Multimodal Imaging in Choroidal Metastasis

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Keywords

Multimodal imaging · Enhanced depth imaging optical coherence tomography · Optical coherence tomography angiography · Choroidal metastasis

Abstract

Background: Choroidal metastasis represents the most common malignant intraocular tumours. **Objectives:** The objective of this study is to detect the structural and vascular features of choroidal metastasis by multimodal imaging. **Methods:** Sixteen eyes of 16 patients with choroidal metastasis were enrolled in this prospective study. The multimodal imaging was performed in all patients: fluorescein angiography, indocyanine green angiography, enhanced depth imaging optical coherence tomography (EDI-OCT), OCT angiography (OCTA), and ultrasonography. **Results:** The choroidal metastasis was located in the macula region in 9 eyes (57%) and in the extramacular region in 7 eyes (43%). EDI-OCT showed a mean thickness of $950 \pm 246 \mu\text{m}$, a smooth anterior tumour surface in 5 eyes (31%), and a lumpy bumpy appearance in 11 eyes (69%). The most frequent EDI-OCT features were represented by choriocapillaris thinning (100%), shaggy photoreceptors (82%), subretinal fluid with speckles (69%), subretinal lipofuscin pigment (6%), absence of drusen (100%), optical shadowing (94%), low-internal optical reflectivity (75%), and retinal pigment epithelium alterations (43%). OCTA revealed an absence of intratumoral vas-

cular network in all cases. **Conclusions:** The multimodal imaging contributed to greater insights into the anatomical and vascular features of choroidal metastasis. It allows for the collection of useful information to establish an appropriate diagnosis and follow-up.

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Introduction

Intraocular metastasis represents the most common malignant intraocular tumours, and they are often the first sign of dissemination of the primary tumour. The incidence of choroidal metastasis has increased over the years because of the improvement of diagnostic techniques and the increased survival of patients due to the improvement of available therapies [1–6].

Until a few years ago, choroidal metastasis was diagnosed not only by ultrasound but also by clinical exam and personal health history. Today, specific characteristics of choroidal metastases can be assessed by numerous other diagnostic procedures such as multicolour imaging, enhanced depth imaging optical coherence tomography (EDI-OCT), OCT angiography (OCTA), fluorescein angiography (FA), and indocyanine green angiography (ICGA) [7–17]. The aim of this prospective study was to use multimodal imaging to evaluate the vascular and morphological features of choroidal metastasis.

Materials and Methods

In this prospective observational study, 18 patients with a diagnosis of choroidal metastasis were recruited from March 2014 to December 2018 at the Eye Clinic of the University of Naples “Federico II.” They underwent complete ophthalmological examination including best-corrected visual acuity, ultrasound examination (A-scan standardized and B-scan), multicolour imaging, EDI-OCT, FA, ICGA, using spectral-domain (SD)-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany, software version 1.10.2.0), and OCTA (AngioVue, RTVue XR Avanti, Optovue, Inc., Fremont, CA, USA). Only 10 patients underwent FA and ICGA.

The choroidal metastasis was evaluated for clinical features including the quadrant location of the tumour epicentre, colour (pigmented, nonpigmented, or mixed), presence of orange pigment, overlying retinal pigment epithelium (RPE) alterations (none, atrophy, or hypertrophy), the presence of subretinal fluid, and lipofuscin pigment and drusen. Multicolour imaging, ultrasonography, and EDI-OCT documented these findings. The features recorded on A-scan and B-scan ultrasonography included the thickness (in millimetres), configuration (plateau, dome, or mushroom), echogenicity (solid or hollow), choroidal excavation (absent or present), and subretinal fluid (absent or present).

SD EDI-OCT was performed to detect the features of choroidal metastasis including the thinning of the choriocapillaris (absent or present), the contour of the anterior surface of the tumour (smooth or lumpy bumpy), the internal quality of the tumour, maximal tumour thickness (micrometres), and posterior choroidal shadowing (absent or present). Moreover, the intratumoral vascularization was evaluated by ICGA and OCTA. Patients were excluded if they had choroidal metastasis measuring more than 5 mm thickness by ultrasound, with the posterior margin of the lesions not visible on EDI-OCT. Further exclusion criteria included significant lens opacities and low-quality OCT and OCTA images.

Optical Coherence Tomography Angiography

OCTA images were obtained with the Optovue AngiVue System (software ReVue XR version 2017.1.0.151; Optovue Inc., Fremont, CA, USA), which is based on the split-spectrum amplitude decorrelation algorithm [18]. The images were captured with the standard angioretina protocol with a resolution of 6×6 mm centred on the lesion. We manually segmented the choriocapillaris from 30 μ m below Bruch’s membrane to 30–60 μ m below the RPE [15]. The images with a signal strength index less than 40, residual motion artefacts, and incorrect segmentations were excluded from the analysis.

Results

During the enrolment period, 18 eyes of 18 patients with choroidal metastases that presented optimal quality of EDI-OCT and OCTA images were examined.

Table 1. Demographic, clinical, and ultrasonographic features of 16 eyes with choroidal metastasis

	N (%)
Eyes, <i>n</i>	16
Age mean (range), years	58 (37–78)
Gender	
Male	5 (31)
Female	11 (69)
Symptoms	
None	1 (6)
Present	15 (94)
Primary site of the carcinoma	
Breast	10 (63)
Lung	4 (25)
Pancreas	1 (6)
Thyroid	1 (6)
BCVA (Snellen)	
$\geq 20/40$	6 (38)
$< 20/40$ – $20/100$	5 (31)
$< 20/100$	5 (31)
Choroidal metastasis location	
Macular	9 (57)
Extramacular	7 (43)
The mean thickness by echography (median, range), mm	2.8 (2.85, 1.0–3.6)
Multicolour imaging	
Yellow (Melanotic)	2 (12)
Green (Amelanotic)	14 (88)
Mixed	0
Subretinal fluid	
Present	11 (69)
Absent	5 (31)
RPE changes	
None	9 (57)
Atrophy	4 (25)
Hyperplasia	3 (18)
Orange pigment	
Present	1 (6)
Absent	15 (94)
Drusen	
Present	0
Absent	16 (100)
Echography configuration	
Plateau	3 (18)
Dome	13 (82)
Mushroom	
Echography hollowness	6 (38)

BCVA, best-corrected visual acuity; RPE, retinal pigment epithelium.

Two eyes were excluded because of low-quality of EDI-OCT and OCTA images due to the peripheral localization of the tumour (at or anterior to the equator), thick tumours (> 5 mm thickness in ultrasound examina-

Table 2. EDI-OCT and OCTA features of 16 eyes with choroidal metastasis

	N (%)
Tumour thickness, mean (median, range) μm	11 (69)
Configuration	
Dome	4 (25)
Plateau	12 (75)
Anterior tumour surface	
Lumpy bumpy	11 (69)
Smooth	5 (31)
Optical shadowing	
Present	15 (94)
Absent	1 (6)
Optical reflectivity	
Low	12 (75)
High	4 (25)
Associated features	
Choriocapillaris thinning	16 (100)
Shaggy photoreceptors	13 (82)
Subretinal fluid with speckles	11 (69)
Subretinal lipofuscin deposition (orange pigment)	1 (6)
Associated retinal features	
Bruch membrane intact	16 (100)
RPE atrophy	4 (25)
RPE hyperplasia	3 (18)
Drusen absent	16 (100)
Ellipsoid portion of photoreceptors alterations	9 (57)
External limiting membrane alterations	7 (43)
Outer nuclear layer alterations	3 (18)
Outer plexiform layer alterations	3 (18)
Inner retinal layers alterations	2 (12)
OCTA findings	
Absence of intratumoral vascular network	16 (100)

RPE, retinal pigment epithelium; EDI-OCT, enhanced depth imaging optical coherence tomography; OCTA, OCT angiography.

tion), significant lens opacities, and lack of patient collaboration.

A total of 16 eyes of 16 patients (11 females and 5 males; mean age 58 ± 11 years) were included in the study. Fifteen eyes (94%) presented ocular symptoms and 1 patient (6%) presented none. The primary site of the carcinoma was located in the breast ($n = 10$, 63%) lung ($n = 4$, 25%), pancreas ($n = 1$, 6%), and thyroid gland ($n = 1$, 6%). Twelve eyes (75%) of patients were usually aware of the presence history of tumour. The location of the choroidal metastasis was represented by the macula in 9 eyes (57%) and the extramacula in 7 eyes (43%). Clinical features included the subretinal fluid in 11 eyes (69%), RPE atrophy in 4 eyes (25%), RPE hyperplasia in 3 eyes (18%), orange pigment in 1 eye (6%), and absence of drusen in all cases.

The mean thickness of choroidal metastasis measured by echography was 2.8 mm (range, 1.0–3.6 mm). At multicolour images, the choroidal metastasis appeared green (amelanotic) in 14 eyes (88%) and yellow (melanotic) in 2 eyes (12%) (Table 1).

The features of the choroidal metastasis recorded by EDI-OCT and OCTA are displayed in Table 2. The choroidal metastasis, measured by EDI-OCT, presented an average thickness of $950 \pm 246 \mu\text{m}$ (median, 851 μm ; range, 560–1,522 μm).

The EDI-OCT characteristics of choroidal metastasis were represented by the tumour configuration that was dome in 5 eyes (31%) and plateau in 11 eyes (69%). The lumpy bumpy ($n = 11$, 69%) and the smooth ($n = 5$, 31%) represented anterior tumour surface appearance (Fig. 1, 2). Optical shadowing was present in 15 eyes (94%).

Other EDI-OCT features were choriocapillaris thinning (100%), shaggy photoreceptors (82%), and subretinal fluid with speckles (69%) (Fig. 3). In all cases, there were no modifications in the inner retinal layers. OCTA displayed an absence of intratumoral vascular network in all 16 eyes.

Discussion

To our knowledge, this is the first prospective study to evaluate multimodal imaging in choroidal metastasis. The ultrasound represented the gold standard in the diagnosis of these lesions that appear as flat or slightly dome-shaped masses, with a medium-high inhomogeneous reflectivity, unlike the choroidal melanomas that are more frequently dome-shaped, with a homogeneous medium-low reflectivity. At ultrasound A-scan in choroidal metastases, the echoes had a moderate amplitude when compared to the echoes of melanomas that have a high-initial amplitude and a low-internal amplitude [19].

The use of the ultrasound presents several limitations, including the low likelihood of detecting very small lesions. Usually, tumours that cause a retinal lift greater than 1 mm can be demonstrated on ultrasound. When the tumour is visible and the ultrasound can be performed under optimal conditions, lesions that cause a lift of 0.5 mm can be detected. Moreover, smaller tumours can escape detection by ultrasound. However, the acoustic profile does not make it possible to differentiate the cytological characteristics of the lesions completely. The acoustic profile can be masked by structures that precede the tumour or by an incorrect alignment of the probe to the vitreous-tumour interface [20].

Fig. 1. The left eye of a patient (female, 67 years) affected by choroidal metastasis. **a** Multicolour imaging shows a yellow lesion, superotemporal to the fovea. **b** Fundus autofluorescence reveals an area of hyper/hypoautofluorescence. **c** EDI-OCT shows the typical “lumpy bumpy” anterior tumour surface. **d** OCTA of choroidal metastasis does not show any vascular network inside the lesion. EDI-OCT, enhanced depth imaging optical coherence tomography; OCTA, OCT angiography.

Color version available online

Fig. 2. The right eye of a patient (female, 65 years) affected by choroidal metastasis. **a** Multicolour imaging shows a green lesion, temporal to the fovea. **b** Fundus autofluorescence reveals an area of hyper/hypoautofluorescence. **c** EDI-OCT, the choroidal metastasis shows a smooth anterior tumour surface. **d** OCTA of choroidal metastasis does not show any vascular network inside the lesion. EDI-OCT, enhanced depth imaging optical coherence tomography; OCTA, OCT angiography.

Color version available online

Typically, the choroidal metastases appear flat or plateau shaped, often associated with serous retinal detachment [7]. Very rarely, metastases may rupture the Bruch membrane and develop a mushroom shape [21].

The introduction of the multimodal imaging was useful in providing appropriate diagnosis and the management of the choroidal metastasis. The role of these techniques has become crucial to identify the anatomical and vascular features of these choroidal lesions and to establish their aetiology. The potential utility of multimodal

imaging is not limited to diagnosis because it can also be beneficial in predicting the clinical course of these lesions.

At multicolour imaging, the choroidal metastases generally appear green because they are not pigmented while infrequently they can be pigmented and appear yellow [11]. The use of the EDI-OCT, a technique of the SD-OCT introduced by Spaide and collaborators, allowed us to increase the resolution of the deeper layers of the choroid and the sclera and to identify better the morphological features of the choroidal metastasis [22].

Fig. 3. The left eye of a patient (male, 60 years) affected by choroidal metastasis. **a** Multicolour imaging shows a green lesion, superonasal to the optic disk. **b** Fundus autofluorescence reveals an area of hyper/hypoautofluorescence. **c, d.** On FA and ICGA, the lesion appears hypofluorescent and hypocyanescent. **e** On EDI-OCT, the choroidal metastasis presents a low-internal reflectivity with the subretinal fluid and hyperreflective dots inside, known as “speckles”. **f** OCTA of choroidal metastasis does not show any vascular network inside the lesion. EDI-OCT, enhanced depth imaging optical coherence tomography; OCTA, OCT angiography; FA, fluorescein angiography; ICGA, indocyanine green angiography.

The main features of these lesions at the EDI-OCT are represented by the irregularity of the anterior surface of the tumour (lumpy bumpy), in contrast to the smooth appearance that appears on the ultrasound; the elongation and swelling of photoreceptors (shaggy photoreceptors); the subretinal fluid often with hyperreflective dots inside, known as “speckles,” which may derive from the outer segment of photoreceptors [11, 13]. The subretinal fluid density can be measured at OCT and appears significantly lower in choroidal metastases than in melanomas.

Other signs, detected by EDI-OCT, are the low-internal tumour reflectivity with enlargement of the suprachoroidal space (internal reflectivity may increase after treatment, due to an increase in the fibrotic component), the thinning of the choriocapillaris above the tumour and the partial masking of the choroid by the tumour, the modifications of the EPR (atrophy or hyperplasia), the loss of external limiting membrane and the external segment-internal segment, and the irregularity of the internal plexiform layer [7, 11, 13]. Compared to ultrasound, EDI-OCT was more sensitive in the evaluation of small tumours both at the time of presentation and after treatment [11, 23].

Regarding the conventional imaging technique, the FA is not decisive for the diagnosis of choroidal metastases, because most choroidal tumours have the same angiographic features. Generally, hypofluorescence is observed in the early stages and a non-homogeneous hyperfluorescence in the late phases, while sometimes small hyperfluorescent points and areas of late leakage on the mass are observed [24]. Unlike FA, the ICGA is useful in the differential diagnosis of choroidal metastases, which usually appear hypofluorescent at all stages [25].

The “double circulation” pattern, described for the first time by Augsburger in choroidal melanomas, is rarely present in choroidal metastases. Tumour vessels are distinguishable from normal choroidal vessels by their random course [26].

ICGA is also useful because it shows an area of choroidal involvement by the broader metastasis than can be observed at the clinical examination or the FA [7]. The introduction of OCTA can help in the differential diagnosis, in a non-invasive way, of the various types of choroidal lesions. OCTA shows a lack of flow at the level of the choroidal metastases and absence of pathological blood flow at the level of the external retinal layers, while in melanomas, haemangioma, and choroid osteomas,

there can be a dense and irregular vascular network within the tumour and a possible increase in flow in the external nuclear layer [15, 16].

In conclusion, the use of multimodal imaging, together with OCTA, contributed to greater insights into the anatomical and vascular features of the choroidal metastasis to distinguish them from other choroidal lesions. The combination of these techniques allowed us to collect useful information that shed light on the different pathogenesis of choroidal tumours and to predict the clinical course of these lesions over time.

Statement of Ethics

This study was approved by the Institutional Review Board of the University of Naples "Federico II" and all investigations adhered to the tenets of the Declaration of Helsinki. Written informed consents were obtained from the patients enrolled in this study.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Gilda Cennamo, Mario R. Romano, and Giovanni Cennamo designed and directed this study. Gilda Cennamo, Daniela Montorio, and Marianna Carosielli collected and analysed the data, edited the manuscript. All authors discussed the results and commented on the manuscript.