

REVIEW ARTICLE



Metastatic tumours to the eye. Review of metastasis to the iris, ciliary body, choroid, retina, optic disc, vitreous, and/or lens capsule

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Metastasis to the eye can involve the choroid (90%), ciliary body (2%), iris (8%), and retina, optic disc, vitreous, and/or lens capsule (<1–4%). The mean number of uveal metastasis per eye (1.7), mean tumour base (11.6 mm) and thickness (3.2 mm), tumour colour (86% yellow), and presence of subretinal fluid (72%), are all clinical features suggestive of the diagnosis. Imaging with ultrasonography demonstrates an echodense mass (80%) and optical coherence tomography shows a “lumpy bumpy” choroidal surface (64%), both important diagnostic features. Uveal metastases typically emanate from primary cancer of the breast (37%), lung (27%), kidney (4%), gastrointestinal tract (4%), cutaneous melanoma (2%), lung carcinoid (2%), prostate (2%), thyroid (1%), pancreas (1%), and other sites (3%). Occasionally, fine needle aspiration biopsy is employed if the primary site is not known. In 16% of cases, the primary site remains unknown. Rarely, metastases affect the retina, vitreous, and lens capsule, most often originating from cutaneous melanoma and in patients previously treated with checkpoint inhibitor therapy. Kaplan–Meier analysis in a series of 1111 patients with uveal metastasis revealed 32% survival at 3 years and 24% at 5 years. Patients with uveal metastasis from carcinoid tumour showed most favourable survival at 5-years (92%), whereas pancreatic and kidney cancer demonstrated least favourable survival (0%). The 5-year survival was better for females (versus (vs.) males) (31% vs. 21%) and older adults (vs. children) (40% vs. 0%). In this review, we examine several large-cohort publications on the topic of ocular metastasis.

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INTRODUCTION

In the 2012 Cambridge symposium, Victoria M.L. Cohen, FRCOphth, and the Chief of Ocular Oncology at Moorfields Eye Hospital, London UK, discussed the current status of ocular metastases, including clinical features, investigations, and treatments [1]. At that time, there was substantial knowledge regarding tumour origin, diagnostic procedures, and treatment of ocular metastasis, but little was known on the outcomes of ocular metastasis in general and per specific tumour or differences in outcomes based on patient age and sex, as well as timing of metastatic tumours before or after the primary cancer.

What we do know is that metastatic tumours to the eye are classically detected within the uvea, mostly within the post-equatorial choroid, and in patients with known systemic cancer [1–7]. Metastatic tumours reach the uvea due to the rich uveal blood supply. Tumour emboli can seed along the vascular uveal tract and produce growing and symptomatic tumours at various sites. Less often, metastasis to the eye can present in other sites of the uvea such as the iris or ciliary body. Quite rarely, metastatic foci reach other intraocular sites such as the retina, optic disc, vitreous, and lens capsule. Many patients with metastatic tumours to the eye are not seen by an ophthalmologist because they have disseminated metastatic foci with more serious systemic cancer concerns, so the ocular metastasis is not documented.

Historically, metastatic tumours to the eye were thought to be rare. A well-known ophthalmic textbook in 1966 stated that few surgeons had observed more than one case of ocular metastasis during their career [8]. Later, it was realised that ocular metastases were more common, and over the past 50 years there have been several fairly large pathology reports on the incidence of patients with metastatic tumours to the eye [9–15]. Albert et al. found that 2% of 213 patients with known systemic cancer with metastases demonstrated choroidal metastases on histopathology [10]. Bloch and Gartner reported that 8% of eyes in 230 patients with autopsy-proven carcinomas had histopathologically-confirmed uveal metastatic foci [12]. Nelson and coworkers, in an autopsy study, noted that 4% of patients who had died from carcinoma demonstrated ocular metastases, and they estimated that 22,000 patients who died of cancer in 1983 had ocular metastatic disease [15]. As noted herein, however, most reports on ocular metastases have emanated from pathology laboratories or from general cancer centres where patients have had known primary cancers and/or metastatic disease and the eyes were subsequently examined following death. These studies have basically focused on the primary tumour source and histopathologic features of the tumour (derived from pathology or autopsy) [8–15].

More recently, there have been a few comprehensive clinical reports from ocular oncology centres on the tumour features,

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treatments, and outcomes of patients with uveal metastatic disease [3, 6, 7, 16–18]. Most recently, large-cohort studies on uveal metastasis in 1111 patients from an ocular oncology centre was documented and the clinical features and outcomes based on primary tumour site [3], patient age [16], sex [17], and timing of onset of metastasis [18] was studied. Furthermore, there are now reports on fairly large series of specific cancers from a single organ that metastasised to the eye such as cancer of the breast, lung, skin melanoma, uveal melanoma, and others [19–26]. Other reports have focused on tumour imaging features for diagnosis, fine needle aspiration biopsy (FNAB) results, treatments for globe preservation, and ocular outcomes following management of ocular metastatic foci [27–39]. There are only few reports on systemic survival following diagnosis and treatment of ocular metastasis [3, 19].

Herein, we review the various sites of ocular metastasis by highlighting large-data reports on the sites with description of clinical features, imaging, treatments, and outcomes.

METASTATIC TUMOURS TO THE UVEA (IRIS, CILIARY BODY, CHOROID)

Uveal metastasis by primary site, age, sex, and timing

The uveal tract is the most common ophthalmic site for hematogenous dissemination of metastatic tumours from systemic cancer [1–18]. The most comprehensive publication on uveal metastatic disease is an analysis of 2214 metastatic tumours in 1111 affected patients [3]. In that analysis, mean patient age was 60 years, Caucasian race (88%) and female sex (64%) were noted. The tumour was unilateral (82%) and the primary tumour site was known before uveal metastasis (67%). The primary tumour originated from cancer of the breast (37%), lung (26%), kidney (4%), gastrointestinal tract (4%), cutaneous melanoma (2%), lung carcinoid (2%), prostate (2%), thyroid (1%), pancreas (1%) and other sites (3%), with primary tumour site remaining unknown, despite systemic evaluation in 16% of cases. Overall prognosis was poor with 5-year survival at 24% and the poorest survival occurred in those with pancreatic metastasis (mean 4.2 months) whereas most favourable survival was with lung carcinoid metastasis (92% at 5 years).

Additional analysis of this large cohort of 1111 patients with uveal metastasis was performed regarding outcomes based on age, sex, and timing of the metastasis [16–18]. Regarding age, it was noted that uveal metastases rarely occur in children (0–20 years) (<1%), and young adults (21–40 years) (7%), but more often occur in middle-aged (41–60 years) (42%), older-aged (61–80 years) (46%), and senior-aged (81–100 years) (4%) adults [16]. The primary cancer to most commonly metastasise to the uvea was either breast or lung cancer in all age groups except children where the metastasis was from rare sarcomas ($n=3$). The Kaplan–Meier survival estimates (at 1 and 5 years) for children (33%, 0%), young adults (48%, 23%), middle adults (60%, 29%), older adults (62%, 25%), and senior adults (76%, 40%) revealed senior adults with most favourable life prognosis.

Regarding patient sex, of 1111 consecutive patients with uveal metastasis, the majority were females (64%) [17]. Comparison (female versus (vs.) male) revealed differences in mean age at metastasis diagnosis (58 vs 63 years, $p<0.001$), presence of bilateral disease (21% vs 11%, $p<0.001$), and mean number of metastases per eye (1.8 vs 1.6 tumours per eye, $p=0.04$). Overall survival was more favourable for females (20 vs. 13 months, $p=0.03$), likely related to the underlying primary cancer. Kaplan–Meier survival estimates (at 5 years) showed better survival in females (31% vs. 21%, $p<0.001$). For specific primary cancers, the survival differed only for lung cancer (24% vs. 9%, $p=0.009$).

Regarding timing, of 1111 consecutive patients with uveal metastasis, the primary cancer presented before (67%) or after (33%) detection of the uveal metastasis [18]. Those with known

primary cancer had a mean delay between primary site and uveal metastasis of 5.2 years, but it differed per primary cancer site including gastrointestinal (2.1 years), lung (2.2 years), breast (6.5 years), and thyroid (13 years). The Kaplan–Meier survival estimates (at 5 years) revealed no difference whether the primary site was known (before vs. after vs. never found) (28% vs. 20%, vs. 33%).

Uveal metastasis by primary cancer

Other reports have specifically focused on a single primary cancer. In 2002, Demirci et al. evaluated 264 patients with choroidal metastasis from breast cancer alone and found Kaplan–Meier survival at 1 year at 65% and at 5 years at 24% [20]. Shah et al. reviewed 229 eyes of 194 patients with lung cancer metastasis to the eye, noting 1-year mortality at 54% [21]. DeBustros et al. presented 12 eyes with intraocular metastasis from cutaneous melanoma and indicated that palliative radiotherapy could assist in slowing the foci and vision loss [23]. Zografos et al. presented a single case and reviewed 28 similar cases in the literature of cutaneous melanoma metastatic to the retina and vitreous, finding patient survival at only 22 months [24]. Harbour et al. studied carcinoid tumour metastatic to the uvea, indicating that this rare disease represented only 2% of all metastasis and tends to arise in the bronchus and with a distinct orange colour [25]. Masoomian et al. reported on 13 patients with uveal melanoma that demonstrated metastatic disease to the contralateral eye [26]. In that cohort, death from uveal melanoma metastasis elsewhere occurred in 11 patients at a mean of 17 months.

Uveal metastasis imaging

There are several methods for imaging of uveal metastasis, particularly choroidal metastasis. By ultrasonography, most tumours appear dome-shaped or placoid, often with echodense appearance (Fig. 1). On fluorescein angiography, choroidal metastases demonstrate early hypofluorescence with late staining and multifocal retinal pigment epithelial pinpoint leaks. Unlike melanoma that can show “double circulation” on angiography from both retinal and dilated choroidal vessels, metastasis tends to not demonstrate the dilation of choroidal vessels. On indocyanine green angiography, choroidal metastasis show hypocyanescence with minimal late staining as opposed to melanoma that commonly demonstrates hypercyanescence.

Optical coherence tomography shows characteristic features in eyes with choroidal metastasis [27–30]. Al-Dahmash et al. reviewed 14 eyes with choroidal metastasis and found choriocapillaris compression (93%), a “lumpy bumpy” anterior contour (64%), and subretinal fluid (79%) [28] (Fig. 2). The “lumpy bumpy” contour is uncharacteristic for choroidal melanoma, nevus, and

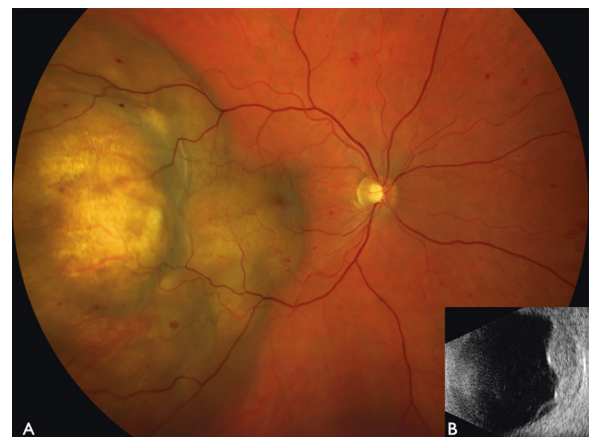


Fig. 1 Multinodular choroidal metastasis. A Large solitary choroidal metastasis from breast cancer documenting (B) echodensity on ultrasonography, typical for metastasis.



Fig. 2 Dome-shaped choroidal metastasis. **A** Large solitary lung metastasis in a smoker with **(B)** echodensity on ultrasonography and **(C)** “lumpy bumpy” surface on optical coherence tomography, typical for metastasis.

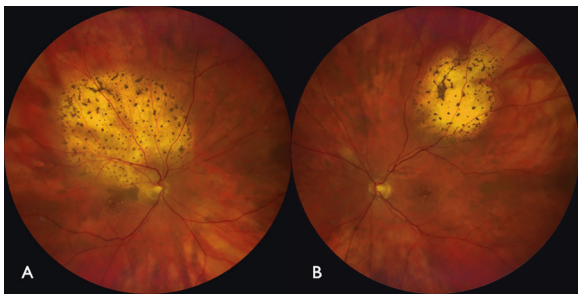


Fig. 3 Treatment of choroidal metastases. Post-treatment, **(A, B)** bilateral choroidal metastases demonstrating overlying retinal pigment epithelial mottling.

haemangioma, but can be seen with choroidal lymphoma and uveal effusion [27, 29, 30].

Fine needle aspiration biopsy

In cases where the diagnosis of uveal metastasis remains obscure, FNAB can be helpful [31–33]. Williams et al. studied posterior segment FNAB for 494 patients with an intraocular tumour and found that adequate tumour sample was achieved in 85% cases and the remainder (15%) had quantity not sufficient for diagnosis [33]. The most common final diagnosis was choroidal melanoma (44%), choroidal metastasis (39%), and choroidal lymphoma (5%). They concluded that FNAB is a reliable technique for cytopathologic confirmation of posterior segment intraocular tumours with clinically challenging diagnoses.

Uveal metastasis management

Management of uveal metastasis involves methods of radiotherapy including external beam radiotherapy (EBRT), proton beam radiotherapy, and plaque radiotherapy as well as systemic chemotherapy, systemic targeted medications and photodynamic therapy [34–39]. Rudoler et al. reviewed 233 consecutive eyes with metastatic tumours treated with EBRT using 30–40 Gy target dose. There were anticipated radiation-related side effects including cataract, retinopathy, papillopathy, keratopathy, iris neovascularization, and glaucoma [34]. Rudoler et al. provided another report on visual outcomes following EBRT of choroidal metastasis and noted that 98% of treated eyes had globe salvage, 57% regained some vision, and 36% of legally blind eyes regained useful vision [35] (Fig. 3).

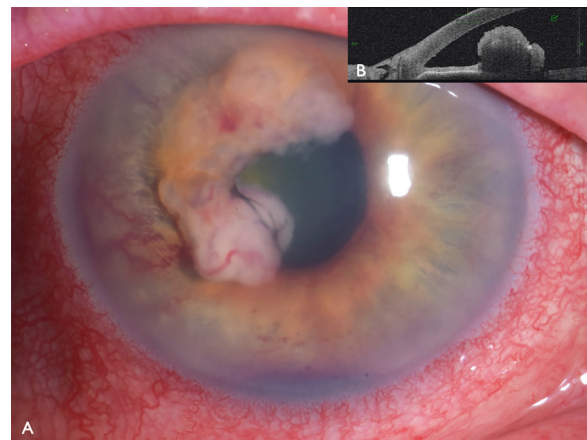


Fig. 4 Iris metastasis. **A** Iris metastasis with hyphema in a patient with lung cancer, **(B)** showing the cross section of the mass on anterior segment optical coherence tomography.

Shields et al. reported on plaque radiotherapy for solitary choroidal metastasis in 36 consecutive cases and found tumour control in 94% following a single session, including those that failed previous EBRT [36, 37]. Radiation side effects were noted in 8% cases. Photodynamic therapy using verteporfin dye for treatment of choroidal metastasis was studied in 58 consecutive cases and accomplished tumour control in 1 session (71%) or 2 sessions (7%) and failed to achieve tumour control in 22% cases who were later treated with radiotherapy. For those successfully treated, visual outcome was 20/20–20/40 in 66% of eyes [39].

Iris metastasis

There are a number of solid (melanocytic and non-melanocytic) and cystic tumours that can occur in the iris and iris metastasis represents only 2% of all cases [40–43]. Iris metastasis can manifest as a single or multiple yellow-white nodules within the iris stroma, occasionally with debris (pseudohypopyon) in the anterior chamber and hyphema that can lead to glaucoma [42, 43] (Fig. 4). In a comprehensive study of 160 iris metastases presenting in 104 patients, with median age at presentation of 60 years, the most common symptoms were pain (32%) and blurred vision (30%) [43].

Iris metastasis was more common in women (62%) and the primary cancer site in all patients included breast (33%), lung (27%), skin melanoma (12%), kidney (7%), and oesophagus (3%). The iris findings included corectopia (37%), secondary glaucoma (37%), iris neovascularization (27%), keratic precipitates (25%), hyphema (11%), ectropion uveae (10%), and pseudohypopyon (8%), often mistaken as uveitis [43]. Management included EBRT (41%), plaque radiotherapy (24%), systemic chemotherapy (22%), surgical excision (5%), and enucleation (4%). The mean time between detection of iris metastasis and death was 24 months [43]. Chen et al. and Goduni et al. documented iris metastasis treated with novel systemic medications [44, 45].

Metastatic tumours to the retina

Metastatic tumours to the eye are typically found in the choroid (88%), iris (9%), or ciliary body (2%), but rarely in the retina (<1%) [2, 6, 46–49]. In the largest published analysis of retinal metastases, only 8 cases were documented [46]. These tumours originated from cutaneous melanoma ($n=3$), breast cancer ($n=2$), oesophageal cancer ($n=1$), and lung cancer ($n=1$), all established before the retinal metastasis, and there was one case of cutaneous melanoma ($n=1$) discovered following retinal metastasis (Fig. 5). The primary tumour origin for retinal metastasis was substantially different from uveal metastasis as cutaneous melanoma represented 50% of retinal metastasis and only 2% of uveal metastasis [3, 46].



Fig. 5 Retina metastasis. **A** Retinal metastasis with **(B)** hypofluorescence on angiography and **(C)** documenting the retinal involvement on optical coherence tomography in a patient with lung cancer.

In the series of 8 patients with retinal metastasis, all were Caucasian, the mean patient age was 62 years, and the median interval from primary cancer to retinal metastasis was 33 months. This long delay was related to misdiagnosis elsewhere before referral as infectious or inflammatory retinitis ($n=5$), retinal haemangioma ($n=1$), choroidal neovascular membrane ($n=1$), or nerve fibre layer infarction ($n=1$). The tumour was unilateral ($n=7$), white or yellow colour ($n=6$) and with mean basal dimension of 7.4 mm and mean thickness of 2.3 mm. Vitreous tumour seeds ($n=3$), vitreous haemorrhage ($n=2$), subretinal fluid ($n=4$), and intraretinal exudation ($n=1$) were present. Management included plaque radiotherapy ($n=1$) for localised disease, enucleation ($n=3$) for extensive disease, or observation ($n=4$) for pre-terminal patients. Systemic cancer-related death ($n=5$, 63%) occurred within 1 month of retinal metastasis as established by ocular oncology. Patient survival with retinal metastasis is far poorer than with uveal metastasis.

Metastatic tumours to the optic disc

Metastatic tumours to the optic disc represent only 4% of all metastases to the eye [50]. In a series of 30 cases, the most common primary cancer sites to metastasise to the optic disc include breast (43%), lung (27%), gastrointestinal tract (3%), kidney (3%), and prostate (3%) cancer [50]. In 20% of cases the primary site was not found. Optic disc metastasis is typically unilateral (97%) and often with adjacent choroidal component (74%). Clinical features include swollen disc, often with surrounding nerve fibre layer haemorrhages. Systemic survival is poor at mean 13 months.

Metastatic tumours to the vitreous

Metastases to the vitreous are notably rare [51–54]. In 1998, Gunduz et al. reported 4 eyes in 3 patients with metastatic cutaneous melanoma to the vitreous, appearing at mean interval of 25 months since skin diagnosis and with findings of sheets or strands of golden yellow or brown cells as well as neovascular glaucoma [51]. At that time, most cases of vitreous metastasis were single case reports. Since then, a higher frequency of vitreous metastasis from treated cutaneous melanoma has been observed, especially in those treated with checkpoint inhibitor medications. Francis et al. reported a multicentre retrospective cohort of 14 eyes of 11 patients with metastatic cutaneous melanoma to the vitreous, most of whom had received checkpoint inhibitors during their course [52]. The eyes showed amelanotic (50%) or melanotic (50%) vitreous cells and the intraocular pressure was elevated (36%). Additionally, vitreous metastasis from other primary cancers have been documented [53].

Metastatic tumours to the lens capsule

There are only a few published case reports on metastatic tumour to the lens capsule, most of which have originated from cutaneous melanoma [51, 55–58]. In 2011, Solomon et al. reported a 71-year-old female with 1 year history of skin melanoma who developed complete opacification of the posterior lens capsule from melanoma metastasis [56]. Given the intraocular dissemination with evidence of vitreous debris on ultrasonography and lack of systemic metastasis, enucleation was performed. Metastatic cutaneous melanoma to the lens capsule, pseudophakic lens, anterior chamber, trabecular meshwork, vitreous, and retina was confirmed and the patient remained without systemic metastasis at 7 months follow up. In 2018, Paul et al. managed a 71-year-old male with known metastatic cutaneous melanoma on checkpoint inhibitor therapy (pembrolizumab) who developed bilateral pseudo-uveitis, lens capsule nodules, and cataract that proved on capsulorhexis at the time of cataract surgery to represent metastases from cutaneous melanoma [57]. The patient died from abdominal metastasis 7 months later. In 2020, Quhill et al. recorded an 80-year-old male with cutaneous melanoma 3 years prior who demonstrated anterior uveitis, ‘mutton fat’ keratic precipitates, and vision loss, ultimately demonstrating tumour deposition on the posterior lens capsule, confirmed on vitrectomy as metastatic cutaneous melanoma to the lens capsule [58]. Further widespread systemic metastasis led to guarded prognosis.

Summary

What is known about this topic

- Metastasis to the eye most often involve the choroid, and rarely affect the ciliary body, and iris.
- In select cases, metastases can manifest in the retina, optic disc, vitreous, and/or lens capsule.
- Most metastatic tumours appear yellow in color, located within the choroid and producing an overlying serous retinal detachment.
- Standard treatment includes systemic chemotherapy, if there are remote metastases, or external/plaque radiotherapy, if the condition is localized to the eye.

What this study adds

- Uveal metastases most often arise from primary cancer of the breast (37%), lung (27%), kidney (4%), gastrointestinal tract (4%), cutaneous melanoma (2%), lung carcinoid (2%), prostate (2%), thyroid (1%), pancreas (1%), and other sites (3%).
- At the time of detection, based on recent literature review, the mean number of uveal metastasis per eye is 1.7, mean tumour base is 11.6 mm and thickness is 3.2 mm.
- Imaging with ultrasonography typically reveals an echodense mass and optical coherence tomography depicts a classic “lumpy bumpy” tumour surface, both suggestive of the diagnosis and important in tumour detection.
- If the primary site is not known, then fine needle aspiration biopsy can be used to aspirate cells for identification of tumour type.
- In a series of 1111 patients with uveal metastasis, Kaplan–Meier analysis revealed only 24% survival at 5 years.
- The most favorable 5-year survival was in those with uveal metastasis from carcinoid tumour (92%) and the least favorable survival were those with primary sites in the pancreas or kidney (0%).
- Newer studies have documented a slowly changing landscape in the incidence of cancer and its management [59]. This could impact outcomes in the future.

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AUTHOR CONTRIBUTIONS

CLS, NEK, MG, MS: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AL, AMVS, KA, SEL, JAS: Substantial contributions to the interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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