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## ORIGINAL ARTICLE

# Clinical Features and Treatment Outcomes in Patients with Choroidal Metastases

**PK Yip[1], CCY Wong[2], FMY Lim[1], RKY Wong[1]**

*[1]Department of Oncology, Princess Margaret Hospital, Laichikok, Hong Kong*
*[2]Department of Ophthalmology, Caritas Medical Centre, Shamshuipo, Hong Kong*

## ABSTRACT

***Introduction:*** *Choroidal metastasis is the most common intraocular malignancy, which causes visual loss and hence adversely affects patient's quality of life. External beam radiotherapy (RT) remains the treatment of choice. This retrospective study aimed to look at the treatment outcomes and clinical features in patients with choroidal metastases.*

***Methods:*** *It is a retrospective single-centre study. Patients with choroidal metastases diagnosed between 2006 and 2016 were identified from RT treatment database. Treatment outcomes after RT in terms of visual and objective response, median time to response were analysed. Clinical features regarding patients' demographics, cancer and ocular disease characteristics and survival were evaluated.*

***Results:*** *21 patients with 28 involved eyes were identified. The median age at diagnosis of choroidal metastases was 55 years. The female-to-male ratio was 4:3. Bilateral choroidal metastases were found in seven (33%) patients. Concurrent or subsequent brain metastases were developed in eight (38%) patients. The most common symptom was blurring of vision (95%). The most common primary tumour type was lung carcinoma (n=9, 43%). The median survival was 5 months. The median prescribed biological effective dose was 39 $Gy_{10}$ (range, 28-39 $Gy_{10}$). Visual improvement was observed in 70% of irradiated eyes. Median time to visual improvement was 3.5 months (range, 2-5 months). Complete and partial remissions were achieved in nine (70%) eyes and two (15%) eyes, respectively.*

***Conclusion:*** *RT can effectively improve vision of patients with choroidal metastases. Prognosis in this group of patient remains poor.*

***Key Words:*** *Choroid; Radiotherapy*

***Correspondence:*** *Dr PK Yip, Department of Oncology, Princess Margaret Hospital, Laichikok, Hong Kong.*
*Email: ypk744@ha.org.hk*

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# 中文摘要

## 眼脈絡膜轉移患者的臨床特徵和治療效果

葉佩潔、黃鉦沅、林美瑩、黃家仁

**引言：**眼脈絡膜轉移是最常見的眼內惡性腫瘤，可導致視力喪失並對患者的生活質素產生不良影響。體外放射放療是首選治療方法。這項回顧性研究旨在研究眼脈絡膜轉移患者的治療結果和臨床特徵。

**方法：**這項回顧性單一中心研究，從放射治療數據庫識別2006年至2016年間診斷為眼脈絡膜轉移的患者，分析放射治療的療效，包括視覺改善和腫瘤客觀治療反應的中位數，以及評估患者的人口統計學、癌症和視覺病患臨床特徵和存活期。

**結果：**在數據庫識別出21名患有眼脈絡膜轉移的患者，涉及28隻眼睛。患病年齡中位數為55歲。女性與男性的比例為4：3。在7名（33%）患者中發現雙側脈絡膜轉移。8名（38%）患者同時或隨後出現腦轉移。最常見的症狀是視力模糊（95%）。最常見的原發性腫瘤類型是肺癌（n=9，43%）。存活期中位數為5個月。患者接受的生物有效劑量中位數為39 $Gy_{10}$（介乎28-39 $Gy_{10}$）。有70%的眼睛在接受放射治療後視覺有所改善。視力改善的中位時間為3.5個月（介乎2-5個月）。9隻眼（70%）和2隻眼（15%）分別達到完全和部分緩解。

**結論：**放射治療可有效改善眼脈絡膜轉移患者的視力，惟這組患者的預後仍然不理想。

## INTRODUCTION

The choroid is the most common site of metastases to the orbit, probably owing to its rich vascular supply. Choroidal metastases will cause visual loss, which is detrimental to patient's quality of life. Metastases to the eye were once considered a rare event. However, Bloch and Gartner performed postmortem examinations on 230 patients who died of systemic carcinoma and found 28 (12%) patients with metastatic tumour of the eye.[1] Improvements in cancer treatment and prolongation of survival are expected to lead to an increase in the number of choroidal metastases. External beam radiotherapy (RT) is the most common and effective treatment of choice for metastases to the eye and orbit. With the advancement in cancer treatment and prolongation of survival, it is likely that more choroidal metastases could be identified and hence better understanding of this disease is needed. The present study reviewed the clinical features of patients with choroidal metastases. In patients who received RT, treatment outcomes were analysed.

## METHODS

This was a single-centre retrospective analysis. Patients with diagnosis of choroidal metastases from 2006 to 2016 were identified from the RT treatment database. Patients who received formal eye assessments by ophthalmologists to confirm the diagnosis were included, and these ophthalmology assessment records were reviewed.

We used SPSS (Windows version 20.0; IBM Corp, Armonk [NY], US) for statistical analysis. Overall survival was defined as the time from diagnosis of choroidal metastases by ophthalmologist to death resulting from any cause and was generated by the Kaplan-Meier method.

Visual acuity tests and fundoscopic exams were done by ophthalmologists at 1- to 2-month intervals. Treatment outcomes included visual improvement and objective tumour response. Visual improvement was measured by percentage of patients who had functional improvement measured by visual acuity. Objective tumour response was assessed by fundoscopic exam, and classified into (1) complete tumour shrinkage replaced by a scar (complete response), (2) tumour shrinkage but not to extent of scar formation (partial response), (3) static tumour size (no change), and (4) increased tumour size (progressive disease). Time to response was defined as the time from completion of RT to first improvement in visual acuity.

Follow-up time was defined as period from diagnosis of choroidal metastases to death or censored time.

RT for choroidal metastases was delivered by linear accelerators using 6-MV photons; computed tomography (CT) 5-mm-thick slices were obtained from vault to whole neck. Patients were immobilised with a thermoplastic cast over head and neck region in the supine position with straight neck. The target volume included choroidal mass and posterior globe of both eyes with 5- to 10-mm margins irrespective of laterality of disease. Whole brain was included when there was synchronous brain metastasis. In order to reduce the lens dose, lateral opposing fields with half-beam block at the anterior border were used, and the anterior field border was placed behind the lens if adequate margin from choroidal mass could be achieved (Figure 1). The commonly prescribed radiation dose and fractionation were 30 Gy in 10 daily fractions (n=12), followed by 22.5 Gy in five daily fractions (n=2) and 20 Gy in five daily fractions (n=1). The dose prescription point was defined at 100% isodose line. The main organ at risk was the lens, and the dose constraint was set at 10 $Gy_3$. Weekly portal images were taken and compared with digital reconstructed radiograph for verification.

# RESULTS

## Patient and Cancer Characteristics

21 patients with 28 involved eyes were identified. Of these 21 patients, 12 were women and nine were men. The median age at diagnosis of choroidal metastases was 55 years (range, 39-78 years).

The most common tumour type was lung carcinoma (n=9; 43%) followed by breast carcinoma (n=8; 38%); the remaining primary tumour sites included urinary bladder, pancreas, salivary gland, and nasopharynx. Thirteen, three and five patients had Eastern Cooperative Oncology Group (ECOG) performance status of 1, 2 and 3, respectively (Table 1).

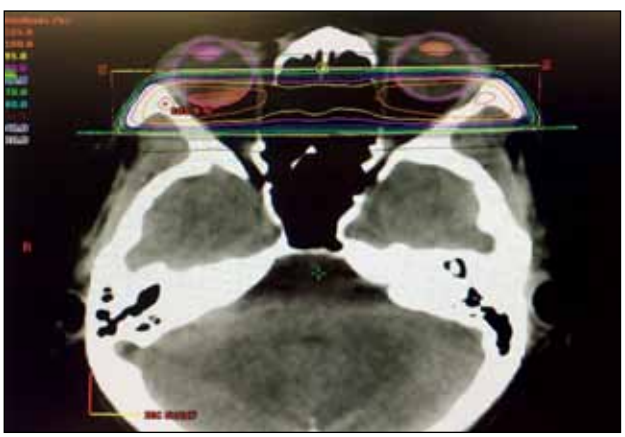

**Figure 1.** Radiotherapy dose distribution, target volume, and organ at risk delineation on axial computed tomography.

The median time from cancer onset to choroidal metastases diagnosis was 11 months (range, 0-87 months). In four (19%) patients, choroidal metastasis was the initial presentation of underlying malignant disease. All of them were later confirmed to have primary lung cancer with extensive metastases. In another two (10%) patients, choroidal metastasis was the first sign of recurrent diseases, and both of them had history of breast cancer 3 years previously. One of these two patients was found to have isolated choroid mass on positron emission tomography–computed tomography (PET-CT). The other patient was found to have disseminated recurrence involving lungs, liver, adrenal glands, and bone metastases.

After diagnosis of choroidal metastases, all patients received brain imaging for any concurrent brain metastases. Among the 21 patients, 13 had CT or magnetic resonance imaging (MRI) of the brain with intravenous contrast, three had PET-CT including the

**Table 1.** Patient and ocular disease characteristics (n=21).*

| Characteristics | Data |
|---|---|
| Age, y, median (range) | 55 (39-78) |
| Sex | |
| Male | 9 (43%) |
| Female | 12 (57%) |
| Eastern Cooperative Oncology Group performance status | |
| 1 | 13 (62%) |
| 2 | 3 (14%) |
| 3 | 5 (24%) |
| Primary tumour | |
| Lung | 9 (43%) |
| Breast | 8 (38%) |
| Others | 4 (19%) |
| Laterality of choroidal metastases | |
| Right | 7 (33%) |
| Left | 7 (33%) |
| Bilateral | 7 (33%) |
| Brain metastases | 8 (38%) |
| Symptoms | |
| Blurred vision | 20 (95%) |
| Floaters | 2 (10%) |
| Flashes | 2 (10%) |
| Pain | 1 (5%) |
| Red eye | 1 (5%) |
| Proptosis | 1 (5%) |

* Data are shown as No. (%) of patients, unless otherwise specified.

brain, and the remaining five patients had plain CT of the brain. Concurrent brain metastases were detected in seven (33%) patients. One other patient developed brain metastases on contrast MRI at 1 month after onset of choroidal metastases, despite a normal finding on PET-CT which included the brain.

## Ocular Disease Characteristics

In 14 (67%) patients, choroidal metastases were unilateral with even distribution between right and left side. In seven (33%) patients, choroidal metastases were bilateral. The frequency of presenting symptoms is detailed in Table 1; blurring of vision was the most common complaint. The diagnosis of choroidal metastases was made by fundoscopic examination. B-scan ultrasonography was done in 10 (48%) patients and was the most common adjunct investigation. In two (9.5%) patients, optical coherence tomography and fluorescein fundal angiography were performed to assist the diagnosis.

## Survival

After diagnosis of choroidal metastases, the estimated 1-year and 2-year overall survival rates were 35% and 18%, respectively. The median survival was 5 months (range, 1-61 months; Figure 2). All deaths were cancer-related. The median survival in patients with ECOG performance status of 1, 2, and 3 was 11 months, 5 months, and 1 month, respectively.

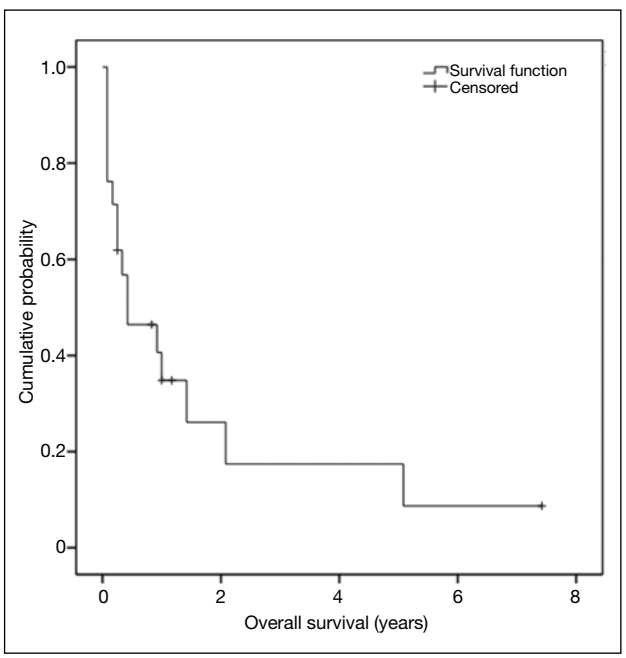


**Figure 2.** Overall survival since diagnosis of choroidal metastases.

## Treatment Outcomes and Safety of External Beam Radiotherapy

### *Treatment*

External beam RT was given in 15 (71%) patients with 21 affected eyes. The reasons for not receiving RT in the remaining six patients included poor general condition that precluded RT (n=3), patient refusal (n=2), and subjective visual improvement while on gefitinib (n=1). In this last patient, left eye vision was improved from complete blindness to light perception after taking gefitinib for 2 months. However, 1 year later the patient experienced severe pain in the left eye due to progressive intraocular disease and subsequently agreed to receive palliative RT for pain relief.

### *Response to Treatment and Complications*

Among the 15 patients who received external beam RT, five patients did not attend eye follow-up owing to poor general condition; all five died within 4 months (range, 1-4 months).

In the remaining 10 patients with regular ophthalmology assessments at 1- to 2-month intervals, 13 involved eyes were irradiated. Median follow-up time was 7.5 months (range, 3-85 months). The visual acuity and choroidal mass size changes before and after RT are presented in Table 2. Visual acuity improvement was noted in nine (70%) eyes. Median change in visual acuity was +0.2 (baseline median visual acuity: 0.5), suggesting a median 40% improvement in resolution after treatment. The median time to response was 3.5 months (range, 2-5 months). For objective tumour response, majority of eyes (85%) had either complete response or shrinkage of tumour after treatment. Complete response was achieved in nine (70%) eyes; the same nine eyes in which visual acuity improvement was noted. Partial response was achieved in two (15%) eyes; however, visual improvement was not observed owing to progressive worsening of underlying diabetic retinopathy in one of these two eyes and age-related macular degeneration in the other. One eye had no change in tumour size after 3 months after RT. One eye had progressive disease with near-total retinal detachment (Tables 2 and 3). During the period of RT treatment, patients were reviewed weekly in the oncology outpatient clinic. No acute adverse effects were reported. One patient with left choroidal metastases developed a cataract over the right eye 1 year after RT; the mean right lens biological effective dose (BED) was 15.5 $Gy_3$ (range, 12 Gy-19.6 $Gy_3$). The high lens dose was necessary owing to the large choroidal mass size, resulting in inevitable lens inclusion during treatment.

**Table 2.** Treatment outcomes of the 10 patients who received external beam RT to choroidal metastases and had regular ophthalmology assessment.

| Patient | Primary tumour | Best VA before RT | Best VA after RT | VA improvement | Size of CM before RT | Size of CM after RT | Objective tumour response | |
|---|---|---|---|---|---|---|---|---|
| 1 | Breast | 0.6 | 0.8 | Yes | 3-4 DD | Scar | CR | |
| 2 | Breast | 0.1 | 0.1 | No | 6 DD | 1.5 DD | PR | Co-existing ARMD |
| 3 | Sublingual gland | 0.1 | 0.1 | No | 3 DD | 1.5 DD | PR | Co-existing DR |
| 4 | Lung | Rt: 0.7 | Rt: 1.2 | Yes | Rt: 1.5 DD | Rt: Scar | CR | |
| | | Lt: 0.5 | Lt: 0.7 | Yes | Lt: 1.5 DD | Lt: Scar | CR | |
| 5 | Breast | 0.3 | 0.5 | Yes | 3 DD | Scar | CR | |
| 6 | Lung | 0.2 | 0.6 | Yes | 5 DD | Scar | CR | |
| 7 | Breast | Rt: LP | Rt: 0.1 | Yes | 3 DD | Rt: Scar | CR | |
| | | Lt: 0.6 | Lt: 0.7 | Yes | 4 DD | Lt: Scar | CR | |
| 8 | Breast | Rt: 0.5 | Rt: 0.7 | Yes | 2 DD | Rt: Scar | CR | |
| | | Lt: 0.5 | Lt: 0.7 | Yes | 2 DD | Lt: Scar | CR | |
| 9 | Lung | 0.2 | LP | No | 4 DD | Progress to central CM with extensive RD | PD | |
| 10 | Lung | 0.5 | 0.1 | No | 2 DD | 2 DD | No change | |
| Median VA before RT | | 0.5 (patients can see an object at 6 m, when a normal person can see at 12 m) | | | | | | |
| Median VA after RT | | 0.7 (patients can see an object at 6 m, when a normal person can see at 8.5 m) | | | | | | |
| Median change in VA | | +0.2 | | | | | | |

Abbreviations: ARMD = age-related macular degeneration; CM = choroidal metastases; CR = complete response; DD = disc diameter; DR = diabetic retinopathy; LP = light perception; Lt = left; PD = progressive disease; PR = partial response; RD = retinal detachment; Rt = right; RT = radiotherapy; VA = visual acuity.

**Table 3.** Treatment response (n=13).

| | |
|---|---|
| Visual acuity improvement | 9 eyes (70%) |
| Objective tumour response | |
| Complete remission | 9 eyes (70%) |
| Partial remission | 2 eyes (15%) |
| No change | 1 eye (7.5%) |
| Progressive disease | 1 eye (7.5%) |

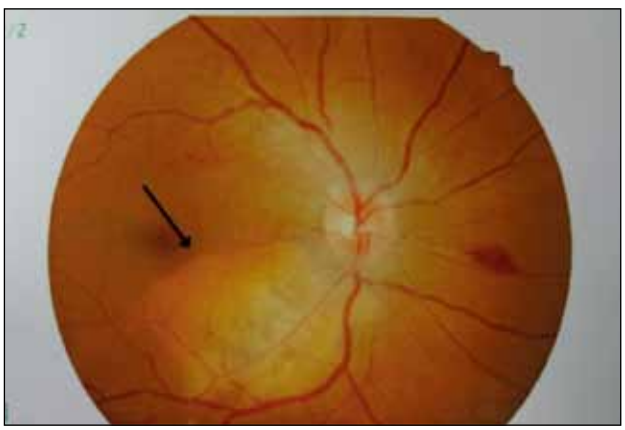

**Figure 3.** Right fundus photograph showing a plaque-like yellowish lesion in the inferotemporal arcade (black arrow indicates the choroidal mass). Courtesy of the Department of Ophthalmology, Caritas Medical Centre.

## DISCUSSION

Choroidal metastases are most commonly seen in lung and breast cancers.[2-5] This is consistent with the present case series, in which the frequency of lung tumour was slightly higher than that of breast cancer. A slight female predominance was detected among our patients.

Blurring of vision was the main presenting symptom in nearly all patients. Choroidal metastasis generally appears as a plaque-like yellowish lesion (Figure 3). On B-scan ultrasonography, choroidal metastasis appears as an echogenic mass with higher internal reflectivity and is sometimes associated with subretinal fluid (Figure 4).

In the present study, synchronous choroidal metastases over both eyes were noted in 33% of patients. This is compatible with previous studies that have reported frequencies in the range of 25% to 40%.[2,3,5]

There is still no consensus of treatment for unilateral choroidal metastases. Some authors advocate bilateral irradiation for sterilisation of the contralateral choroid, whereas others treat the ipsilateral eye with one lateral field. In one prospective study, 35 of 50 patients with choroidal metastasis had unilateral disease and received unilateral irradiation with a lateral field using 6-MV photons (40 Gy in 20 daily fractions) without sparing

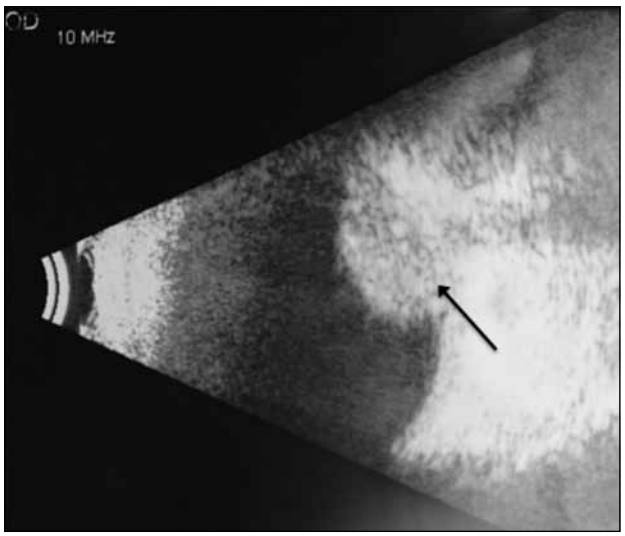


**Figure 4.** B-scan ultrasonography showing an echogenic choroidal mass with high internal reflectivity (black arrow indicates the choroidal mass). Courtesy of the Department of Ophthalmology, Caritas Medical Centre.

the contralateral choroid.[4] The posterior part of the contralateral choroid received 50% to 70% of the total dose (20-28 Gy) for suspected micrometastases. None of those patients developed contralateral choroidal metastases during the median follow-up time of 11.5 months.[4,5] Despite those findings, patients with unilateral choroidal metastasis and irradiation of the involved choroid have a risk of about 20% to develop contralateral choroidal metastases.[5] One retrospective study found that when the contralateral eye was not primarily irradiated, metachronous metastases occurred in three of 26 patients, whereas none occurred in 10 patients after bilateral irradiation.[2] In the present study, all patients with unilateral choroidal metastases received bilateral eye irradiation and none developed contralateral choroidal metastases after a median follow-up of 7.5 months. Only one out of 10 patients (10%) developed a RT-related cataract 1 year after RT, with mean lens BED 15.5 $Gy_3$. This result is consistent with previously reported incidences of 8%, 3.3%, and 2.7% for RT-induced cataract, retinopathy, and optic neuropathy, respectively.[6] One possible reason for the low rate of adverse effects after RT is the short expected lifespan of these patients before late adverse effects could appear.[4]

One retrospective study showed a significantly better complete response rate for BED >35.5 $Gy_{10}$ (72% vs. 33%; p=0.009), as well as the visual acuity improvement or stabilisation (72% vs. 51%; p=0.014).[2] Other studies have reported visual improvements after RT in 55% to 63% of patients.[3] The median prescribed BED in our series was 39 $Gy_{10}$ (range, 28-39 $Gy_{10}$). Visual acuity improvement was seen in 70% of patients, and complete or partial response was seen in 85% of patients, consistent with previous reports. Our response rate was higher than that reported previously, likely because two patients who reported subjective visual improvement had no formal eye assessments owing to poor condition. Another two patients with objective partial response on fundoscopy did not gain functional visual improvement, owing to progressive underlying diabetic retinopathy or age-related macular degeneration. Therefore, patients with pre-existing retinopathy should be counselled before commencement of RT on the lower chance of visual improvement and possible worsening of visual acuity.

Although there are high rates of response and visual improvement after RT for choroidal metastasis, these effects take time to become apparent, with a median of 3.5 months in our patients (range, 2-5 months). This is a particularly important concern for patients with a short life expectancy. In the present study, the median survival in patients with performance status of 3 was only 1 month. The survival of patients in the present study was poor, with a median of 5 months; this was not an improvement over previous studies, which have reported overall survival ranging between 5 and 7 months.[3,4] This short survival is probably because of the high incidence of brain metastases (38%) and disseminated nature of the disease upon diagnosis of choroidal metastases. These findings suggested that in patients with poor performance status and limited lifespan, careful judgement should be made on whether the patient would benefit from RT. In a previous case series, breast cancer was consistently associated with a significantly better survival outcome when compared with other cancers[2,4]; however, this result was not reflected in the present study owing to the small sample size.

Over the past decade, targeted therapies have improved the available options for treatment of choroidal metastases in the initial stage of care. Because the choroid is external to the blood-ocular barrier, systemic medications diffuse efficiently into the choroid via the fenestrated endothelium of the choriocapillaris. Previous case reports have shown dramatic visual improvements after initiation of targeted agents. One of our lung cancer patients also showed initial visual response to gefitinib, without receiving RT. However, that patient eventually received RT to the choroidal metastases as his disease progressed while on gefitinib. This demonstrated that

regular visual monitoring and a timely delivery of RT still play an important role to help patients regain the functional vision after disease progression.

One of the limitations of this study is the small sample size owing to the low incidence of choroidal metastases, trivial eye symptoms that could be missed in medical consultation, and potential incomplete patient identification through the RT database. Multi-centre collaboration is recommended for future studies. In addition, the treatment outcomes in this study were affected by many confounding factors, such as primary diseases, co-existing benign eye pathologies, and the use of systemic treatments, especially targeted agents. Some of our patients who received RT did not receive regular assessment by ophthalmologists, so our results were not truly representative. Finally, the ophthalmology follow-up procedure was not standardised in each patient; however, the 1- to 2-month follow-up interval in this study was sufficient to detect changes in visual acuity and tumour response.

## CONCLUSION

This was a retrospective review of clinical features and RT treatment outcomes in a small group of patients in a single oncology centre. External beam RT is still the mainstay of treatment for choroidal metastases to effectively improve patient visual function. Functional visual gain was seen in 70% of RT-treated eyes. Despite recent advances in systemic oncological treatment, the prognosis remains poor in this group of patients. In patients with poor performance status and limited life expectancy, the use of RT needs to be carefully justified, as RT treatment response takes a few months.

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