Size Overlap between Benign Melanocytic Choroidal Nevi and Choroidal Malignant Melanomas

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Purpose. To estimate size overlap between large choroidal nevi and small choroidal melanomas by using plotted frequency distributions of tumor size.

Methods. Frequency distributions of largest linear basal diameter (LBD) and thickness (TH) of choroidal nevi and melanomas were plotted from published data and cases in the senior author’s practice. Relative frequencies of choroidal nevi and melanomas were estimated from published data. Relative frequency distributions of the tumors were plotted to illustrate the extent of overlap between them.

Results. Comparison of plotted frequency distribution curves for thickness indicated that there were approximately 125 nevi for every melanoma in the TH range 1.5 to 2 mm, approximately 25 nevi for every melanoma in the TH range 2 to 2.5 mm, and approximately 5 nevi for every melanoma in the TH range 2.5 to 3 mm. Similarly, comparison of the plotted frequency distribution curves for LBD of these tumor types indicated that there were approximately 70 nevi for every choroidal melanoma in the LBD range 5 to 6 mm, approximately 10 nevi for every melanoma in the LBD range 6 to 7 mm, and approximately 3 nevi for every melanoma in the LBD range 7 to 8 mm.

Conclusions. Because of the markedly greater cumulative lifetime incidence of choroidal nevi, the results of this analysis suggest considerable size overlap between larger nevi and smaller melanomas. Attempts to classify small melanocytic choroidal tumors clinically as benign nevi versus malignant melanomas on the basis of tumor size appear likely to result in multiple misclassifications.

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Accurate clinical classification of small melanocytic choroidal tumors as benign nevi or malignant melanomas is a great challenge for ophthalmologists.1,2 If one is sure that a melanocytic choroidal tumor is a benign nevus, one is likely to recommend only periodic monitoring of that lesion to watch for enlargement or other danger signs of possible malignancy. In contrast, if one is certain that a melanocytic choroidal tumor is a malignant melanoma, one is likely to advise prompt aggressive treatment of that lesion.

Several factors are generally considered in the clinical differential diagnosis of benign melanocytic choroidal nevi versus choroidal melanoma.3-5 These include shape, color, and size (both thickness and basal diameter) of the tumor; the presence or absence of (1) surface clumps of orange pigment (lipofuscin), (2) surface drusen, (3) associated serous subretinal fluid overlying and surrounding the tumor, and (4) invasive clinical features (focal eruption through Bruch’s membrane, retinal invasion, optic disc invasion, scleral invasion, transscleral extension); and enlargement of the lesion if it is monitored without treatment after initial documentation. In our opinion, tumor size (especially lesion thickness) is the most important feature in this clinical exercise. Most choroidal melanomas that have ultimately been associated with metastatic disease have been >7 mm in basal diameter and >2 mm in thickness at the time of diagnosis and initial treatment.6-9 Although some melanocytic choroidal lesions less than 2 mm thick are diagnosed clinically as possible or probable choroidal melanomas, most such lesions are likely to be classified (at least initially) as suspect choroidal nevi or indeterminate melanocytic choroidal tumors and are observed rather than treated promptly.5,9 Ophthalmologists generally consider both tumor thickness and the presence or absence of several associated clinical prognostic factors for subsequent tumor growth (e.g., clumps of orange pigment [lipofuscin] on the surface of the lesion and serous subretinal fluid overlying and possibly surrounding the lesion) when deciding how soon to reevaluate such lesions after initial documentation.1,5,8-10 If the lesion enlarges convincingly during follow-up, most ophthalmologists reclassify the tumor as a probable choroidal melanoma and recommend and perform some form of focal obliterative therapy (e.g., transpupillary thermotherapy and plaque radiotherapy) shortly thereafter. Most small melanocytic choroidal tumors in this nevus-versus-melanoma category are ultimately classified as melanoma and treated, but are not managed by enucleation of the affected eye. Consequently, the clinical diagnosis is not confirmed by histopathologic study in most of these individuals. In contrast, most melanocytic choroidal tumors >2 mm thick are likely to be classified as probable or definite choroidal melanomas in most centers, regardless of their associated clinical features. Ones that are associated with prognostic factors for lesion enlargement are likely to be treated promptly, but ones not associated with such features, but exhibiting prognostic factors for lesion dormancy if followed up, are frequently subclassified as dormant melanomas and are monitored periodically for progression. As long as these lesions do not enlarge significantly during follow-up, they continue to be regarded as low-grade or inactive melanomas in most centers. Such lesions are also rarely managed by enucleation, and so histopathologic verification of the clinical diagnosis is also not available for most such tumors.

In contrast, the largest basal diameter of a melanocytic choroidal tumor in the absence of clinically significant thickness is not generally regarded as an important factor in differential diagnosis of nevi and melanomas. A melanocytic choroidal lesion that is completely flat (i.e., not measurably thicker than normal choroid by B-scan ultrasonography) is unlikely to be classified as a choroidal melanoma, even if its diameter is 10...
mm or more. Flat but broad-based melanocytic choroidal lesions are probably more appropriately classified as patches of choroidal melanocytosis and not as either choroidal nevi or choroidal melanomas.10

The purpose of this work was to estimate the size overlap between large choroidal nevi and small choroidal melanomas by using a graphic comparison technique with frequency distribution curves that take into account the relative frequencies of the two lesions in the general population.

**Patients and Methods**

Frequency distribution tables and corresponding frequency distribution curves of tumor thickness and largest linear basal diameter for melanocytic choroidal nevi and choroidal melanomas were generated by using original data from patients with clinically diagnosed melanocytic choroidal nevi and choroidal melanomas in the private referral practice of the senior author (JJA), published information regarding the size distributions of melanocytic choroidal nevi1,8,11,12 and choroidal melanomas,9,9,13 and published data on the frequencies of these two lesions in the Caucasian population.1,2,11,14–17

Because this is a retrospective observational study, the Declaration of Helsinki does not apply. The data collection used in this study was approved by the Institutional Review Board of the University of Cincinnati. Furthermore, the appropriate measures were taken to prevent patient identification.

In plotting the curves for choroidal nevi, we accepted the concept (as stated by Gass9) that at least 95% of melanocytic choroidal nevi are ≤5 mm in largest basal diameter and ≤1 mm in maximum thickness. The largest allowed dimensions for largest basal diameter and thickness on the plotted nevus frequency distribution curves were 10 and 3.5 mm, respectively (even though published case reports indicate that such tumors occasionally achieve larger dimensions than these).10,23 For the purposes of this analysis, the frequency distribution curves for largest basal diameter and thickness of both choroidal nevi and choroidal melanomas were assumed to have a normal (Gaussian) shape.

The first step in our comparative graphic analysis consisted of plotting relative (as opposed to raw) frequency distribution curves (i.e., curves that were plotted using data points determined by dividing each tabulated value in the respective frequency distribution table by the mode [maximum value] of the particular dimension and tumor type) for thickness and largest linear basal diameter for choroidal nevi and choroidal melanomas. When plotted, these curves all had a relative frequency scale on the y-axis (ordinate) that extended from 0 to 1. Because these curves reveal the central tendency and relative spread of the data points (but do not reflect the relative frequencies of the two lesions accurately), we refer to them as shape-location frequency distribution curves.

The second step in our graphic analysis entailed adjustment of the shape—location frequency distribution curves of largest basal diameter and thickness for choroidal nevi to reflect their substantially narrower size range compared with choroidal melanomas. To determine the appropriate adjustment values, we first measured the area under each shape—location frequency distribution curve. They then divided the area under the melanoma curves of thickness and largest basal diameter by the corresponding area under the nevus curves for these dimensions. These calculations yielded an adjustment value of 11× for tumor thickness and 4.4× for largest basal diameter. The plotted values on the shape—location frequency distribution curves for choroidal nevi were multiplied by the calculated adjustment values, and the vertically expanded frequency distribution curves of choroidal nevi were plotted along with the original shape—location frequency distribution curves of choroidal melanomas for tumor thickness and largest basal diameter. When plotted in this way, the area under the respective curves is equal. Because of this equality, we refer to these plotted curves as equivalent area frequency distribution curves. These curves show the relative sizes (as well as the comparative shapes) of the curves if choroidal nevi and choroidal melanomas were equally frequent in the general population.

Of course, we recognize that choroidal nevi and choroidal melanomas are not equally frequent in the general population. Although some investigators have estimated the frequency of choroidal nevi in the adult Caucasian population to be as high as 30% to 33%,2 most have estimated this frequency to be between 1% and ~10%.1,11,14,17 For the purpose of this study, we used the value 6.5% determined by Sumich et al.17 in a prospective clinical study of choroidal nevi in the general adult Caucasian population. In contrast, the cumulative lifetime incidence of choroidal melanoma in the Caucasian population has been estimated to be only ~1 in 2000 persons.15,16 To determine the appropriate adjustment value due to the greater frequency of choroidal nevi in the population, we divided the estimated frequency of choroidal nevi (6.5%, or 130/2000 persons) by the frequency of choroidal melanomas in the general population (1/2000) to obtain a value of 130×. The equivalent area frequency distribution curves for thickness and largest basal diameter of choroidal nevi were multiplied by this adjustment, and the adjusted curves for choroidal nevi were plotted alongside the original shape-location curves for choroidal melanomas for both tumor thickness and largest basal diameter. These curves show the true relative frequency distributions of thickness and largest basal diameter for choroidal nevi and melanomas after adjustment for the substantially greater frequency of nevi in the population. We refer to these curves in this report as cumulative lifetime incidence-adjusted frequency distribution curves.

The last step in our graphic analysis entailed counting the number of tumors under the respective curves of choroidal nevi and melanomas for 0.5-mm-wide intervals of tumor thickness between 1.5 and 3 mm and for 1-mm-wide intervals of largest basal diameter between 5 and 9 mm to facilitate this last step, the adjusted frequency distribution curves were replotted with the maximum y-axis value again set to 1.

**Results**

The plotted shape—location frequency distribution curves for thickness and largest linear basal diameter of choroidal nevi and choroidal melanomas are shown respectively in Figures 1A and 1B. The curves for tumor thickness (Fig. 1A) showed a mean of 6.5 mm and an SD of 1.8 mm for choroidal melanomas and a mean of 0.6 mm and an SD of 0.13 mm for choroidal nevi. The curves for largest basal diameter (Fig. 1B) showed a mean of 12.0 mm and an SD of 3.0 mm for choroidal melanomas and a mean of 3.0 mm and an SD of 0.67 mm for choroidal nevi. There did not appear to be a substantial overlap between the respective curves when they were plotted in this way.

The plotted equivalent area frequency distribution curves for thickness and largest basal diameter for choroidal nevi and melanomas are shown respectively in Figures 2A and 2B. These curves show the correct relationship between the frequency distributions of tumor thickness and largest basal diameter if choroidal nevi and choroidal melanomas were equally frequent in the population. There still seemed to be limited overlap between the respective curves when they were plotted this way.

The plotted cumulative lifetime incidence-adjusted frequency distribution curves for thickness and largest basal diameter of choroidal nevi and choroidal melanomas are shown in Figures 3A and 3B, respectively. Note that the curves for the melanomas were reduced in height to virtual invisibility at the scale required on the y-axis (ordinate) for plotting of the curves for choroidal nevi. Figures 4A and 4B show these same curves (i.e., Figs. 3A, 3B replotted with the maximum value on the y-axis [ordinate] reduced to 1. This replotting showed the frequency distribution curves for choroidal melanoma in their entirety but only the upper and lower tails of the curves for choroidal nevi. When plotted in this way, there appeared to be substantial overlap between the upper tail of the frequency distribution curves for thickness and basal diameter of choroidal nevi and the lower tail of the frequency distribution curves for these dimensions of choroidal melanomas.
The magnitude of the overlap between the upper region of the choroidal nevus curves and the lower region of the choroidal melanoma curves (i.e., between 1.5 and 3 mm for tumor thickness and between 5 and 9 mm for largest basal diameter) revealed by comparison of the respective curves is as follows. There were \( \frac{125}{1} \) nevi for every choroidal melanoma in the thickness range of 1.5 to 2 mm, \( \frac{25}{1} \) nevi for every melanoma in the thickness range of 2 to 2.5 mm, and \( \frac{5}{1} \) choroidal nevi for every melanoma in the thickness range 2.5 to 3 mm. Similarly, there were \( \frac{70}{1} \) choroidal nevi for every choroidal melanoma in the largest basal diameter range 5 to 6 mm, \( \frac{10}{1} \) nevi for every melanoma in the largest basal diameter range 6 to 7 mm, and \( \frac{3}{1} \) nevi for every melanoma in the largest basal diameter range 7 to 8 mm.

**DISCUSSION**

The diagnostic criteria for choroidal nevi used by the several cited investigators and research groups over the years have been quite varied and usually arbitrary. Tamler and Maumenee defined a choroidal nevus as a “small melanocytic choroidal tumor ranging in size from a fraction of a disc diameter to several disc diameters in size [diameter]. It is flat in most instances, but can be questionably elevated up to but not beyond 1 D [\( \sim 0.33 \) mm]. Its pigmentation varies from light gray to slate gray to black.” It is clear from this definition that tumor thickness was the major criterion used by these investigators to differentiate nevi from melanomas.

Ganley and Comstock, in possibly the most frequently cited article on the relative frequencies of choroidal nevi and choroidal melanomas in the U.S. population, do not provide any diagnostic criteria for distinguishing between such lesions. The diagnosis attributed to any given lesion by the attending ophthalmologist in the case was apparently regarded as the correct diagnosis. They indicate that, of the lesions identified as nevi by the examining ophthalmologist, the lesions “ranged from 0.5 to 4.0 disc diameters in size [diameter], from a barely perceptible smudge of pigmentation with indistinct edges to slightly elevated lesions with drusen present in overlying Bruch’s membrane. The elevation was usually too slight to measure. The nevi were generally black to slate gray in color; the borders definite but somewhat feathery in appearance.’” It appears from this information that they regarded tumor thickness as the most important differential diagnostic criterion.

Gass defined a choroidal nevus as a “flat or slightly elevated slate-gray tumor that is oval or round and has well-defined but not...
sharp margins.” He goes on to indicate that such lesions “may be located anywhere throughout the fundus.” He states that “most choroidal nevi range in size from one to two disc diameters” but acknowledges that some “may be sufficiently large and elevated to cause suspicion of being malignant melanomas.” Of interest, in a later article, Gass5 defined a “suspected malignant melanoma” as “an elevated choroidal or choroidal and ciliary body tumor diagnosed [as such] by at least one member of our staff [i.e., the faculty of BPEI].” It appears that Gass believed he and his colleagues could distinguish between choroidal nevi and melanomas by their clinical features, although he did not describe what his threshold criteria were.

In the Collaborative Ocular Melanoma Study, a small choroidal melanoma was defined as a clinically diagnosed melanocytic choroidal tumor that was “between 1 mm and 3 mm in apical height and between 5 mm and 16 mm in basal diameter.” (Tumors that involved the ciliary body substantially, i.e., >50% of the tumor was in the ciliary body were excluded from this study.) If a melanocytic choroidal tumor was <1 mm thick, we could not register it as a choroidal melanoma in the COMS. The study designers clearly used thickness of the tumor as the most important arbitrary differential diagnostic criterion.

Naumann et al.12 defined a uveal (choroidal or ciliary body) nevus histopathologically as a tumor composed of “atypical but benign appearing uveal melanocytes (nevus cells).” The authors of this landmark report studied only those melanocytic choroidal tumors that had been classified as a choroidal or ciliary body nevus in the original ophthalmic disease report generated by the ophthalmic pathologist who reviewed the specimen initially at the Armed Forces Institute of Pathology (AFIP; all before 1967). As the reader probably knows, melanocytic choroidal tumors classified as spindle Melanoma at the AFIP and in most other ophthalmic disease laboratories at that time were regarded as truly malignant (i.e., capable of metastasis). Subsequent reevaluation of such cases at the AFIP by McLean et al.7 and Callender24 resulted in the reclassification of many of these lesions (a substantial proportion of which were >1 mm thick) as benign melanocytic nevi. Because Naumann et al.12 did not include such cases in their study group, their reported findings and conclusions must be construed as pertaining to only a portion of the complete spectrum of melanocytic uveal nevi. Their descriptive study of the included cases indicated that “the diameter of the nevi ranged from 0.5 to 11.0 mm; 33 were smaller than 2.5 mm, 56 were between 2.5 and 5.5 mm, and 13 were larger than 5.5 mm.” They also indicate that “these nevi were typically flat, discoid lesions, but 67 [of 102 lesions] exceeded the thickness of the adjacent choroid. Their thickness varied from 0.05 mm to 1 mm.” Once again, it appears that the authors of a report on choroidal nevi...
actually used an arbitrary upper limit of allowable thickness of lesions thus classified.

Sumich et al. defined a choroidal nevus as “an unequivocal pigmented choroidal lesion at least 500 μm in diameter and slate blue or green gray.” They indicated that “an ophthalmologist examined all participants clinically and excluded the presence of melanoma on the basis of [tumor] size and elevation.” Once again, it appears that the authors considered tumor size to be the essential differential diagnostic feature for distinguishing between nevi and melanomas.

The conclusion we gained from review of the aforementioned published diagnostic criteria was that the authors of virtually all published articles on this topic regard tumor size (particularly lesion thickness) as the most important and most consistently mentioned clinical diagnostic feature.

Clinical classification of melanocytic choroidal tumors into either a benign nevus or malignant melanoma category presupposes that such lesions exist in a discrete dichotomous spectrum (i.e., they are either one lesion or the other). Although we acknowledge that most choroidal melanomas that have been confirmed pathologically are indeed >7 mm in diameter and >2 mm in thickness at the time of initial treatment and most choroidal nevi are ≤5 mm in maximum basal diameter and ≤1 mm in maximum thickness at the time of initial detection, this graphic comparison study still suggests that there is substantial overlap between choroidal nevi and melanomas, especially for tumors having thickness between 1.5 and 3 mm and a largest basal diameter between 5 and 9 mm.

Histopathologic evidence indicates that melanocytic choroidal tumors actually comprise a continuous spectrum that ranges from completely benign lesions incapable of metastasizing to aggressively malignant lesions that almost always metastasize, regardless of how the primary tumor is managed. According to this view, the location of the size boundary that is used to classify such lesions into benign (nevus) and malignant categories is always somewhat arbitrary. As a practical matter, investigators attempt to specify a boundary location that provides a high level of diagnostic accuracy (high true-positive rate and low false-positive rate for each subgroup). Such an arbitrary dichotomization precludes any meaningful consideration of the spectrum of lesions categorized as nevi. When Callender attempted to classify choroidal melanomas into ordinal categorical prognostic groups on the basis of histomorphologic features of tumor tissue, he assumed that any melanocytic choroidal tumor which prompted an ophthalmic surgeon to perform an enucleation was malignant (i.e., had at least a limited potential to spawn metastasis). Subsequent re-evaluation of survival outcomes as a function of tumor histomorphology at the AFIP of the United States in the late 1970s and early 1980s clearly indicated that melanocytic choroidal tumors composed exclusively of Callender’s spindle A cells are benign (i.e., virtually never giving rise to metastasis). There are several obvious limitations to this study: the first important one is that the frequency distribution curves for choroidal nevi presented in this analysis were not verified by histopathologic evidence. We assumed that most small melanocytic choroidal tumors <5 mm in diameter and <1 mm in thickness encountered in our practice and reported in the literature were genuine choroidal nevi; however, some of these small melanocytic choroidal tumors were almost certainly choroidal melanomas that had been misdiagnosed clinically. Unfortunately, the only way one can be sure all clinically diagnosed choroidal nevi are really nevi and not melanomas would be to obtain a biopsy specimen of each tumor by some generally agreed on method or to enucleate each eye containing such a tumor and verify (or refute) the diagnosis pathologically. Obviously, this is not a reasonable or medically acceptable approach to this uncertainty. A second limitation is uncertainty about the true frequency of choroidal nevi in adult Caucasian population. Although we used the value 6.5% as a reasonable estimate of this frequency, the actual frequency may be higher or lower. The higher the true frequency of choroidal nevi and the lower the true cumulative lifetime incidence of choroidal melanomas in the Caucasian population, the greater the overlap that would be predicted by the graphic comparison method used in this study. Regarding plotting, the frequency distribution curves for thickness and largest basal diameter of choroidal nevi and choroidal melanomas were assumed to be normal (Gaussian) in shape for this study. If these curves are actually skewed rather than normal, the overlap between these lesions may be substantially different from that estimated by this study. Finally, we set arbitrary upper allowable limits of thickness and largest basal diameter for choroidal nevi in this study. Because some nevi undoubtedly attain dimensions larger than these arbitrary values, the comparative graphic analysis method used in this study may underestimate or overestimate the true extent of overlap between the lesion types.

Ophthalmologists who diagnose small melanocytic choroidal tumors that do not exhibit invasive features and treat them by locally destructive methods such as diode infrared laser hyperthermia or plaque radiotherapy are probably treating a substantial number of benign choroidal nevi. This comment echoes a sentiment expressed by Tamler and Maumenee in 1959.

References


