Imaging the Microvasculature of Choroidal Melanomas With Confocal Indocyanine Green Scanning Laser Ophthalmoscopy

Arthur J. Mueller MD, PhD; Dirk-Uwe Bartsch, PhD; Robert Folberg, MD; Mary G. Mehaffey, MD; H. Culver Boldt, MD; Margaret Meyer; Lynn M. Gardner; Michael H. Goldbaum, MD; Jacob Pe’er, MD; William R. Freeman, MD

Objective: To image the microvasculature of choroidal melanoma with a new confocal scanning laser ophthalmoscope.

Methods: Eighteen consecutive patients, each with a unilateral choroidal melanoma, were examined prospectively. Indocyanine green angiography was performed with a new confocal scanning laser ophthalmoscope that enabled serial optical sectioning through the tumor. Two additional patients were studied with indocyanine green angiography and confocal scanning laser ophthalmoscopy just before enucleation for posterior choroidal melanomas. The histologic identification of microvasculature patterns was compared with the angiograms for these patients.

Results: In the series of 18 patients, 16 (89%) indocyanine green angiograms with optical sectioning revealed tubular structures within the melanoma that were identified as tumor vessels based on their angiographic appearance. The microvasculature patterns identified by indocyanine green angiography correlated well with the histologic appearance of these microvasculature patterns in both patients for whom histologic verification was available.

Conclusions: This preliminary study suggests that indocyanine green angiography with confocal scanning laser ophthalmoscopy images the microvasculature of choroidal melanomas and may be capable of detecting microvasculature patterns that have been shown to be prognostically significant from histopathological studies.


CHOROIDAL and ciliary body melanomas are among the few forms of cancer that are treated before a pathologist can examine tissue and assign a histologic grade to indicate the likelihood of metastasis. In designing new treatments for these patients, it would be helpful to separate those patients at high risk for metastasis from those at lower risk clinically.1

Nine microvasculature patterns have been described histologically in choroidal and ciliary body melanomas: normal vessels, avascular zones, straight vessels, parallel straight vessels, parallel vessels with cross-linking, arcs, arcs with branching (incomplete loops), microvascular loops that encircle small microdomains of tumor, and microvascular networks, composed of at least 3 back-to-back closed microvascular loops.2 In univariate analysis, one pattern, the presence of an avascular (silent) zone, was associated with a favorable prognosis3 whereas several other patterns, including arcs, arcs with branching, loops, networks, parallel vessels, and parallel vessels with cross-linking were all associated with metastasis.4 Melanomas frequently contain combinations of patterns. In multivariate Cox proportional hazards models, 2 histologic microvasculature patterns were strongly associated with death from metastatic melanoma: networks and parallel vessels with cross-linking.5-7

Ophthalmic pathologists are now being encouraged to report the presence or absence of microvascular networks and parallel vessels with cross-linking as prognostic factors in diagnostic reports describing eyes removed for malignant melanoma.7,8 If it were possible to detect prognostically significant vascular patterns clinically, ophthalmologists might eventually be able to separate patients into histologic risk groups based on these patterns without removing tissue.

It is reasonable to suspect that angiography would be capable of detecting microvasculature patterns in vivo. Unfortunately, fluorescein angiography does not show a pathognomonic fluorescence pattern in choroidal melanomas nor are tu-
PATIENTS AND METHODS

This study was divided into 2 phases: a clinical study of the angiographic appearance of the microcirculation with confocal scanning laser ophthalmoscopy and indocyanine green angiography, and an angiographic-histologic correlation in 2 patients.

ANGIOGRAPHY

In the first phase, all patients with clear media and with prominent choroidal masses of the posterior pole suspected to be choroidal melanomas who were seen at the University of California, San Diego, Shiley Eye Center between January 1994 and April 1996 were examined prospectively. Diagnosis of choroidal melanoma was established by indirect ophthalmoscopy based on the characteristic appearance of this tumor and confirmed using standardized A- and B-scan ultrasound. Only tumors with a maximum apical height of at least 1.5 mm and low or medium internal reflectivity according to standardized A-scan ultrasound were enrolled. Thereafter, indocyanine green angiography was performed using a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph [HRA], Heidelberg Engineering, Heidelberg, Germany). The instrument has been described in detail previously.20

The optics of this instrument allowed for spherical aberration compensation between −12 and +12 diopters (D). By automatically adjusting the focal plane in steps of 1 D, confocal serial optical sectioning could be obtained. This facilitates visualization of deep tumor vessels. In addition, the tumor height could be measured with this technique by calculating the difference between the confocal plane, in which the apex of the tumor is in focus and the confocal plane, in which the adjacent attached retina is in focus (Figure 1). This method is only valid when performed in areas where the adjacent retina is attached, and, in patients, where the tumor is situated at the posterior pole. Using axial refractive error eye model assumptions for the HRA, the measurement can be converted easily from diopeters to millimeters (3 D = 1 mm for emmetropic eyes with an axial correction factor of 2.25% per diopter spherical equivalent for nonemmetropic eyes). For example, if a tumor vessel appears most clearly in a “+6-D confocal plane” in an emmetropic eye, the tumor vessel is located 2 mm anterior to the “0-D starting point” of this series. In a patient with a refraction of +10-D spherical equivalent, the same tumor vessel would be calculated to be 2.45 mm anterior to the “0-D starting point” of this series.

The confocal indocyanine green angiography sequences were reviewed for the presence of complete serial optical sectioning. Complete serial optical sectioning was defined as including both an optical sectioning at the level of adjacent attached retina and at the level of the tumor apex; such sectioning was performed in 11 patients. Subsequently, maximum tumor height according to serial optical sectioning was corrected for the refraction of the patient, assuming that the refractive error is entirely caused by axial length differences of the eye. The resulting corrected tumor height was compared with ultrasound measurements obtained at corresponding dates.

One pixel is equivalent to approximately 33 μm in a 30° angiogram in emmetropic eyes and the lateral correction factor for nonemmetropic eyes is 1.5% per diopter of spherical equivalent. We also validated the pixel counting method in each series by measuring a peripapillary vein, the diameter of which is usually taken to be 125 μm.22,23

ANGIOGRAPHIC-HISTOLOGIC CORRELATIONS

Two patients with posterior choroidal melanomas seen at the University of Iowa Hospitals and Clinics, Iowa City, who did not qualify for the Collaborative Ocular Melanoma Study were studied by indocyanine green angiography 2 weeks prior to a scheduled enucleation. Each enucleated eye was fixed in 10% neutral-buffered formalin for at least 48 hours and opened using the alternative gross pathology protocol in which the anterior segment was separated from the posterior pole by a coronal section through the pars plana. This technique permits the pathologist to visualize the surface of the tumor in the same plane as fundus photograph or angiographer and permits precise clinicopathologic correlations and tumor measurements.25

Each tumor was bisected along the axis of maximum scleral contact and the plane of sectioning was noted on gross photographs. The gross photographs were compared with the indocyanine green angiograms to permit a precise clinicopathologic correlation of angiographic-histologic findings. One half of the tumor block was processed for routine light microscopy in the usual section plane (perpendicular to the surface of the tumor) for purposes of confirming the diagnosis. The other half of the tumor section was embedded and sectioned parallel to the tumor apex (parallel to the sclera) to generate a histologic section plane oriented in the same fashion as the optical cuts through the tumor acquired with HRA. Tumor sections were stained with the modified periodic acid–Schiff stain without hematoxylin counterstaining. This stain correlates well with stains more specific for the endothelium and microcirculation.26-27 Histologic sections were digitized and converted to gray-scale images after selecting the green channel to highlight the magenta-stained microcirculation. The resulting image was converted digitally into a “negative,” a procedure that makes the microcirculation appear white against a dark tumor background for easy histologic-angiographic correlations.28

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cause the near-infrared light used for indocyanine green angiography penetrates the pigmented layers of the fundus more easily than the short wavelength light used in fluorescein angiography, indocyanine green angiography has been primarily used to study leakage of dye in choroidal neovascularization during the late phase and thereby to detect changes in the vascular permeability of these vessels. Some of these early studies also have indicated a possible role for indocyanine green angiography in investigating choroidal masses, but this was not further investigated. Recently, we adapted the confocal scanning laser technology to perform indocyanine green angiography. This technique uses sensitive digital image acquisition and processing. The horizontal image resolution has considerably improved to below 20 µm. The reported histologic microvasculature pat-

![Figure 1. Illustration of an optical sectioning series in a tumor of 3 mm height in an emmetropic eye. In this series, the scanning laser beam would be rapidly and consecutively focused in 1 diopter (D) steps from 0 D (tumor basis) to 9 D (tumor apex). Representative steps in this drawing include focusing on the plane of adjacent retina (top, 0 D), on a tumor vessel (middle, 4 D), and on the tumor apex (bottom, 9 D).](image1)

![Figure 2. Correlation of tumor height measurements according to standardized ultrasound (US) and serial optical sectioning using indocyanine green angiography (ICG).](image2)

**Clinical Features of Patients**

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<th>Patient No./ Sex/Age, y</th>
<th>Eye</th>
<th>Best-Corrected Spherical Equivalent, D</th>
<th>Best-Corrected VA</th>
<th>US, mm</th>
<th>Vessel Type†</th>
<th>ICG Height,‡ D/Corr mm</th>
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*VA indicates visual acuity; US, maximal apical height according to standardized A-scan; HM, hand motion; ICG, indocyanine green angiography; and NP, tomography not performed.†Lg, elong indicates large elongated vessels approximately 132 µm in diameter; sm, dense conv, small densely convoluted vessels between 66 and 99 µm in diameter; sm, parallel, small-diameter parallel vessels approximately 32 µm or smaller in diameter; and none, silent, avascular.‡Tumor height according to the measurements in serial optical sectioning. The values are given in diopters (D) and in corrected millimeters according to the refraction of the patients (2.25% per diopter of spherical equivalent) and rounded to the nearest 1⁄100.
terns of prognostic significance fall in this range and should therefore be detectable.3

This study was designed to evaluate the ability of indocyanine green angiography performed with a new confocal scanning laser ophthalmoscope to image microcirculatory patterns in choroidal melanomas.

RESULTS

The clinical features of the 18 patients examined prospectively by HRA are summarized in the Table. One patient (patient 7, Table) had an amelanotic melanoma. The other tumors were pigmented. In 9 patients, the mass was located partially or completely within the major temporal vascular arcades. In the other 9 patients, the tumor mass was localized entirely outside the arcades. Maximum apical height ranged from 1.5 to 12 mm with a mean (±SD) height of 4.2 (±2.7) mm according to standardized A-scan ultrasound. All patients were untreated at the time the indocyanine green angiography was obtained.

In 16 (89%) of these 18 patients, visualization of deep tumor vessels was possible by using confocal indocyanine green angiography. The tumor vessels could be identified clearly within the first 30 seconds after injection of dye and fluorescence lasted at least 5 minutes. Thereafter, slow decrease of fluorescence was noted until 10 minutes after injection of dye. Fifteen minutes after injection of dye, no fluorescence within the tumor vessels could be detected and we did not observe late staining in the tumor region in any of our cases. In 2 patients, no tumor vessels could be detected in any confocal plane.

In 11 patients, complete serial optical sections during confocal indocyanine green angiography could be used for tumor height measurements. Maximum tumor heights according to these series were calculated between 5 D and 18 D (Table). In 7 patients, no serial optical sections could

Figure 3. Patient 4. Choroidal melanoma located in the upper temporal quadrant of the left eye. Maximum height is measured with 4.9 mm according to standardized ultrasound. A, Fundus photograph focused at apex of tumor. Note the localization of retinal vessel bifurcation. B, Fluorescein angiography photograph 39 seconds after injection of dye. No details within the tumor can be seen. C, Optical section using confocal indocyanine green angiography 4 minutes, 33 seconds after dye injection. Confocal plane is taken at about half of maximum tumor prominence (+7 diopeters [D] from retinal plane and −8 D from tumor apex). Note localization of retinal vessel bifurcation and compare with photographs A and B. Large elongated vessels, clearly filled with indocyanine green dye, are present within the border of the tumor. D, Confocal section using indocyanine green angiography (16 minutes, 54 seconds after injection of dye). Confocal plane is at same height as in photograph C (+7 D from retinal plane and −8 D from tumor apex). Tumor vessels can no longer be seen. No late staining occurs within the tumor.

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be performed due to subretinal fluid of the adjacent retina. In the 11 tumors with complete serial optical sectioning, the end points of the series included the focal plane at the apex of the tumor as well as the focal plane at the adjacent attached retina. In these patients, the tumor height according to the optical sectioning was corrected according to the spherical equivalent of the patient’s refraction (Table). All measurements were within 0.25 mm compared with the measurements obtained by standardized ultrasound. For these 11 complete measurements, the correlation coefficient is 0.99 ($P < .001$) and the mean square root error is 0.11 (Figure 2).

Form, diameter, and localization of the tumor vessels were highly characteristic. In 7 patients, we detected large (132 µm in diameter) elongated vessels with collaterals to other vessels within the tumor (Figure 3). These vessels tended to be present in the center of the tumor and about half the tumor height. In 6 patients, we detected dense convolutions of smaller vessels varying between 66 and 99 µm in diameter (Figure 4) that were located near the tumor surface and at the tumor edges. In 3 patients, we detected tumor vessels measuring 33 µm in diameter or smaller that were elongated and oriented parallel to each other (Figure 5); these vessels could be imaged throughout the whole tumor mass. The tumors of 2 patients contained no vessels (Figure 6); they were angiographically silent. The 2 patients who had angiographic studies before enucleation are described in the following case reports.

**REPORT OF CASES**

**CASE 1**

An 85-year-old woman was seen for a flat, posterior choroidal lesion that she had in her left eye for 16 years. The lesion became elevated over a 3-year period and her visual acuity decreased to 20/200. The patient was excluded from the Collaborative Ocular Melanoma Study because of the presence of an optic nerve pit in the right eye that reduced visual acuity to 20/200. The patient elected to have an enucleation. Two weeks before enucleation, the patient was examined by indocyanine green angiography. The angiogram revealed large diameter vessels (132 µm in diameter) within the tumor on multiple section planes (Figure 7, A). Convoluted vessels and parallel vessels were not identified angiographically. The angiogram revealed large diameter vessels (132 µm in diameter) within the tumor on multiple section planes (Figure 7, A). Convoluted vessels and parallel vessels were not identified angiographically. The tumor was bisected vertically, with the temporal half processed for routine histopathology (sections taken perpendicular to the tumor apex) and the nasal half sectioned parallel to the apex and sclera for correlation with the angiogram (Figure 7, B). The tumor was composed
of spindle B melanoma cells without evidence of extraocular extension. The histopathologic sections confirmed the presence of large, dilated normal vessels without evidence of parallel vessels with cross-linking, loops, or networks, both in the conventional section plane, and in the plane parallel to the tumor apex, equivalent to the plane of the angiogram (Figure 8). We concluded that the large caliber vessels seen angiographically corresponded to the dilated normal vessels detected histologically on a section plane matched with the angiogram.

CASE 2

A 79-year-old woman with an elevated posterior choroidal mass was referred to University of Iowa Hospitals and Clinics after experiencing a superior visual field defect and decreased visual acuity in the right eye. The patient elected to have an enucleation; she was not eligible for the Collaborative Ocular Melanoma Study because of the large tumor size. Three days before enucleation, the patient was examined by indocyanine green angiography.

The angiogram revealed numerous angiographic thin convoluted vessels that formed vascular arcs, arcs with branching, and closed vascular loops (Figure 9, A). The tumor was bisected vertically, with the nasal half processed for routine histopathology (sections taken perpendicular to the tumor apex) and the temporal half sectioned parallel to the apex and sclera for correlation with the angiogram (Figure 9, B). The tumor was composed of spindle B melanoma cells with evidence of infiltration into the sclera around a vortex vein but without extracocular extension. The histopathologic sections confirmed the presence of thin vascular arcs, arcs with branching, and loops but without the formation of networks (defined as at least 3 back-to-back vascular loops; Figure 10).

Indocyanine green angiography permits visualization of choroidal vasculature as a result of good penetration of absorption and emission light in the near-infrared range.

Figure 5. Patient 16. Choroidal melanoma located temporally to the macula of the left eye. Maximum prominence is measured with 3.7 mm according to standardized ultrasound. A, Fundus photograph of the melanoma. B, Optical section using confocal indocyanine green angiography 31 seconds after dye injection. Confocal plane is taken at half of maximum tumor prominence (+5 diopters from the retinal plane). Small-diameter parallel vessels are seen within the tumor borders.

Figure 6. Patient 6. Choroidal melanoma located inferior to the optic nerve head of the right eye. Maximum prominence is measured with 2.0 mm according to standardized ultrasound. A, Fundus photograph of the melanoma. B, Optical section using confocal indocyanine green angiography 1 minute, 34 seconds after dye injection. Confocal plane is taken at half of maximum tumor prominence (+3 diopters from the retinal plane). No vessels are seen within the tumor borders.
through the melanin of retinal pigment epithelium.\textsuperscript{28-30} It has been previously suggested that indocyanine green angiography therefore may have a role in the diagnosis of intraocular tumors, but this was not further investigated at that time.\textsuperscript{14-16} Another more recently published study also investigated the value of indocyanine green angiography in diagnosing and differentiating various choroidal tumors including choroidal melanomas.\textsuperscript{29} The authors used a conventional nonscanning and nonconfocal technique. They investigated quantitatively fluorescence intensity changes over time but did not study the visibility of tumor vessels.

Because the confocal scanning laser ophthalmoscope we have used allows for confocal serial optical sectioning, the tumor height can be measured with this method by calculating the difference between the lens power, with which the highest and the lowest plane of a prominent mass is in focus.\textsuperscript{30} In our pilot study, comparison with ultrasonographic measurements in the 11 patients with complete series revealed that this method is accurate. Thus, we assumed that the same accuracy applies for the localization of microvasculature patterns in the tumor mass.

We noted that the diameter of some tumor vessels measured from the indocyanine green angiogram is larger than the diameter of vessels in the histologic microvascular networks or parallel with cross-linking vessels.\textsuperscript{3} Electron microscopy studies of these vessels showed severe alterations of the basement membrane as well as gaps in the interendothelial junctions.\textsuperscript{3} This could facilitate staining of vessel walls, which would give the vessel a wider appearance in the angiogram than is present histologically. However, if staining of the vessel wall occurred, this would most probably happen significantly later than the appearance of fluorescence inside the blood vessel. In addition, one would also expect late fluorescence of the vessel walls, but we did not observe a change in the diameter of the vessels over time, nor did we observe late staining in any of our patients. In contrast, it is conceivable that the histologic measurements do not reflect the diameter of these vessels in vivo. Collapsing of vessels due to lack of perfusion pressure as well as a “shrinkage” due to fixation and/or preparation steps may alter the lumen of the vessel as imaged with indocyanine green angiography.
In the present study, the serial confocal optical sectioning permitted us to detect tumor vessels. Various optical sections through each tumor of 16 patients revealed tubular structures filling with indocyanine green during the early and middle phases. These structures were located within the melanoma borders when compared with fluorescein angiograms and fundus photographs, respectively. The circulation was separate from the retinal circulation and in none of the cases could indocyanine green fluorescence be detected during the late phase in any confocal plane. This indicates that these vessels were not leaking moderate size molecules. For all these reasons, these structures were identified as tumor vessels.

The results of this study suggest that indocyanine green angiography and confocal scanning laser microscopy may detect at least some of the microcirculatory patterns described in histologic sections of choroidal and ciliary body melanomas. For example, the large vessels (132 µm in diameter) detected in the tumor described in the first of the 2 case reports corresponded histologically to the normal vascular pattern by means of detailed histologic-angiographic correlations (Figure 3, C, and Figure 7). Additionally, vessels that were convoluted angiographically forming arcs, arcs with branching, and closed vascular loops (Figure 4, C and D) were detected in the tumor of the patient described in the second case report: a careful angiographic-histologic correlation confirmed the identity of the angiographic patterns in tissue sections from corresponding planes (Figures 9 and 10). Moreover, the convoluted vessels detected angiographically tended to appear at the periphery and beneath the surface of the tumors, a finding that is significant because microvascular networks in histologic sections of choroidal and ciliary body melanomas tend to form in the same locations. Finally, some tumors did not contain vessels angiographically. Although none of these tumors was available for histologic study, it is possible that these angiographic silent tumors correspond to histologic avascular zones.

Our results therefore suggest that further angiographic-histologic correlations are warranted to deter-
mine if indocyanine green angiography with confocal scanning laser ophthalmoscopy can be used to detect clinically those histologic tumor vascular profiles that have been associated with more or less favorable prognosis from histologic tissue sections. Indocyanine green angiography with confocal scanning laser ophthalmoscopy may eventually provide a technique by which ophthalmologists can extract information from the noninvasive study of a patient’s tumor. In the absence of available tissue for pathologic examination, this technique might substitute for the description of prognostically significant microcirculatory patterns.

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Reprints: William R. Freeman, MD, University of California, San Diego, Department of Ophthalmology, Shiley Eye Center, 9415 Campus Point Dr, La Jolla, CA 92039-0946.

REFERENCES


Announcement

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