Legacy of the Collaborative Ocular Melanoma Study

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ZIMMERMAN ET AL\(^1\) CAUSED MUCH CONSTERNATION when in the 1970s they suggested that enucleation of eyes with uveal melanoma accelerated metastatic death by disseminating tumor cells into the general circulation. Their hypothesis was based on the peak in mortality in the second postoperative year. Around the same time, Manschot and van Strik\(^2\) declared that radiotherapy of uveal melanoma was unjustifiable because histology frequently demonstrated viable melanoma cells in irradiated eyes. Studies reporting no significant differences in survival between enucleation and radiotherapy were unconvincing because they were nonrandomized with inadequate patient numbers and short follow-up. The “Zimmerman-Manschot debate” stirred much controversy about the treatment of choroidal melanoma, unsettling both patients and ophthalmologists. For these reasons, it was entirely reasonable to undertake large, collaborative studies that would provide definitive answers on how survival and quality of life are influenced by enucleation, preenucleation radiotherapy, and brachytherapy.

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The Collaborative Ocular Melanoma Study (COMS) has done truly impressive work in successfully performing large, randomized, prospective studies. The data are highly credible, thanks to excellent compliance with protocols and near-perfect diagnostic accuracy.

The trial of enucleation alone vs pre-enucleation radiotherapy included 1003 patients with large choroidal melanoma and concluded that there was no difference between treatment arms.\(^3\) This COMS study is so convincing that any conflicting results from smaller, nonrandomized evaluations of pre-enucleation radiotherapy are disregarded.\(^4\) Enucleation is now performed without the expense of adjuvant radiotherapy. Financial savings should exceed the cost of the COMS investigation. This negative finding confounds Zimmerman’s hypothesis, reassuring patients and their ophthalmologists that enucleation does not accelerate death from metastatic disease.

Another influential COMS conclusion was that in 1317 patients with medium-sized choroidal melanoma, the 5-year mortality with histopathologically confirmed melanoma metastasis after brachytherapy with iodine 125 was no worse than after enucleation.\(^5\) This provided reassurance that brachytherapy is “as safe as enucleation.” Eyes saved as a result of COMS conclusions should quickly outnumber eyes enucleated in the study if this has not already happened.

The number of patients enrolled in the COMS is a remarkable achievement, considering the rarity of uveal melanomas. However, neither of the randomized studies provides sufficient statistical power to state that there is no survival difference between rival treatments. In the brachytherapy study, for example, the 95% confidence intervals for unadjusted risk ratios were excessively wide (ie, 0.86-1.24 for all-cause mortality and 0.81-1.41 for histopathologically confirmed metastasis during the 12-year follow-up).\(^6\) In addition, many would not be satisfied that brachytherapy is as effective as enucleation unless they are reassured that local recurrence does not increase mortality; however, the COMS did not address this question. Furthermore, since the ocular treatments essentially aimed to prevent metastatic spread, the significance of the COMS results was diminished by the fact that in the brachytherapy and pre-enucleation radiotherapy studies, at least 10% and 35% of patients, respectively, died within 5 years of treatment and hence as a result of preexisting systemic disease, if calculations based on uveal melanoma doubling times are accepted.\(^6,7\) Finally, the follow-up times, although impressive, were perhaps insufficient to detect differences between treatments in preventing metastasis. A meta-analysis of breast cancer patients indicates that an adverse effect of local treatment failure on mortality takes about 15 years to become evident statistically.\(^8\) Few COMS patients were followed up for 10 years and there is little power to detect differences in this area of the survival curves. The reassurance provided by COMS is not as statistically sound as one might like.

The COMS would probably have reached exactly the same conclusions even if the sample sizes and follow-up were sufficient. Basic science research elsewhere has re-
vealed that uveal melanomas develop nonrandom chromosomal abnormalities such as monosomy 3, which correlate strongly with mortality.9,10 These findings support the hypothesis that there are 2 subtypes of uveal melanoma: high-grade melanomas, which are all fatal because they metastasize before treatment of the primary tumor, and low-grade melanomas, which grow slowly without ever metastasizing, even if untreated. There is growing suspicion that with medium and large uveal melanomas, ocular treatment is only palliative and that it is only with small tumors that there is any hope of preventing metastasis. In concentrating on medium-sized and large tumors, the COMS may have backed the wrong hypothesis regarding the time of onset of metastatic spread of melanoma from the eye. Future studies evaluating how ocular treatment influences survival should ideally focus on patients with a "small" melanoma, in whom any opportunities for preventing or delaying metastatic disease are greatest.

Unfortunately, we cannot identify clinically the minority of small melanomas that are life-threatening and we do not know when high-grade tumors start to metastasize. Patients with a "good melanoma" are therefore overtreated, unnecessarily sacrificing vision and the eye, whereas those with "bad" tumor may be treated only belatedly, perhaps after preventable metastatic spread has occurred.11 The COMS observational results will help design future investigations addressing the management of small malignant tumors of uncertain metastatic potential.12

In view of the profound prognostic differences between low-grade and high-grade uveal melanomas, some form of tumor grading at the time of initial treatment should ideally be performed routinely, as happens with other cancers. Routine grading would enhance the evaluation of ocular treatments with respect to ocular and systemic outcomes and should reduce the number of patients required for such studies. Grading would probably involve routine biopsy, which should stimulate interest in histological and cytogenetic markers of tumor grade. The COMS pathological investigation of 1527 eyes with uveal melanoma provides much information on the histology of these tumors.13 Such data would become more meaningful if correlated with survival. This tissue bank and the accompanying survival data could prove invaluable in validating markers of tumor grade.

The COMS publications on ocular and psychological outcomes after brachytherapy and enucleation are important additions to the literature, especially because the data originate from many independent treatment centers. The brachytherapy with iodine 125 was followed by high rates of visual loss, enucleation, and local treatment failure so that any initial gains in quality of life vis-à-vis enucleation diminished over time.14-16 The COMS concluded that this analysis allows individual patients and their physicians to make informed choices regarding treatment based on personal preferences; however, quality of life was not measured in relation to factors such as tumor size and location, visual acuity in each eye, and the development of any complications. Furthermore, one wonders whether ocular morbidity after brachytherapy was caused by the choice of plaque isotope (ie, iodine 125) or whether it reflected the surgeons’ inexperience in centers treating small numbers of patients (no slant intended as internationally most patients with uveal melanoma are treated by surgeons who administer brachytherapy infrequently). In any case, I hope that these COMS results will encourage future investigations comparing brachytherapy with iodine 125 with brachytherapy with ruthenium 106 as well as with proton beam and stereotactic radiotherapy. Future evaluations of patient care should take into account the fact that more centers now offer a wide range of therapies, which allows for selecting the best treatment and combining different modalities to improve results.

There is scope for more studies, such as treatment of juxtapapillary melanomas, iris melanomas, and melanosomes with extraocular extension, not to mention adjuvant systemic therapy in high-risk patients. Thanks to the COMS, participating clinicians in many centers have learned how to define and measure variables and outcomes in a uniform manner. In addition, ophthalmic researchers have gained vast experience in conducting multicenter studies.17 Measures are required urgently to preserve this precious COMS know-how. It would be ideal if perpetual collaborative studies could be undertaken, routinely categorizing all patients and following every patient until death. Multicenter collaboration would also help participating centers improve their own standards of care by comparing their outcomes with those of other centers, anonymously or otherwise.

The COMS may not have answered the (possibly unanswerable) question, “Do I take the eye out or leave it in?&quot; however, it has provided a wealth of knowledge and information yet to be fully reaped. This reminds me of the fable about a farmer who told his sons that they would find a treasure in a neglected field. They did not unearth any gold, but having dug up the entire ground, they decided to raise a crop and were rewarded by a bumper harvest more valuable than the trove they imagined.

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REFERENCES

In the late 1970s and early 1980s, US ophthalmologists who diagnosed uveal melanoma in a patient confronted a difficult decision: whether to recommend enucleation of the eye with the tumor, in accord with a century of ophthalmic practice, or to refer the patient to one of a small number of ophthalmologists who were advocating eye-conserving radiotherapy for many such tumors. The dilemma was exacerbated by reports regarding a large series of patients who had undergone enucleation that showed that the period with the highest incidence of death was 1 to 2 years following enucleation. Also, although of lesser concern with decreasing rates of misdiagnosis, the ophthalmologist had to choose between 2 options: remove the affected eye and possibly hasten the patient’s death (or disease) or refer the patient for radiotherapy and possibly hasten his or her death should radiotherapy prove to be less effective than enucleation to control the tumor and avoid metastasis.

As survival data from uncontrolled series of patients treated with eye-conserving radiotherapy accumulated and comparisons were made to historical series of patients whose tumors were treated with enucleation, the available evidence suggested that enucleation and radiotherapy were equally effective (or equally ineffective, depending on one’s point of view) with respect to prolonging life. However, because of the retrospective nature of the comparisons and differences in the characteristics of patients and tumors selected for enucleation and radiotherapy, most ophthalmologists in the United States remained uncertain regarding the best course for their patients. Furthermore, the location of the largest clinical practices specializing in radiotherapy for uveal melanoma on the Atlantic and Pacific coasts meant that most patients who elected eye-conserving radiotherapy incurred significant expenses.

During a series of meetings of retinal specialists, a consensus gradually emerged that a scientifically valid prospective study was needed of comparable cases of uveal melanoma, some of whom were treated with enucleation and others by eye-conserving radiotherapy. However, the appropriate design of such a study was debated at length. Several meetings were held in 1984 to design a study, with most ophthalmologists and biostatisticians advocating a randomized clinical trial. A key meeting was held in Bethesda, Maryland, in December 1984 under the auspices of the National Eye Institute of the National Institutes of Health with the goal of reaching consensus on the design of one or more randomized trials. At that time, the 2 methods of eye-conserving radiotherapy for which the largest experience was available were charged particles (either protons or helium ions) and brachytherapy via an episcleral radioactive plaque.

**THE INVESTIGATORS’ PERSPECTIVE ON THE COLLABORATIVE OCULAR MELANOMA STUDY**

Stuart L. Fine, MD; Barbara S. Hawkins, PhD

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**DESIGN ISSUES AND DECISIONS**

Decisions to be made during the design of the Collaborative Ocular Melanoma Study (COMS) included the number of clinical trials to be conducted, the method(s) of delivering radiotherapy and the number of treatment arms in each trial, and the difference in mortality rates between treatment arms that would lead to a preference for one treatment over the other if a difference of that magnitude were observed. Initially, 3 randomized trials were considered, one each for large, intermediate, and small choroidal melanoma. Consensus rapidly was achieved regarding the design and treatment arms for randomized trials for large and “medium-sized” tumors. However, the risk of misdiagnosis was believed to be high in small tumors, with many pos-