



Nina Mikhailenko. *Chebov Most*. Oil on canvas, 16" × 20".

All-cause mortality rates after treatment for ocular melanoma with enucleation vs brachytherapy are similar.

The Collaborative Ocular Melanoma Study: An Overview

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Background: *The Collaborative Ocular Melanoma Study (COMS) is a 3-arm study that includes two multicenter randomized clinical trials designed to compare the effectiveness of brachytherapy to enucleation for treatment of medium-size choroidal melanomas, and the effectiveness of enucleation with and without preoperative external-beam radiotherapy for large choroidal melanomas. The third arm is an observational study of small choroidal melanomas. Patient accrual ran from 1987 to 1998.*

Methods: *A review of COMS published reports was conducted.*

Results: *There is no difference in 5-year all-cause mortality for large- and medium-size choroidal melanomas with COMS-designated treatments. Preoperative radiation for large choroidal melanomas does not improve survival. The accuracy of the clinical diagnosis of choroidal melanoma is excellent.*

Conclusions: *Data from the trials are still being collected and analyzed, but primary outcomes will unlikely change significantly in the future. Similar rates of mortality after treatment with enucleation and brachytherapy shift the emphasis of selection of therapy to secondary outcomes such as preservation of vision. The findings highlight the need to better understand the biological mechanisms and timing of hematogenous dissemination to achieve an appreciable impact on choroidal melanoma survival.*

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The author participated in COMS as a certified pathologist while at the University of South Florida from 1988 to 1989.

Abbreviations used in this paper: COMS = Collaborative Ocular Melanoma Study; CI = confidence interval.

Introduction

Melanoma of the choroid is an uncommon malignancy, occurring in approximately 6 individuals per million population annually, or approximately 1,400 new cases in the United States each year.¹ The incidence of choroidal melanoma is about one tenth that of cutaneous melanoma, but unlike skin melanoma, its incidence has remained fairly stable.^{2,3} The mean age at diagnosis is the mid 50s.¹ Choroidal melanomas are rare among non-whites.^{4,5} Other than an infrequent report of family cluster, choroidal melanoma occurs sporadically. The role of

Table 1. — Definitions of Choroidal Melanoma Size

Study	Small Size	Medium Size	Large Size
Meta-analysis 1966-1988 ⁸ *	<3 mm height and <10 mm diameter; <10 mm diameter; <11 mm diameter; <300 mm ³	10–15 mm diameter; 10–15 mm diameter; 11–15 mm diameter; <15 mm diameter	>15 mm diameter; >15 mm diameter or >5 mm height
COMS ^{20,22,27}	1.5–2.4 mm height and 5–16 mm diameter	2.5–10 mm apical height** and ≤16 mm diameter	>10 apical height and >16 mm diameter

* Included 8 studies with overlapping size criteria.
** Changed November 1990 from 3.1 to 8.0 mm.

sunlight and other environmental factors in the pathogenesis of uveal melanoma remains unknown.

Enucleation has been the standard of care for the treatment of choroidal melanoma since the latter part of the 19th century. However, the effectiveness of surgical removal of the eye to improve survival has not been unequivocally demonstrated because the natural history of uveal melanoma has never been documented.⁶ Most early published series on the treatment of choroidal melanoma by enucleation were small, of poor quality, or noncomparable; thus, the potential benefit of treatment has been difficult to assess.⁷ A meta-analysis of 76 published reports of all-cause mortality of patients with choroidal melanoma treated by enucleation from 1966 through 1988 found only eight studies suitable for data extraction.⁸ The meta-analysis confirmed that tumor size correlated strongly with survival and provided the best estimates to date for all-cause mortality following enucleation. Classification of tumor size varied among studies

with some overlap (Table 1). The combined weighted estimates from these eight studies for 5-year mortality were 16% for small tumors (95% CI, 14% to 18%), 32% for medium tumors (CI, 29% to 34%), and 53% for large tumors (95% CI, 50% to 56%).⁸

Few long-term studies of uveal melanoma are available. A study from the Helsinki University Central Hospital looked at the long-term prognosis of patients treated by enucleation between 1962 and 1981.⁹ The study adapted the standardized definitions for coding the cause of death used by the Collaborative Ocular Melanoma Study (COMS).¹⁰ The accuracy of previous biopsy and autopsy material was verified by histopathologic review. Tumor size was considered a continuous variable for regression analysis. Death was attributable to melanoma in 145 (61%) of the 239 patient deaths.⁹ The 5-year, 15-year, 25-year, and 35-year uveal melanoma-related mortality rates were 31% (95% CI, 26% to 37%), 45% (95% CI, 40% to 51%), 49% (95% CI, 43% to 55%), and 52% (95% CI, 45% to 58%), respec-

Table 2. — All-Cause and Tumor-Related Mortality Rates With Choroidal Melanoma

	Large-Size Melanoma Mortality (95% CI)	Medium-Size Melanoma Mortality (95% CI)	Small-Size Melanoma Mortality (95% CI)
Meta-analysis ⁸			
5-yr all-cause mortality	53% (50-56%)	32% (29-34%)	16% (14-18%)
COMS ^{20,21}			
5-yr all-cause mortality	43% (38-48%) ^a 38% (34-43%) ^b	19% (16-23%) ^c 18% (15-21%) ^d	6% (2.7-9.3%)
5-yr tumor-related mortality	28% (24-32%) ^a 26% (22-31%) ^b	11% (8-13%) ^c 9% (7-11%) ^d	1% (0 - 2.5%)
Helsinki Study ⁹		ALL SIZES	
4-yr tumor-related mortality		31% (26-37%)	
15-yr tumor-related mortality		45% (40-51%)	
25-yr tumor-related mortality		49% (43-55%)	
35-yr tumor-related mortality		52% (45-58%)	

COMS = Collaborative Ocular Melanoma Study
CI = confidence interval
^a enucleation alone
^b enucleation with preoperative radiation
^c following enucleation
^d following brachytherapy

tively (Table 2). These mortality data reflect a substantial proportion of patients dying of metastatic disease 5 or more years after treatment, and they underscore the importance for long-term follow-up in any treatment trial for choroidal melanoma.

The desire to improve survival and preserve vision in patients with choroidal melanoma stimulated the development of alternative therapies. Most popular among these was brachytherapy using radioactive plaques.¹¹⁻¹⁵ Despite considerable data from clinical series on the effectiveness of radiotherapy, no randomized clinical trial was conducted to compare tumor-related mortality of radiotherapy with enucleation. By the 1980s, there was conflicting evidence to suggest that enucleation hastens tumor-related mortality,⁶ that radioactive plaque brachytherapy incurs worse survival than enucleation,¹⁶ and that radioactive brachytherapy was as effective as enucleation in preserving life.^{11,14,17}

In 1985, a multicenter randomized clinical trial (COMS) comparing radiation to enucleation was funded by the National Eye Institute to help resolve the dilemma over the selection of therapy. This article reviews specific aspects of the design, execution, and results of the COMS as they pertain to primary and secondary outcomes.

Study Design

The COMS consists of two multicenter clinical trials designed to compare the outcome of therapies for large and medium choroidal melanomas and a third arm to assess the natural history of small choroidal melanomas.¹⁸ Patients with large choroidal melanomas were randomized to enucleation alone or enucleation preceded by external-beam radiation (20 Gy). Patients with medium choroidal melanomas were randomized to enucleation or brachytherapy using iodine-125. Patients with small choroidal melanomas were enrolled in a registry and followed clinically. Entrance criteria established at the beginning of the study defined large choroidal melanoma as more than 8 mm in thickness and/or greater than 16 mm in longest base diameter. Medium choroidal tumors were 3.1 to 8 mm in thickness and no more than 16 mm in longest base diameter. Small choroidal melanomas were 1 to 3 mm in apical thickness and at least 5 mm in diameter (Table 1). The primary outcome was time to death from all-cause mortality. Secondary outcomes included metastasis-free survival, cancer-free survival, and years of useful vision.

The COMS had strict inclusion and exclusion criteria. For example, patients with coexisting disease that could compromise survival or those on immunosuppressive therapy were ineligible. A stringent certification process ensured that all procedures were done in the same manner and according to protocol at all of the clinical centers. The certification process was required of all participants

from the visual acuity tester to the surgeons performing enucleation and plaque insertion. Standardized forms for data collection were forwarded to appropriate COMS centers (ie, coordinating, pathology, photography, echography, and radiological physics) for review. A Mortality Coding Committee was established to assess the cause of death in each case and determine if death was related to the underlying choroidal melanoma.¹⁰ The guidelines use autopsy with histopathologic confirmation of melanoma metastasis at the time of death and antemortem imaging studies of suspected metastasis with and without histopathologic confirmation. The Mortality Coding Committee did not rely on death certificates alone, which they found underestimated the proportion of deaths due to metastatic choroidal melanoma.¹⁹

Clinical Outcome

In the large choroidal melanoma clinical trial, 1,003 patients were randomized to either enucleation or enucleation preceded by external-beam radiation. Patients receiving preoperative radiation had no statistically significant difference in 5-year survival (Table 2).²⁰ The trial had a 90% probability to detect a difference in mortality of 20%. There were no significant differences in the two groups in terms of local orbital outcome, although there were fewer biopsy-confirmed tumor recurrences of the orbit in patients receiving preenucleation radiation (none for the radiation group vs 5 in the nonradiation group; $P=.03$).²⁰ The 5-year all-cause mortality rate for large melanomas was 40% (95% CI, 37% to 44%). The 5-year melanoma-related mortality rate was 27% (95% CI, 23% to 32%). Postoperative complications were infrequent and minor and did not differ significantly between the two groups.²¹

The 18th report of the COMS described the initial mortality findings following iodine-125 brachytherapy and enucleation of medium-size melanomas.²² Over the 12-year accrual period, 1,317 patients with medium-size melanomas were enrolled, with 660 assigned to enucleation and 657 to brachytherapy. Ninety-seven percent (1,274 patients) were followed for at least 3 years, 81% (1,072 patients) for 5 years, and 32% (416 patients) for 10 years or more.

Survival data revealed that 188 patients (28%) assigned to enucleation and 176 patients (27%) assigned to brachytherapy died.²² The 5-year cumulative mortality rates were 19% (95% CI, 16% to 23%) for enucleation and 18% (95% CI, 15% to 21%) for brachytherapy. A Cox proportional hazards model with the treatment arm as the only covariate showed nearly identical mortality rates in the two groups. There was no statistically significant difference in the unadjusted or adjusted mortality rates.

The Mortality Coding Committee classified 345 (95%) of the 364 deaths from all causes. One hundred and one patients from each group (57% from the enucleation

group; 60% from the brachytherapy group) had metastatic melanoma confirmed or suspected at death. Diagnostic accuracy based on eyes treated by enucleation was excellent. Among the 647 eyes enucleated, only 2 (<0.01%) did not contain a choroidal melanoma.²³

After the first 5 years following brachytherapy, 69 patients underwent enucleation and 57 of these were for treatment failure.²⁴ The risk of treatment failure was 10.3% (95% CI, 8% to 13.2%). Risk factors for treatment failure were greater tumor thickness, older age, and proximity of tumor to the foveal avascular zone.²⁴

Visual acuity declined in a substantial proportion of eyes treated with brachytherapy.²⁵ There was a quadrupling of the minimum angle of resolution, or loss of 6 or more lines of visual acuity from baseline, in 18% of patients by 1 year, 34% by 2 years, and 49% by 3 years.²⁵ Visual acuity was 20/200 or worse in 43% of eyes. The risk of vision loss was associated with a history of diabetes, thick tumors, tumors close to or beneath the macula, tumors with secondary retinal detachments, and tumors that were not dome-shaped.

Forty-two patients who were eligible for the COMS clinical trial for medium-size melanoma deferred treatment or had no treatment for choroidal melanoma and enrolled in a natural history study.²⁶ The estimated 5-year melanoma mortality rate was 30% (95% CI, 16% to 20%). While these results are not statistically different from the 5-year melanoma risk of death in the clinical trial, the trend for a higher death rate suggests that a real survival benefit of therapy may be found with greater long-term follow-up.²⁶

As of August 1989, 204 patients were enrolled in the small choroidal melanoma registry.²⁷ The median length of follow-up was 92 months. Eight patients opted for treatment at the time of enrollment, and another 67 decided on treatment during follow-up. Twenty-seven patients died, but only 6 deaths were due to metastatic melanoma. Four of the 6 deaths occurred more than 5 years after enrollment. The estimated 5-year all-cause mortality rate was 6.0% (95% CI, 2.7% to 9.3%) and 8-year all-cause mortality rate was 14.9% (95% CI, 9.6% to 20.2%). The 5-year and 8-year tumor-specific mortality rates were 1% (95% CI, 0% to 2.5%) and 3.7% (95% CI, 0.7% to 6.6%), respectively.²⁷

Comments

The COMS has been collecting and analyzing data from more than 40 clinical centers for greater than 15 years. Because there were strict exclusion criteria, these results are not generalizable to all patients with choroidal melanoma. Most importantly, patients with medium-size melanoma near the optic nerve were excluded because it precluded application of the radioactive plaque. Also, patients with predominantly ciliary body melanomas were not included.

Thus, the results of the COMS should not be extrapolated to melanomas of the peripapillary choroid or ciliary body.

The accuracy of clinical diagnosis in the COMS was excellent (>99% accuracy confirmed by histopathology) and far superior to any previous reports in the literature on choroidal melanoma.²³ These results, however, must be examined in context of the study's design that excluded patients with cloudy media that would interfere with ophthalmoscopic examinations, fluorescein angiography, and fundus photography. The COMS provides a goal for potentially achievable accuracy in diagnosis, but these results should not be considered a benchmark for community physicians who have to establish diagnoses in all patients with choroidal tumors, including those with poor or no ophthalmoscopic view of the lesion.²⁸

The COMS was a study of equivalency with the objective of testing whether a new intervention (ie, brachytherapy) is as good as enucleation.²⁹ At the time of its inception, the most effective method to treat medium-size choroidal melanoma was not known. Most available data suggested that survival following the more recently developed brachytherapy was similar to enucleation.³⁰ Thus, the clinical necessity and the ethical justification for conducting a randomized clinical trial existed — clinical uncertainty. However, randomized clinical trials in which two therapies produce nearly identical outcomes pose certain logistical problems, the most obvious of which is the large sample size needed to test for equivalency.²⁹ In situations when the primary outcomes of differing treatments are essentially the same, any preference of one therapy over another would have to be based on other criteria, such as severity of adverse effects, quality of life issues, or treatment costs. In the case of medium-size choroidal melanoma, the selection of brachytherapy over enucleation offers patients the possible salvage of an eye and potential vision.

Knowledge about the impact of enucleation for choroidal melanoma on the performance of vision-dependent activities might influence patient selection of equivalent therapies. To this end, Edwards and Schachat³¹ performed standardized interviews to determine functional outcomes after enucleation. Interviews were conducted on 71 patients who underwent removal of an eye for choroidal melanoma 2 to 25 years earlier. Fifteen years after enucleation, 90% of patients were able to drive and 96% retained the ability to read. The results of this survey showed, in general, that most patients were not visually impaired by their surgery and continued to perform at preenucleation levels.³¹ The COMS has developed ocular melanoma-specific scales for measurement of quality of life issues.³² These scales address such concerns of perception of appearance and fear of cancer recurrence. Initial use of these scales reveals that they have good internal consistency and that they measure clinically relevant information not available from other standard mental health scales.³²

Conclusions

The COMS is one of the largest and most challenging clinical trials ever conducted by the National Eye Institute. To date, its major findings are (1) that preenucleation external-beam radiation to the orbit for large choroidal melanoma does not improve survival compared with enucleation alone and (2) that there is no difference in 5-year survival of patients with medium-size choroidal melanoma treated with iodine-125 brachytherapy or enucleation. The fact that preenucleation radiation does not confer any survival advantage over standard enucleation argues against the hypothesis by Zimmerman et al⁶ that tumor emboli at surgery accelerate tumor-related death. There have been no clinical trials evaluating the effectiveness of therapies other than enucleation for large melanomas.³³

A major criticism of the COMS is that its primary findings essentially confirm what was strongly suspected but never proven 15 years ago — that for medium-size choroidal melanomas, there is no difference in survival benefit between brachytherapy or enucleation. The argument that the cost and the length of time to complete the COMS used limited national resources needed for the development of more promising therapies or for the advancement of basic research into melanoma biology is no longer relevant. Since large, multicenter clinical trials will be required to test the effectiveness of new therapies in the future, the COMS has emphasized the need for more efficient methods of conducting multicenter trials for uncommon clinical conditions. Ocular oncologists should be encouraged that more efficient strategies for conducting clinical trials in ophthalmology are being developed.³⁴

Still unresolved is the clinical importance of localized treatment failure with brachytherapy. There is evidence from clinical series that failure to achieve local control after radiation therapy, even when treated by subsequent enucleation, is associated with increased risk of metastasis.^{35,36} Local treatment failure after brachytherapy in the COMS demonstrated a trend toward reduced survival after adjustment for other risk factors (adjusted risk ratio of 1.5; $P=.08$).²⁴ Long-term follow-up will determine if this trend becomes clinically important.

The results of the COMS confirming that the century-old procedure of enucleation has the same survival benefit as brachytherapy stress the need to better understand the biological mechanisms of metastasis. Refinements in the current approach to therapy of choroidal melanoma will at best show only modest improvement in survival without knowledge of when micrometastases occur.³⁷ Research into the early detection and treatment of micrometastases needs to be given the highest priority.

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