0 [0.5, 0–18]	
≥81 years (n = 9 pts.)	0.6 [0.1, 0–3.7]	
Race		$P = 1.00$
White (n = 166 pts.)	2.2 [0.5, 0–88]	
Black (n = 16 pts.)	2.1 [0.8, 0–12]	
Asian (n = 2 pts.)	0.2 [0.2, 0.1–0.3]	
Hispanic (n = 2 pts.)	0.4 [0.4, 0–0.7]	
Middle Eastern (n = 2 pts.)	0.8 [0.8, 0.3–1.2]	
Other (n = 4 pts.)	0.4 [0.4, 0–1.0]	
Sex		$P = 0.97$[b]
Male (n = 89 pts.)	2.1 [0.4, 0–88]	
Female (n = 103 pts.)	2.1 [0.6, 0–51]	
Laterality		$P = 0.94$[b]
Unilateral (n = 170 pts.)	2.2 [0.5, 0–88]	
Bilateral (n = 22 pts.)	2.2 [0.2, 0–18]	
Primary Site		$P = 0.82$
Breast (n = 24 pts.)	1.7 [0.1, 0–26]	
Lung (n = 140 pts.)	1.8 [0.5, 0–88]	
Kidney (n = 2 pts.)	1.1 [1.1, 0.1–2.1]	
GI (n = 6 pts.)	2.5 [0.8, 0.1–11]	
Cutaneous melanoma (n = 1 pts.)	0.8	
Lung Carcinoid (n = 8 pts.)	8.6 [0.3, 0–51]	
Prostate (n = 2 pts.)	1.5 [1.5, 0–3.0]	
Thyroid (n = 1 pts.)	3.5	
Pancreas (n = 3 pts.)	1.7 [1.1, 0.3–3.6]	
Others (n = 5 pts.)	3.0 [0.8, 0.1–12]	

GI = gastrointestinal; pts. = patients.
[a] Single factor analysis of variance (ANOVA).
[b] Independent sample t-test. Primary cancer sites classified as Others are listed in the footnotes of Table 1. Bold values indicate significant values at $P < 0.05$.

While others have documented life prognosis in the setting of uveal metastasis, including reports based on primary cancer site,[1] and patient age,[16] there is no published report exploring survival by timing of primary cancer diagnosis (whether before, after, or never found in relation to uveal metastasis). Freedman and Folk[6] reported median survival time for patients with uveal metastasis due to breast cancer

Table 4. Uveal metastasis based on timing of primary cancer diagnosis in 1111 patients. Clinical features.

Feature	Timing of primary tumor diagnosis					
	Primary tumor diagnosed before uveal metastasis [n = 926 tumors]	Primary tumor diagnosed after uveal metastasis [n = 219 tumors]	*P* value[a] Diagnosed before vs after uveal metastasis	Primary tumor never found [n = 196 tumors]	*P* value[a] Diagnosed before uveal metastasis vs never found	*P* value[a] Diagnosed after uveal metastasis vs never found
Tumor location, no. (%)						
Iris	77 (8)	12 (5)	0.16	11 (6)	0.24	1.00
Ciliary body	18 (2)	9 (4)	0.08	1 (<1)	0.23	**0.02**
Choroid	831 (90)	198 (90)	0.90	184 (94)	1.00	0.21
Number of tumors per eye, mean [median, range]	1.9 [1.0, 1–29]	1.4 [1.0,1.0–6]	**<0.001**[b]	1.4 [1.0, 1.0–7]	**<0.001**[b]	0.90[b]
Iris metastasis (largest tumor)						
Base, mean, mm	6.4	7.8	0.29[b]	7.1	0.62[b]	0.52[b]
Thickness, mean, mm	2.6	2.7	0.89[b]	2.5	0.84[b]	0.72[b]
Color, no. (%)						
Yellow	41 (53)	6 (50)	1.00	7 (64)	0.75	0.68
Orange	7 (9)	1 (8)	1.00	1 (9)	1.00	1.00
Brown	9 (12)	0	0.60	0 (0)	0.60	1.00
Other	20 (26)	5 (42)	0.31	3 (27)	1.00	0.67
Hyphema, no. (%)			1.00		0.68	1.00
Yes	14 (18)	2 (17)		1 (9)		
No	63 (82)	10 (83)		10 (91)		
Ciliary body metastasis (largest tumor)						
Base, mean, mm	11.8	12.1	0.92[b]	8.0	NE	NE
Thickness, mean, mm	5.3	5.8	0.78[b]	3.4	NE	NE
Color, no. (%)						
Yellow	9 (50)	6 (67)	0.68	1 (100)	1.00	1.00
Orange	3 (17)	0 (0)	0.59	0 (0)	1.00	1.00
Brown	2 (11)	1 (11)	1.00	0 (0)	1.00	1.00
Other	4 (22)	2 (22)	1.00	0 (0)	1.00	1.00
Choroidal metastasis (largest tumor)						
Base, mean, mm	9.2	10.7	**<0.001**[b]	9.7	0.30[b]	0.06[b]
Thickness, mean, mm	2.9	3.9	**<0.001**[b]	3.7	**0.001**[b]	0.65[b]
mm to foveola, mean	2.2	1.9	0.30[b]	1.9	0.29[b]	0.96[b]
mm to optic disc, mean	2.6	2.3	0.22[b]	2.0	**0.018**[b]	0.33[b]
Color, no. (%)						
Yellow	721 (87)	174 (87)	0.73	148 (80)	**0.04**	**0.05**
Orange	70 (8)	12 (6)	0.31	14 (8)	0.88	0.69
Brown	30 (4)	5 (3)	0.66	15 (8)	**0.02**	**0.02**
Other	10 (1)	7 (4)	**0.03**	7 (4)	**0.02**	1.00
Subretinal fluid, no. (%)			**<0.001**		0.06	0.16
Yes	573 (69)	163 (82)		140 (73)		
No	258 (30)	35 (17)		44 (26)		
Ultrasound Density			0.73		0.39	0.74
Dense, %	81	78		75		
Hollow, %	19	22		25		

mm = millimeter; no. = number.

[a] Fisher's exact test.

[b] Independent sample t-test; Bold values indicate significant values at $P < 0.05$.

(666 days), lung cancer (188 days), and those with unknown primary (236 days). The median survival time for patients with unknown primary in that study was not significantly different from the breast and lung cancer patients.[6] Our data agree with these findings as no significant survival difference was seen between those with known primary (whether diagnosed before or after uveal metastasis) and those whose primary tumor was never found. It has been shown that females and

Table 5. Uveal metastasis based on timing of primary cancer diagnosis in 1111 patients. Kaplan Meier survival analysis and mean survival.

Timing of primary cancer diagnosis	Kaplan Meier survival analysis					Mean survival, months [median, range]	
	1 year	3 year	5 year	Comparison			
				P value[a]	Hazard ratio for death [95% CI]		*P* value[b]
All patients with primary cancer							
Diagnosed before uveal met (n = 742 pts, 498 censored)	0.62	0.35	0.28	0.36	0.9 [0.6–1.2]	17.3 [8.4, 0.3–209]	0.98
Diagnosed after uveal met (n = 192 pts, 132 censored)	0.54	0.33	0.20			17.2 [8.5, 0.6–111]	
All Patients with primary cancer							
Found (whether before/after met) (n = 934 pts, 630 censored)	0.61	0.34	0.26	>0.99	1.0 [0.7–1.4]	17.3 [8.4, 0.3–209]	0.89
Never found (n = 177 pts, 131 censored)	0.58	0.40	0.33			16.6 [6.4, 0.3–105]	
Male							
Found before uveal met (n = 216 pts, 150 censored)	0.50	0.17	0.11	0.63	1.1 [0.7–1.7]	11.0 [5.4, 0.3–155]	0.27
Found after uveal met (n = 89 pts, 60 censored)	0.42	0.30	0.24			16.8 [8.1, 0.6–111]	
Female							
Found before uveal met (n = 526 pts, 348 censored)	0.66	0.39	0.32	0.51	0.9 [0.6–1.3]	19.9 [9.9, 0.3–209]	0.71
Found after uveal met (n = 103 pts, 72 censored)	0.63	0.34	0.17			17.7 [8.5, 1.5–61]	
Breast cancer							
Found before uveal met (n = 392 pts, 250 censored)	0.69	0.38	0.30	0.78	0.9 [0.4–2.0]	21.9 [11.0, 0.4–209]	0.65
Found after uveal met (n = 24 pts, 17 censored)	0.69	0.34	0			27.7 [32.7, 4.9–52.3]	
Lung cancer							
Found before uveal met (n = 155 pts, 109 censored)	0.44	0.17	0.12	0.10	1.4 [0.9–2.2]	9.0 [4.9, 0.3–68.9]	0.16
Found after uveal met (n = 140 pts, 98 censored)	0.51	0.29	0.19			14.4 [8.4, 0.6–111]	

CI = confidence interval; dx = diagnosis; met = metastasis; mo = month; pts = patients.

[a] Log-rank test.

[b] Independent sample t-test.

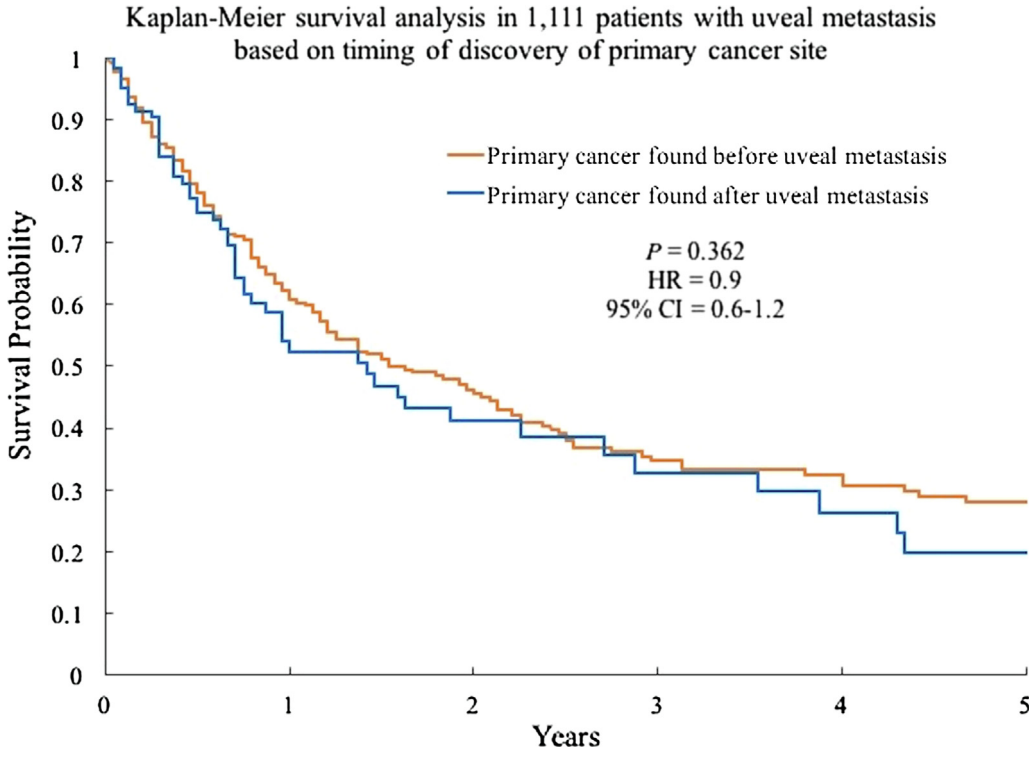

Fig. 3. Kaplan-Meier survival analysis for patients with uveal metastasis based on timing of primary cancer diagnosis showing no significant difference between groups, Log rank *P* = 0.362. Hazard ratio (HR) for death was 0.9 with a 95% confidence interval of 0.6–1.2.

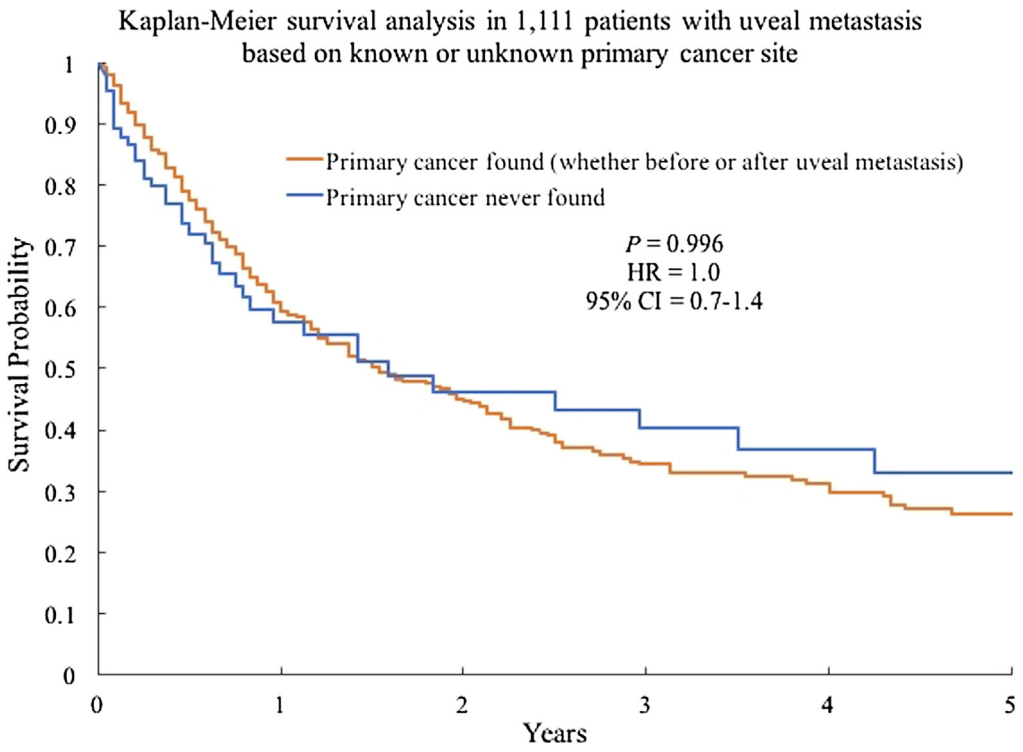

Fig. 4. Kaplan-Meier survival analysis for patients with uveal metastasis based primary cancer site (whether found before or after uveal metastasis) versus primary cancer never found showing no significant overall survival difference, Log rank $P = 0.996$, hazard ratio (HR) for death was 1.0 with 95% confidence interval of 0.7–1.4.

patients with uveal metastasis due to breast cancer[1] or lung carcinoid[1] have longer survival; however, this study shows survival was not significantly different based on whether primary cancer was diagnosed before or after uveal metastasis. This may speak to the difficult nature of managing metastatic cancer, no matter when the primary cancer diagnosis is made in relation to distant metastasis.

In conclusion, this single-center investigation of 1111 patients with uveal metastasis, with analysis based on timing of the primary cancer, revealed several key findings. We found that 67% patients with uveal metastasis presented with known primary cancer and 33% had no known primary cancer. Of those with known cancer, the interval between primary cancer diagnosis and uveal metastasis varied by sex, age, and type of primary tumor with lung and GI cancers presenting with earlier metastasis and breast and thyroid cancers presenting with later uveal metastasis. Of those with no known primary cancer, the primary tumor was eventually found in 52% of cases, leading most often to detection of underlying lung or breast cancers in females and lung or GI cancers in males. Kaplan-Meier 5-year survival was no different for patients with known primary cancer (28%) compared to those whose primary was diagnosed later (20%) or never diagnosed (33%). This information could be of help to physicians evaluating patients with uveal metastasis and in determining ocular treatment plans with overall patient survival in mind.

Conflict of interest

The authors declared that there is no conflict of interest.

Acknowledgement

Support provided by the Eye Tumor Research Foundation, Philadelphia, PA (JAS, CLS). The funders had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review or approval of the manuscript. Carol Shields, M.D. has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. No conflicting relationship exists for any author.

References

1. Shields CL, Welch RJ, Malik K, et al. Uveal metastasis: clinical features and survival outcome of 2214 tumors in 1111 patients based on primary tumor origin. *Mid East Afr J Ophthalmol* 2018 in press.
2. Shields CL, Shields JA, Gross NE, et al. Survey of 520 eyes with uveal metastases. *Ophthalmology* 1997;**104**:1265–76.
3. Demirci H, Shields CL, Chao AN, et al. Uveal metastasis from breast cancer in 264 patients. *Am J Ophthalmol.* 2003;**136**:264–71.
4. Shah SU, Mashayekhi A, Shields CL, et al. Uveal metastasis from lung cancer: clinical features, treatment, and outcome in 194 patients. *Ophthalmology* 2014;**121**(1):252–7.
5. Konstantinidis L, Rospond-Kubiak I, Zeolite I, et al. Management of patients with uveal metastases at the Liverpool Ocular Oncology Centre. *Br J Ophthalmol* 2014;**98**:92–8.
6. Freedman M, Folk JC. Metastatic tumors to the eye and orbit patient survival and clinical characteristics. *Arch Ophthalmol* 1987;**105**(9):1215–9.
7. Stephens RF, Shields JA. Diagnosis and management of cancer metastatic to the uvea. A study of 70 cases. *Ophthalmology* 1979;**86**:1336–49.
8. Ferry AP, Font RL. Carcinoma metastatic to the eye and orbit. I. A clinicopathologic study of 227 cases. *Arch Ophthalmol* 1974;**92**:276–86.

9. Shields JA, Shields CL, Kiratli H, de Potter P. Metastatic tumors to the iris in 40 patients. *Am J Ophthalmol* 1995;**119**(4):422–30.
10. Shields CL, Kaliki S, Crabtree GS, et al. Iris metastasis from systemic cancer in 104 patients: the 2014 Jerry A Shields Lecture. *Cornea* 2015;**34**(1):42–8.
11. Arepalli S, Kaliki S, Shields CL. Choroidal metastases: origin, features, and therapy. *Indian J Ophthalmol* 2015;**63**(2):122–7.
12. Shields JA, Shields CL. *Intraocular tumors: an atlas and textbook*. 3rd ed. Philadelphia: Lippincott Wolters Kluwers; 2016. p. 213–45.
13. Shah SU, Shields CL, Bianciotto CG, Shields JA. Pancreatic cancer metastasis to choroid. *Ophthalmology* 2011;**118**(7):1483.
14. de Bustros S, Augsburger JJ, Shields JA, et al. Intraocular metastases from cutaneous malignant melanoma. *Arch Ophthalmol* 1985;**103**:937–40.
15. Harbour JW, De Potter P, Shields CL, Shields JA. Uveal metastasis from carcinoid tumor. Clinical observations in nine cases. *Ophthalmology* 1994;**101**(6):1084–90.
16. Shields CL, Acaba-Berrocal LA, Selzer EB, et al. Uveal metastasis based on patient age in 1111 patients. Comparison of clinical features and outcomes per age category. Submitted for publication.
17. Horner MJ, Ries LAG, Krapcho M, et al. SEER Cancer statistics review, 1975–2006, National Cancer Institute. Bethesda, MD <https://seer.cancer.gov/csr/1975_2006/> based on November 2008 SEER data submission, posted to the SEER web site, 2009.
18. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: diagnosis and management of lung cancer. 3rd ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;**143**(5 Suppl):e78S–92S.
19. Besic N, Luznik Z. Choroidal and orbital metastases from thyroid cancer. *Thyroid* 2013;**23**(5):543–51.
20. Yeh AC, Ramaswamy S. Mechanisms of cancer cell dormancy – another hallmark of cancer? *Can Res* 2015;**75**(23):5014–22.
21. Friberg S, Nystrom A. Cancer metastasis: early dissemination and late recurrences. *Can Growth Metastasis* 2015;**8**:43–9.