# Principles and Practice of Clinical Electrophysiology of Vision


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A Year Book Medical Publishers imprint of Mosby-Year Book, Inc.

Mosby-Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, MO 63146



1 2 3 4 5 6 7 8 9 0 CL CL MV 95 94 93 92 91

**Library of Congress Cataloging-in-Publication Data**
Principles and practice of visual electrophysiology / [edited by]
John R. Heckenlively, Geoffrey B. Arden.
p. cm.
Includes bibliographical references.
Includes index.
ISBN 0-8151-4290-0
1. Electroretinography. 2. Electrooculography. 3. Visual evoked response. I. Heckenlively, John R. II. Arden, Geoffrey B. (Geoffrey Bernard)
[DNLM: 1. Electrooculography. 2. Electrophysiology. 3. Electroretinography. 4. Evoked Potentials, Visual. 5. Vision Disorders—physiopathology. WW 270 P957]
RE79.E4P75 1991 91-13378
617.7 1547—dc20 CIP
DNLM/DLC
for Library of Congress

# 84

# Malignant Melanoma

William W. Dawson

Malignant melanoma of the choroid (MM) is one of the few primary eye diseases that is life threatening. Recent reviews are provided by Shields[16] and Foulds.[8] According to Yanoff and Fine[20] approximately 1 case is found in every 2,500 white persons, with the incidence in blacks being approximately 1/15 of that number. About 59% of these occur in the posterior third of the eye. The tumors are generally 0.5 mm or larger in apparent diameter, are frequently associated with drusen, and are thought to be of mesodermal, retinal pigment epithelium, neuroid, or nevoid origin. Yanoff and Fine[20] tend to support the nevoid theory and state that size and elevation are the most reliable prognostic signs. MMs may be confused with hemorrhages, cysts, serous detachment, lesions of the pigment epithelium, subretinal neovascularization, and other tumors.

Attention has been focused on MM and its surgical treatment by the relatively poor survival rates reported by Zimmerman and McLean.[21] There is little controversy over the adequacy of the diagnosis of advanced MM, but some authorities consider the accuracy of diagnoses in early cases to be unsatisfactory.[7, 16] An editorial[7] states,

> MM is an elusive intraocular tumor. It is notoriously unpredictable, not following rules. In some cases large tumors may remain local or regress for many years while others much smaller in size, with innocent appearances, may shower lethal metastases. Mistakes in the diagnoses of melanotic lesions are not uncommon. Depending upon the experience of the surgeon, the location of the growth, the availability of diagnostic aids, awareness of simulating lesions and the prevalent attitude toward intraocular malignancy, the incidence of unwarranted enucleation may vary from 3 to 24%.

Davidorf et al.[4] estimated misdiagnosis to range between 20% and approximately 2%, while Shelby et al.[15] used the model population of Rochester and Olmstead Counties in Minnesota and calculated an incidence rate of 7,000,000 MMs per year. Burtsell et al.[3] used a Canadian population study to support the assertion that therapy for MMs has not improved significantly in the last two decades. Most authorities feel that diagnostic accuracy has improved because of the recent tendency to delay surgery until a rapid-growth phase.

There is evidence that high-accuracy diagnoses may be less frequent away from major eye research centers. Shields et al.[17] report that of 770 patients referred as cases of "posterior uveal melanoma" to their center, 400 (52%) proved (with further clinical evaluation in their center) to have a "pseudomelanoma" of one or another of 40 classes. The most common class was the choroidal nevus (26.5%, 106 patients). They state that "many choroidal nevi are difficult if not impossible to clinically differentiate from malignant melanomas except by arbitrary criteria." The major diagnostic criterion applied by the authors was growth during a 1- to 5-year follow-up period.

A population study of 484 cases in Australia seems to establish that there is a critical interrelationship between discovery of the tumor, its size at enucleation, and long-term survival rate. Greer et al.[10] found a 95%, 15-year survival rate if enucleation

occurred while the melanoma was "small." This dropped to 70% after enucleation for "medium" tumors and 42% after enucleation with "large" tumors. The size limits defined by the authors are a quotient of crude height vs. extent. Thus the "small" category included all tumors less than "20" (millimeters depth times extent). If very early detection is the key to effective treatment (measured as survival), new size-independent, growth-independent diagnostic technology becomes very important.

## USE OF ELECTRO-OCULOGRAPHY IN MALIGNANT MELANOMA

Zrenner et al.[22] reported a great loss of pattern-evoked retinal potential (an "inner retinal" signal) in one case of MM with serous detachment. But the pigment epithelium is much closer to this tumor's usual position. Elsewhere in this volume, the electro-oculogram (EOG), the light/dark (L/D, Arden) ratio, and its relations to the anatomy and physiology of the pigment epithelium has been described. The sensitivity of the pigment epithelium and its standing potential (SP), the transepithelial potential, to influences of the chemical milieu of the choroid and outer retina make the SP a likely indicator of nearby tumors. Whether the malignant melanoma originates in the choroid or in the pigment epithelium itself may make little difference in the responsiveness of the SP. These considerations must have influenced Bohar and Farkas[2] and Ponte and Lauricelli[14] who published the first case reports that describe large changes in the L/D ratio in eyes with MMs. Soon followed relatively large sample studies, 54 patients from Florida (Staman et al.[18]), 22 patients from Wisconsin (Jones et al.[11]), 15 patients from the Netherlands (Graniewski-Wijnands and van Lith[9]), and 30 patients from Pennsylvania (Markoff et al.[12]). These papers all agree that the presence of MM with or without retinal detachment or whether large or small in apparent dimensions resulted in large reductions in the L/D ratio.

Table 84–1 summarizes the results of four of the five publications. With rare exception, the L/D ratio for the affected eye was found to be less than for the unaffected eye or from the eyes of other persons where nevi were found. When statistics were applied,[12, 18] statistical differences were higher than the .001 level. Jones et al.[11] reported a weak relationship ($r = -0.62$) for the correlation between the L/D ratio and the lesion size. However, Staman et al.[18] and Markoff et al.[12] found no relationship between MM size and L/D ratio. Thaler et al.[19] did not analyze the relationship between size and L/D ratio, but examination of their data revealed none. Perhaps most interesting was their finding that the L/D ratio was closely related to the position of the lesion relative to the posterior retinal pole. Those tumors being most central had the greatest effect on the L/D ratio, while those closer to the ciliary body were less effective. They cite one tumor of the ciliary body where the associated L/D ratio was within the limits of normal eyes. Jones et al.[11] reported one normal L/D ratio in an eye with MM, but the primary tumor was in the ciliary body and extended into the adjacent choroid. However, McCormick et al.[13] describe a case of pathologically proven mixed cell–type MM that presented as a 10-mm flat pigmented lesion of the posterior choroid with an overlying retinal detachment. This eye had a "normal" L/D ratio.

While the EOG has a long history of significant

**TABLE 84–1.**

Arden (L/D) Ratios and Related Variables Reported by Several Investigators*

| | L/D Ratio† | | | |
|---|---|---|---|---|
| Variable | Markoff et al.[12] | Staman et al.[18] | Jones et al.[11] | Thaler et al.[19] |
| Melanoma (h)‡ | ND‡ | 1.25 (13)§ | 1.38 (9) | 1.39 (8) |
| Melanoma (c)‡ | 1.25 (20) | 1.30 (8) | 1.61 (5) | 1.41 (1) |
| Fellow eye | 2.33 (20) | 1.8 (13) | 1.94 (9) | 1.77 (8) |
| Nevus | 2.12 (10) | 1.75 (33) | 1.90 (8) | ND |
| Light (Ft·L) | 500 | 11.5 | 438 | 277 |
| Movements (degrees)¶ | 30 | ND | 60 | 30 |

*Criteria for MM diagnosis: Staman et al., L/D <150 plus L/D >23% below the normal fellow eye value; Jones et al., L/D <170; Thaler et al., no recommendation; Markoff et al., no recommendation.
†Average values.
‡h = histopathopathologically proven; c = judged on clinical grounds; ND = not done/reported.
§Numbers in parentheses are numbers of eyes.
¶Eye saccades.

variance between and within individuals, it is difficult to review these data without concluding that the EOG is a potentially useful and quantitative method of discriminating between MM and a number of "pseudo-melanomas." Reduced EOG variability would enhance the clinical value of the procedure. A number of methods are described elsewhere in this volume. One procedure[5] utilizes the pooling of amplitudes of small groups of saccadic movements to eliminate the subjective choice of dark trough and light peak amplitudes. The interaction between monocular electrical dipoles appears to add confusion to interpretation of the EOG data in the presence of MM. Some years ago Alexandridis[1] showed that EOGs recorded simultaneously from an individual are not entirely independent, that is, the electrical field generated by the rotation of one eye probably intersects the field of the second eye and adds to it. Alexandridis[1] showed that the L/D ratio of a normal eye was reduced by choroidal detachment and other changes in the pigment epithelial function of the fellow eye. Recently, Denny and Denny[6] described an "eye blink EOG" that may be helpful in producing binocular L/D "independence." Their methodology is based on the observation that skin electrodes inferior and superior to the pupil record an "EOG"-like potential when the eye is quickly closed and opened, thereby avoiding lateral eye movement. If this signal is followed through a light and dark phase, an L/D ratio may be calculated. The results appear to be consistent with the results of EOGs recorded when the eyes are moved from left to right. They demonstrated that an eye in the orbit is necessary in order to record the "eye blink potential."

EOG recordings using clinical methodologies described elsewhere in this book are satisfactory for discriminating between small MMs of the posterior choroid, nevi, and other "pseudo"-melanomas with high accuracy. Diagnostic errors reported in the literature have been of the "false-negative" type.

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