Chapter 44

Collaborative Ocular Melanoma Study

Barbara S. Hawkins
Andrew P. Schachat

A large number of excellent clinical studies concerning treatment of ocular melanoma have been cited elsewhere in this text. The Collaborative Ocular Melanoma Study (COMS) is the first set of randomized clinical trials designed and conducted with sufficient power to compare survival outcomes between two or more treatments with a high degree of confidence.

BACKGROUND

The choice of management of choroidal melanoma was controversial at the time the COMS was designed and initiated, and it remains controversial for tumors of small size. No data comparing enucleation or any other treatment with natural history were available; however, most ophthalmologists and oncologists were unwilling to undertake a randomized trial in which observation was one of the treatment arms. Large choroidal melanoma in the absence of metastasis traditionally has been treated with enucleation of the affected eye. Pre-enucleation irradiation of the eye had been proposed with the goal of minimizing the possibility of dissemination of viable tumor cells at time of enucleation.[1–8] Other adjunctive treatments also had been proposed, including postenucleation irradiation of the socket, cryotherapy before enucleation, and chemotherapy.

A consensus had been reached that growing choroidal melanoma of intermediate size ("medium") should be treated. However, the choice of treatment, enucleation or some type of radiotherapy to avoid loss of the eye and preserve some vision, was unclear. At the time the COMS was designed, radiotherapy was available at relatively few centers within the United States and Canada, where patients who elected radiotherapy were referred. Finally, concerns regarding diagnostic accuracy, particularly for small choroidal melanoma, had persuaded most ophthalmologists to observe smaller tumors for growth before treating.

The length of survival after a diagnosis of choroidal melanoma is quite variable. A meta-analysis of data published from 1966 through 1988 regarding survival following enucleation yielded 5-year survival rates of 50% for large choroidal melanoma, 70% for medium choroidal melanoma, and 85% for small choroidal melanoma.[9] However, few studies reported survival or mortality rates according to tumor size. It is accepted that the most important predictor of survival is tumor cell type. However, because of concerns regarding complications and inadequate sampling during fine-needle aspiration biopsy, choroidal melanoma typically is not biopsied. Thus cell type is not known until the eye is removed or the patient dies.

DESIGN OF THE COLLABORATIVE OCULAR MELANOMA STUDY

The COMS was designed as a set of clinical trials of treatment for choroidal melanoma to be conducted by a group of investigators in the United States and Canada. Initially, three separate studies were undertaken, two randomized clinical trials and one observational study.[10] Initial funding was provided in 1985 by the National Eye Institute, National Institutes of Health, U.S. Department of Health and Human Services; beginning in 1991, both the National Eye Institute and the National Cancer Institute provided funding to conduct the study.

Randomized trials of radiotherapy

For COMS purposes, choroidal melanomas were categorized broadly by size. Size criteria and other eligibility criteria are summarized in Table 44-1 and Boxes 44-1 to 44-3. The clinical trial for large choroidal melanoma was designed to compare enucleation alone with pre-enucleation radiation treatment (PERT). Pre-enucleation radiation was chosen for comparison with enucleation alone because a similar approach had been shown to be effective in other types and sites of cancer in which surgery was employed. In addition, external radiation was widely available throughout the United States and Canada. Patients were assigned randomly, with equal probability, between the two treatment arms and were to be followed for a minimum of 5 years or until death. The sample size was estimated on the basis of overall survival. Taking account of possible losses to follow-up, treatment crossovers, and treatment refusals, a target sample size of 1000 patients was established.[10,11]

A second randomized clinical trial was designed to compare enucleation alone with I-125 brachytherapy for treatment of medium choroidal melanoma. Brachytherapy was chosen as the most feasible method of radiation delivery to the melanoma with respect to standardization of dosimetry and ability to monitor adherence to the radiotherapy protocol. I-125 was selected as the isotope because of the ability to protect the surgeon and other tissues in the orbit from radiation damage by

Section 3 Choroidal Melanoma and Related Issues

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Table 44-1 Collaborative Ocular Melanoma Study classification of size of choroidal melanoma

Size	Parameter		
	Apical height (mm)	Longest tumor basal diameter (mm)	Distance to optic disc (mm)
November 1986 through November 1990			
Large			
Subgroup 1	>8	–	–
Subgroup 2	≥2	>16	–
Medium	3.1–8	≤16	≥2
Small			
Subgroup 1	≤3	–	–
Subgroup 2	<2	>16	
After November 1990			
Large			
Subgroup 1	>10	–	–
Subgroup 2	≥2	>16	–
Subgroup 3	>8	–	<2
Medium	2.5–10	≤16	≥2
Small			
Subgroup 1	<2.5	<16	–
Subgroup 2	<2	>16	–

–, No restriction.

using a gold shield and because of the half-life of the isotope.[12] Patients were assigned randomly with equal probability between enucleation and I-125 brachytherapy. All patients were to be followed for a minimum of 5 years or until death. The minimum sample size targeted was 1250 patients for comparison of overall survival between treatment arms; a desired sample size of 2400 patients was established to ensure meaningful comparisons of survival rates within patient subgroups and for evaluation of secondary outcomes.[10,11]

A parallel study of quality of life of patients enrolled in the randomized trial of I-125 brachytherapy for medium choroidal melanoma was initiated in 1994.[13] The purpose of the parallel study was to compare treatment arms over time with respect to general health, visual function, and anxiety and depression using scores from several standard interview instruments. The study had two components: (1) a prospective randomized component consisting of 209 patients who enrolled in the trial of I-125 brachytherapy and were interviewed prior to random treatment assignment, at 6 months following treatment, and on annual anniversaries of enrollment for up to eight years; and (2) a cross-sectional component consisting of 645 additional patients who had enrolled in the randomized trial before the quality of life study was initiated and who were interviewed at least once during scheduled follow-up. These 854 patients represent 90% of patients who were eligible for the quality of life study and 65% of all patients who enrolled in the trial of I-125 brachytherapy.

Observational study

A nonrandomized observational study of small choroidal melanoma was included in the initial COMS design with the goal of providing sufficient information to design a randomized clinical trial for small tumors. Primary objectives were to estimate the number of patients with small choroidal melanoma available for inclusion in a randomized trial, the methods of treating small choroidal melanoma most widely used by COMS investigators, and, to the extent feasible within a small pilot study with short patient follow-up, rates of tumor growth and patient death.

METHODS

The COMS design and many of the methods have been published; the *COMS Manual of Procedures*[11] is available. Patients were evaluated for eligibility, enrolled, and treated at 43 different clinical centers, 41 in the United States and two in Canada. A standard schedule of clinical examinations was followed for data collection purposes. An unusual feature of the COMS design was that the participating ophthalmologists reported

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Box 44-1 Collaborative Ocular Melanoma Study general eligibility criteria

Each patient enrolled in the COMS had to meet the following requirements:
1. Primary choroidal melanoma in one eye only
2. Tumor size accurately delineated on echograms
3. Age of 21 years or older
4. Able to give informed consent
5. Able to return for scheduled follow-up examinations

To be enrolled in either randomized trial, the patient had to meet the following additional requirements:
6. No contraindication to surgery or radiation
7. Size criteria for individual trial satisfied, based on best clinical judgment of enrolling ophthalmologist

Box 44-2 Collaborative Ocular Melanoma Study

Exclusion criteria
Patients were excluded from participation in COMS randomized trials whenever any of the following criteria were met:
1. Social, mental, or physical condition that either impaired ability to give informed consent or to return for follow-up clinical examinations
2. Use of immunosuppressive therapy that might alter the body's response to melanoma
3. Previous treatment for choroidal or ciliary body melanoma
4. Previous treatment for any ocular condition secondary to the tumor
5. Previous fine-needle aspiration biopsy
6. Gross extrascleral extension of the melanoma
7. Diffuse, "ring," or multifocal choroidal melanoma
8. One half or more of the tumor in the ciliary body
9. Any other known primary or metastatic malignancy, except nonmelanotic skin cancers and carcinoma in situ of the uterine cervix

Box 44-3 Additional eligibility criteria for Randomized Trial of I-125 Brachytherapy for Medium Choroidal Melanoma

1. Visual acuity of fellow eye 20/200 or better
2. No secondary or neovascular glaucoma in eye with choroidal melanoma
3. Tumor not contiguous to optic disc. If tumor border within 2 mm of optic disc, tumor subtended no more than 90-degree sector
4. Tumor not involved with either the iris or the anterior chamber angle
5. Ocular media of sufficient clarity to permit accurate observation of tumor

basic demographic information (age, gender, race or ethnicity) and tumor dimensions for all cases of choroidal melanoma examined during the period of patient accrual, regardless of tumor size, eligibility for the COMS, or willingness of eligible patients to enroll in the COMS.

Random assignment to treatment, oversight of data collection, data management, and data analysis were assigned to the COMS Coordinating Center in Baltimore, Maryland. This center also had major responsibility for monitoring the quality of data provided by the participating centers. Other centers with major quality assurance and monitoring responsibilities included an Echography Center (in Mars Hill, North Carolina; initially in Miami, Florida), where tumor height was measured independently from photoechograms, a Photograph Reading Center (in Iowa City), where tumor characteristics at baseline and postirradiation changes in the posterior retina during follow-up were assessed and recorded, a Pathology Center (in Madison, Wisconsin; initially in Boston), where tumor size and diagnosis were confirmed from all eyes enucleated, and the Radiological Physics Center in Houston, Texas, where adherence to the radiotherapy protocols was monitored. Overall leadership responsibility for the COMS Group was vested in the COMS Chairman's Office (in Philadelphia; initially in Baltimore).

An independent Data and Safety Monitoring Committee, appointed by the Director of the National Eye Institute, was the only group with access to outcome data from the randomized clinical trials by treatment arm until this committee judged that the objective of an individual trial had been met. This group had responsibility for ensuring that COMS trials were conducted in a scientifically valid and ethically sound manner. Scientific leadership of the COMS was provided by the Executive Committee, whose members include representatives of both the resource centers and the participating clinical centers. Three ophthalmic pathologists comprised the Pathology Review Committee who reviewed every enucleated eye from COMS patients to determine whether the clinical diagnosis of choroidal melanoma was correct. Mechanisms for quality assurance and monitoring were developed by the Quality Assurance Committee, which oversaw all aspects of data collection and protocol adherence. Classification of causes of death was the responsibility of the Mortality Coding Committee, whose members did not have responsibility for medical care of COMS patients.

CURRENT STATUS OF THE COMS

Accrual of patients to the randomized trial of pre-enucleation radiation (PERT) of large choroidal melanoma began in November 1986 and ended in December 1994, with 1003 patients enrolled. Scheduled clinical follow-up of all surviving patients for vital status, incidence of metastasis and second cancers, and complications continued until July 31, 2000. Initial mortality findings and related information that emphasized 5-year outcomes were published in 1998[14–16]; mortality findings through 10 years and prognostic factors have also been published.[17]

Accrual of patients to the randomized trial of I-125 brachytherapy for medium choroidal melanoma began in January 1987 and ended in July 1998, with 1317 patients enrolled. Scheduled clinical follow-up of all surviving patients, for clinical and vital status and for quality of life, continued until July 31, 2003, and October 31, 2003, respectively. Initial mortality findings,[18] complications,[19,20] and related information[21] have been published.

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Patient accrual to the nonrandomized study for small choroidal melanoma began in 1987 and ended in 1989, with 204 patients enrolled. Annual follow-up examinations were halted in 1991 as a result of funding constraints. Vital status and treatment status were reassessed in 1993 through 1994, and again in 1995 through 1996, for all patients who had not been lost to follow-up. Findings from this study have been published.[23,24]

FINDINGS FROM THE COMS TRIAL OF PRE-ENUCLEATION RADIATION FOR LARGE CHOROIDAL MELANOMA

Participants

From November 1986 through December 1994, COMS investigators reported 6078 patients with choroidal melanoma. Of these, 1860 had tumors classified as large by COMS criteria (see Table 44-1 for definitions used). Of those classified as large, 1302 were judged eligible for enrollment; 1003 gave signed consent and enrolled. The two treatment arms were well-balanced with respect to most of the many characteristics of patients, eyes, and tumors considered.[15] Adherence to the COMS protocol was excellent, as was diagnostic accuracy.[15,24] Only nine patients, three assigned to standard enucleation and six assigned to pre-enucleation radiation, were not treated as assigned at time of enrollment.

Survival estimates

By July 31, 1997, the vital status at 3 years after enrollment was available for all but 26 patients, who had enrolled during the last few months of patient accrual. The 5-year vital status was known for 801 (80%) of all patients enrolled; 238 patients assigned to enucleation alone (47%) and 219 patients assigned to pre-enucleation radiation (44%) were known to have died. The estimated 5-year cumulative survival rates and 95% confidence intervals (CIs) were 57% (95% CI: 52% to 62%) for patients assigned to enucleation alone and 62% (95% CI: 57% to 66%) for patients assigned to pre-enucleation radiation. Neither 5-year survival rates nor survival rates over the first 8 years after enrollment differed between treatment arms, to either a statistically or clinically significant degree. Mortality by treatment arm and by time since enrollment when clinical follow-up ended in July 2000 is summarized in Fig. 44-1. Among baseline characteristics of the patients, eyes, and tumors evaluated for their potential as prognostic factors, only patient age at time of treatment and longest tumor basal diameter had statistically significant effects on the length of overall survival.[17] Among patients assigned to enucleation alone, 130 (26%) had died with histologically confirmed metastatic melanoma, compared with 139 (28%) patients assigned to pre-enucleation radiation, based on review of 435 of the 457 deaths by the Mortality Coding Committee.[25] Time to death with histologically confirmed metastatic melanoma is displayed in Fig. 44-2. The liver was the most common site of melanoma metastasis.[26]

Complications

Only 17 patients treated with enucleation alone and 19 patients treated with pre-enucleation radiation had any surgical or anesthetic complication reported at the time of initial treatment.[16]

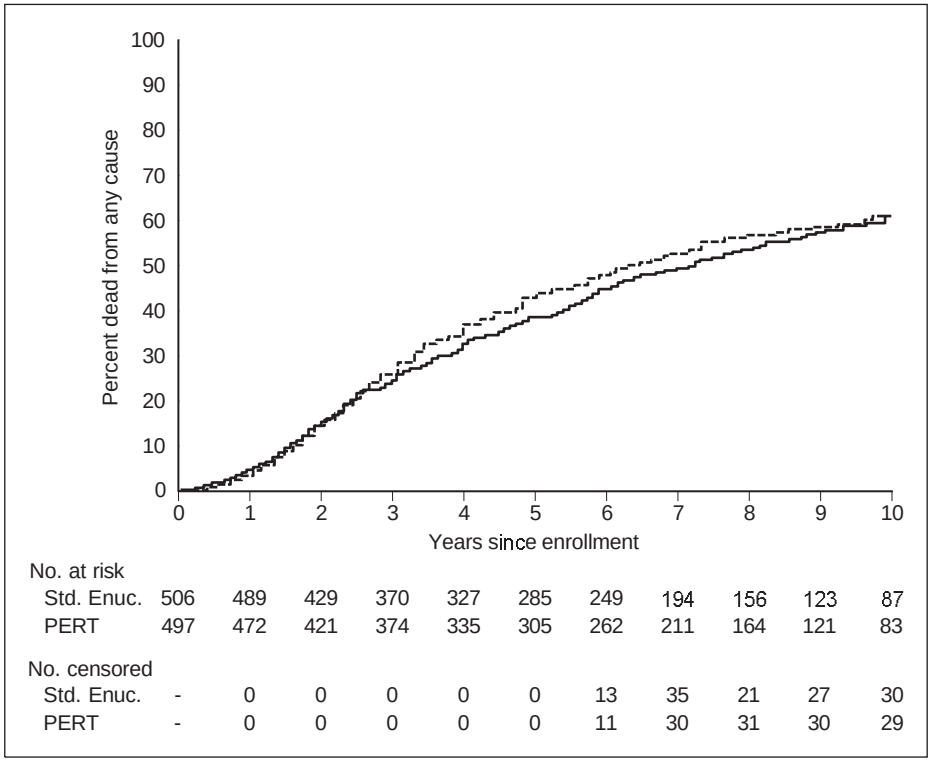

Fig. 44-1 The cumulative percentage of patients in the COMS trial of pre-enucleation radiation (PERT) for large choroidal melanoma who had died by specified times after enrollment. Blue line: patients assigned to PERT. Red line: patients assigned to enucleation alone. The numbers of patients at risk of death and numbers censored, based on date of enrollment, are given at annual anniversaries of enrollment by treatment assignment. Event is death from any cause. (Adapted from Collaborative Ocular Melanoma Study Group. Am J Ophthalmol 2004; 138:936–957.)

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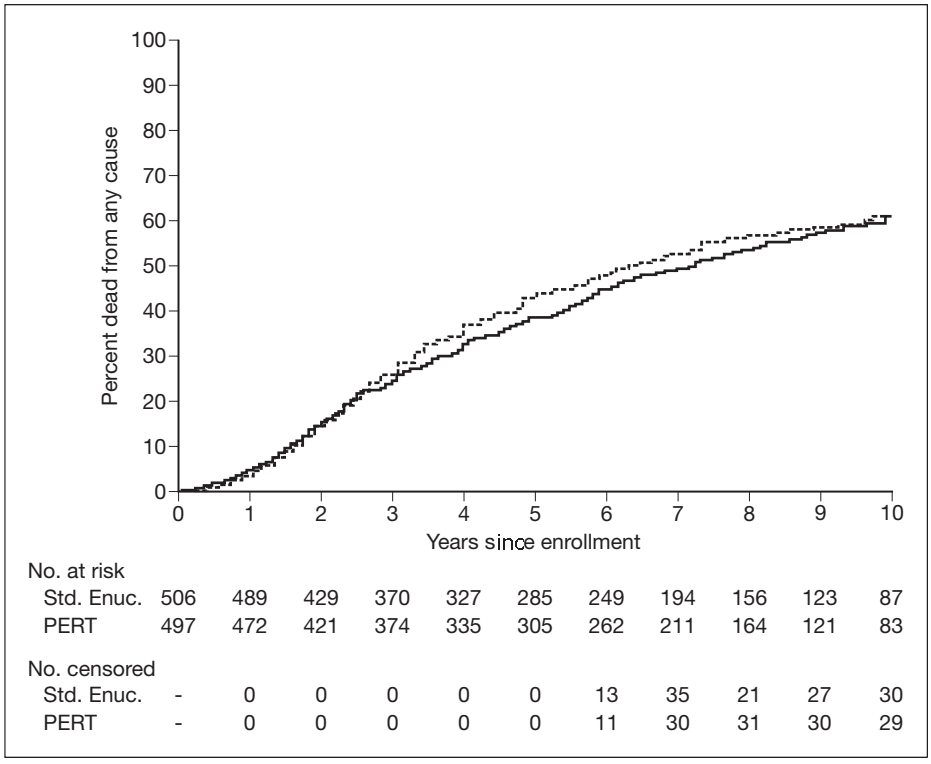

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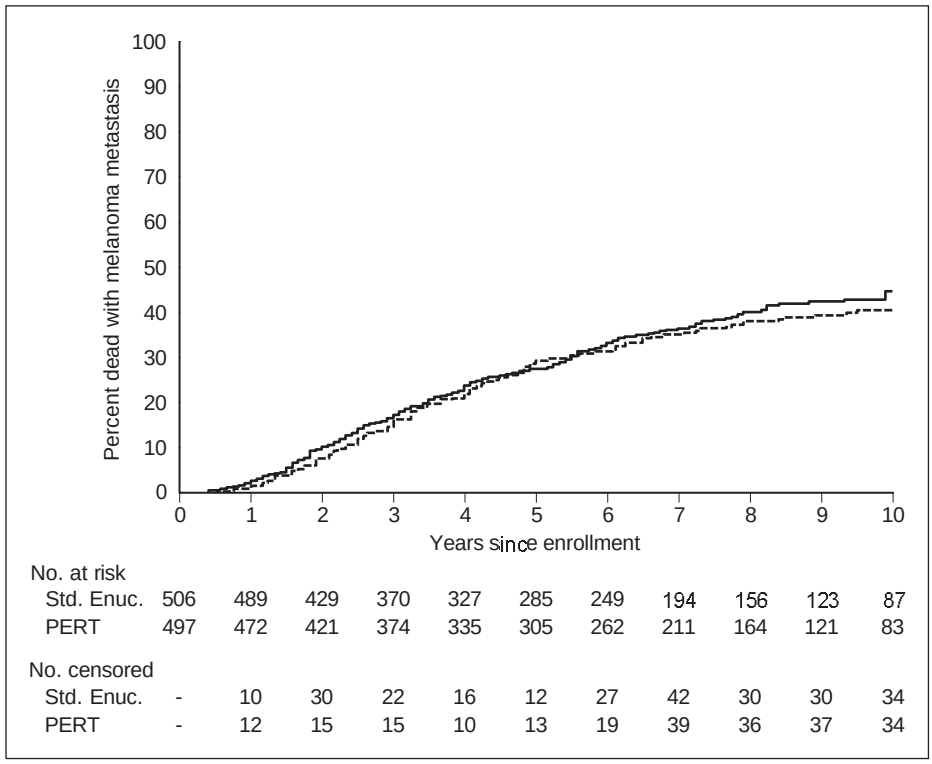

Fig. 44-2 The cumulative percentage of patients in the COMS randomized trial of PERT who had died with metastatic melanoma by the specified times since enrollment. Blue line: patients assigned to PERT; Red line: patients assigned to enucleation alone. The numbers of patients at risk of death and numbers censored based on date of enrollment, are given at annual anniversaries of enrollment by random treatment assignment. Event is death with histologically confirmed metastatic melanoma. (Modified from Collaborative Ocular Melanoma Study Group. Am J Ophthalmol 2004; 138:936–957.)

Orbital tumor recurrence was reported during the first 5 years of follow-up for six patients treated with enucleation alone and for one patient treated with pre-enucleation radiation; patients treated with enucleation alone had nearly twice the 5-year incidence of severe ptosis as reported for patients treated with pre-enucleation radiation.[16]

FINDINGS FROM THE COMS TRIAL OF I-125 BRACHYTHERAPY FOR MEDIUM CHOROIDAL MELANOMA

Participants

By July 1998, a total of 8712 patients with choroidal melanoma had been reported by COMS investigators; 5046 were classified as medium by COMS criteria (Table 44.1). Among 2882 patients eligible for the randomized trial of I-125 brachytherapy versus standard enucleation, 1317 patients gave signed consent, enrolled, and were assigned randomly to treatment arm: 660 to standard enucleation and 657 to I-125 brachytherapy. Treatment arms were well balanced; adherence to the COMS protocol was excellent.[21] All but 21 patients, seven in the brachytherapy arm and 14 in the enucleation arm, were treated promptly as assigned. Three patients assigned to brachytherapy crossed over to enucleation; seven enucleation patients crossed over to brachytherapy and two had proton beam radiation as the initial treatment.

Survival estimates

By September 30, 2000, all patients had been followed for vital status for 2 years or longer, with 1274 patients followed for 3 years or longer and 1072 patients eligible for 5 years of follow-up. Among patients in the enucleation arm, 188 (28%) were known to have died compared to 176 (27%) of those in the brachytherapy arm. Cumulative mortality by treatment arm and time since enrollment are summarized in Fig. 44-3. Estimated 5-year survival rates and 95% confidence intervals were 81% (95% CI: 77% to 84%) in the enucleation arm and 82% (95% CI: 79% to 85%) in the brachytherapy arm. Of the 364 decedents, 159 were judged to have had melanoma metastasis at time of death. Neither all-cause mortality rates nor rates of death with histopathologically confirmed melanoma metastasis (Fig. 44-4) differed between treatment arms. Adjustment of mortality rates for independent and statistically significant predictors of time to death (baseline age, tumor dimensions, tumor location, tumor shape, smoking history, and coexisting medical conditions) changed the estimated risk ratio from 0.93 (unadjusted; 95% CI: 0.76 to 1.14) to 0.99 (95% CI: 0.80 to 1.22).

Complications

As reported in 2002,[19] 69 of the 650 patients whose eyes were treated with brachytherapy had the eye enucleated during the first five years after initial treatment, yielding a 5-year rate of 12% (95% CI: 10% to 16%); local treatment failure was reported for 57 eyes in the same time period, with a 5-year cumulative rate of 10% (95% CI: 8% to 13%). Local treatment failure accounted for 39 of the 69 enucleations. Loss of visual acuity during the first three years after brachytherapy also has been reported.[20] The 3-year cumulative rate of loss of six or more lines of visual acuity from baseline was 49% (95% CI: 44% to 53%) and the 3-year cumulative rate of loss of visual acuity to 20/200 or worse was 43% (95% CI: 38% to 48%).

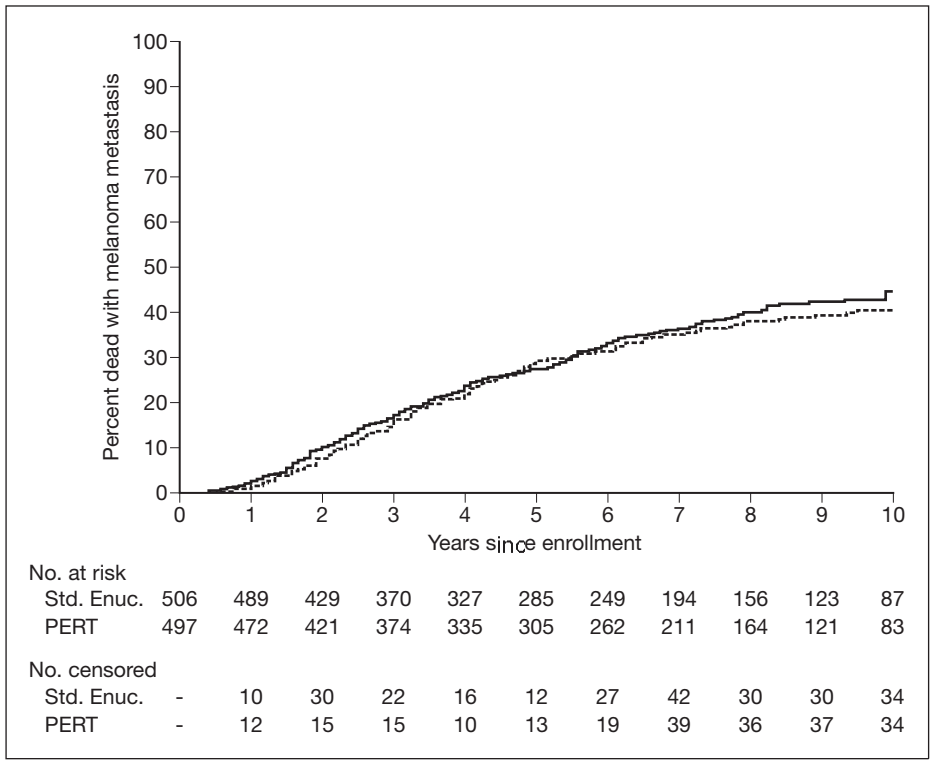

Fig. 44-2 The cumulative percentage of patients in the COMS randomized trial of PERT who had died with metastatic melanoma by the specified times since enrollment. Blue line: patients assigned to PERT; Red line: patients assigned to enucleation alone. The numbers of patients at risk of death and numbers censored based on date of enrollment, are given at annual anniversaries of enrollment by random treatment assignment. Event is death with histologically confirmed metastatic melanoma. (Modified from Collaborative Ocular Melanoma Study Group. Am J Ophthalmol 2004; 138:936–957.)

Orbital tumor recurrence was reported during the first 5 years of follow-up for six patients treated with enucleation alone and for one patient treated with pre-enucleation radiation; patients treated with enucleation alone had nearly twice the 5-year incidence of severe ptosis as reported for patients treated with pre-enucleation radiation.[16]

FINDINGS FROM THE COMS TRIAL OF I-125 BRACHYTHERAPY FOR MEDIUM CHOROIDAL MELANOMA

Participants

By July 1998, a total of 8712 patients with choroidal melanoma had been reported by COMS investigators; 5046 were classified as medium by COMS criteria (Table 44.1). Among 2882 patients eligible for the randomized trial of I-125 brachytherapy versus standard enucleation, 1317 patients gave signed consent, enrolled, and were assigned randomly to treatment arm: 660 to standard enucleation and 657 to I-125 brachytherapy. Treatment arms were well balanced; adherence to the COMS protocol was excellent.[21] All but 21 patients, seven in the brachytherapy arm and 14 in the enucleation arm, were treated promptly as assigned. Three patients assigned to brachytherapy crossed over to enucleation; seven enucleation patients crossed over to brachytherapy and two had proton beam radiation as the initial treatment.

Survival estimates

By September 30, 2000, all patients had been followed for vital status for 2 years or longer, with 1274 patients followed for 3 years or longer and 1072 patients eligible for 5 years of follow-up. Among patients in the enucleation arm, 188 (28%) were known to have died compared to 176 (27%) of those in the brachytherapy arm. Cumulative mortality by treatment arm and time since enrollment are summarized in Fig. 44-3. Estimated 5-year survival rates and 95% confidence intervals were 81% (95% CI: 77% to 84%) in the enucleation arm and 82% (95% CI: 79% to 85%) in the brachytherapy arm. Of the 364 decedents, 159 were judged to have had melanoma metastasis at time of death. Neither all-cause mortality rates nor rates of death with histopathologically confirmed melanoma metastasis (Fig. 44-4) differed between treatment arms. Adjustment of mortality rates for independent and statistically significant predictors of time to death (baseline age, tumor dimensions, tumor location, tumor shape, smoking history, and coexisting medical conditions) changed the estimated risk ratio from 0.93 (unadjusted; 95% CI: 0.76 to 1.14) to 0.99 (95% CI: 0.80 to 1.22).

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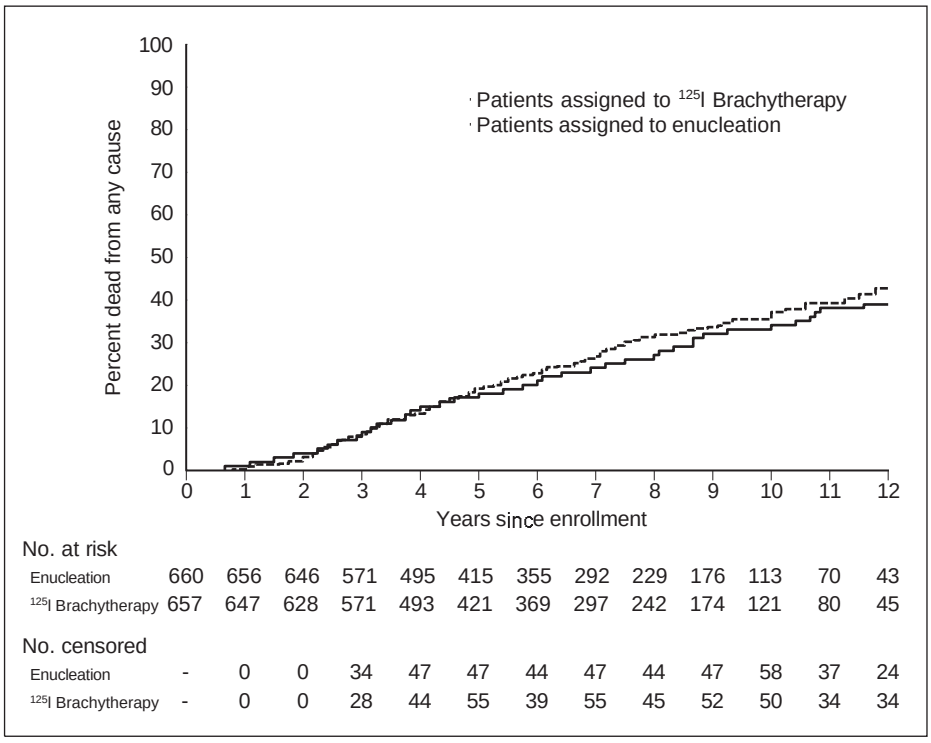

Fig. 44–3 The cumulative percentage of patients in the COMS trial of I-125 brachytherapy for medium choroidal melanoma who had died by specified times after enrollment. Blue line: patients assigned to brachytherapy. Red line: patients assigned to enucleation. The numbers of patients at risk of death and numbers censored, based on date of enrollment, are given at annual anniversaries of enrollment by treatment assignment. Event is death from any cause. (Reproduced from Collaborative Ocular Melanoma Study Group. Arch Ophthalmol 2001; 119:969–982. Copyright © (2001) American Medical Association. All rights reserved.)

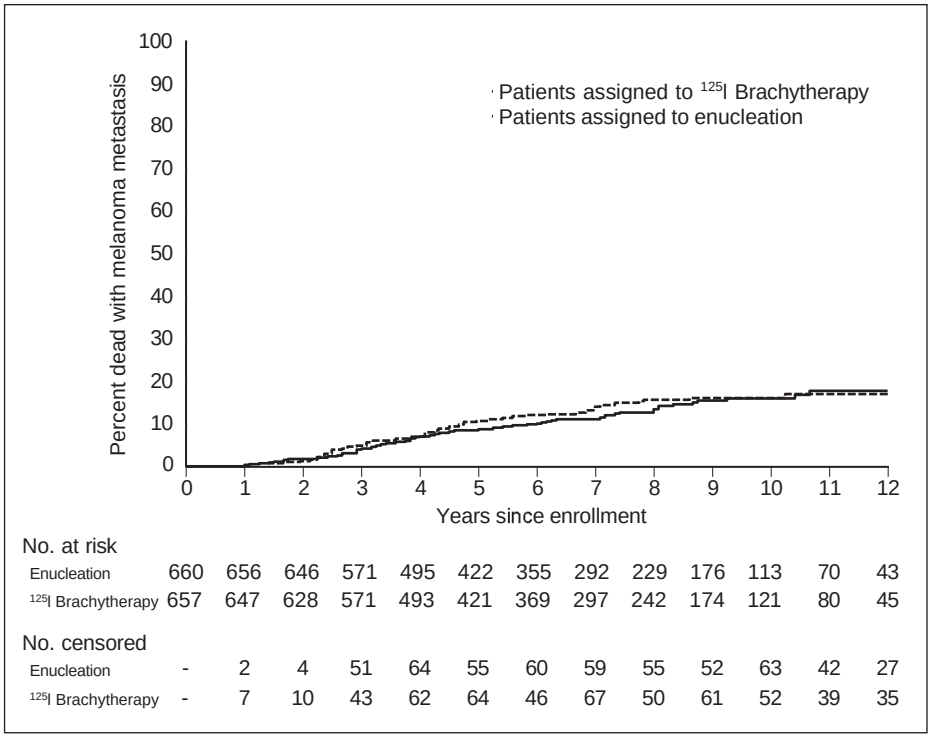

Fig. 44-4 The cumulative percentage of patients in the COMS randomized trial of I-125 brachytherapy who had died with metastatic melanoma by the specified times after enrollment. Blue line: patients assigned to brachytherapy. Red line: patients assigned to enucleation. The numbers of patients at risk of death and numbers censored, based on date of enrollment, are given at annual anniversaries of enrollment by random treatment assignment. Event is death with histologically confirmed metastatic melanoma. (Reproduced from Collaborative Ocular Melanoma Study Group. Arch Ophthalmol 2001; 119:969–982. Copyright © (2001) American Medical Association. All rights reserved.)

FINDINGS FROM THE NONRANDOMIZED PROSPECTIVE STUDY OF SMALL CHOROIDAL MELANOMA

Of 300 patients with small choroidal melanoma (by COMS criteria) reported from December 1986 through August 1989, 220 were judged eligible for this COMS study; 204 gave signed consent and enrolled. The majority of the patients enrolled within 1 year of the initial diagnosis of choroidal melanoma.[23] No attempt was made to establish uniform criteria for treatment timing or to recommend the type of treatment. The patients and their ophthalmologists made these decisions.

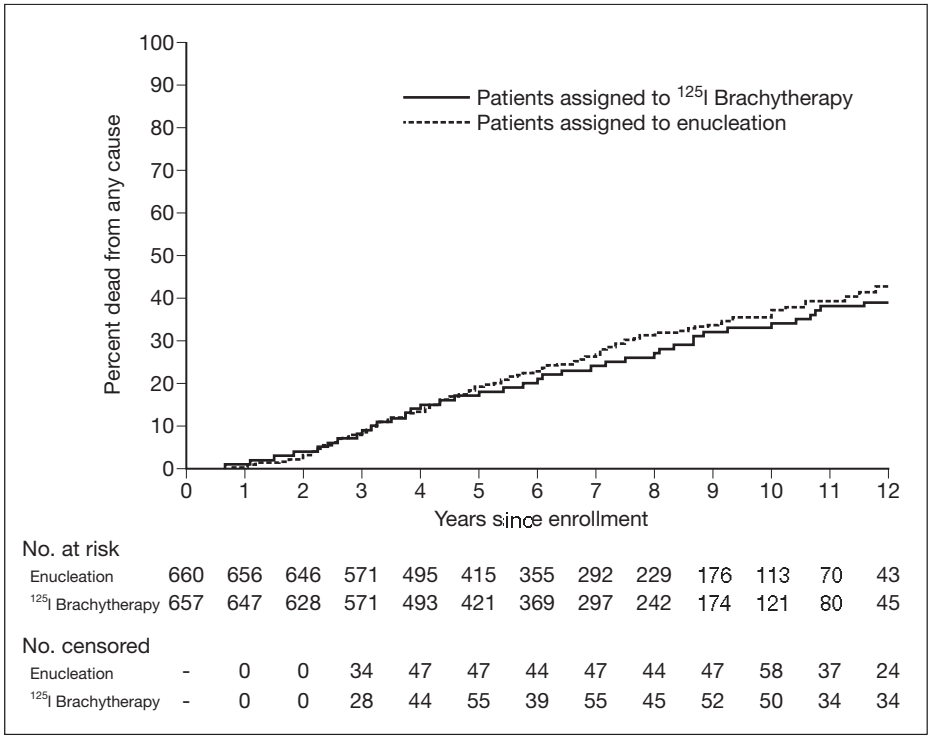

Fig. 44–3 The cumulative percentage of patients in the COMS trial of I-125 brachytherapy for medium choroidal melanoma who had died by specified times after enrollment. Blue line: patients assigned to brachytherapy. Red line: patients assigned to enucleation. The numbers of patients at risk of death and numbers censored, based on date of enrollment, are given at annual anniversaries of enrollment by treatment assignment. Event is death from any cause. (Reproduced from Collaborative Ocular Melanoma Study Group. Arch Ophthalmol 2001; 119:969–982. Copyright © (2001) American Medical Association. All rights reserved.)

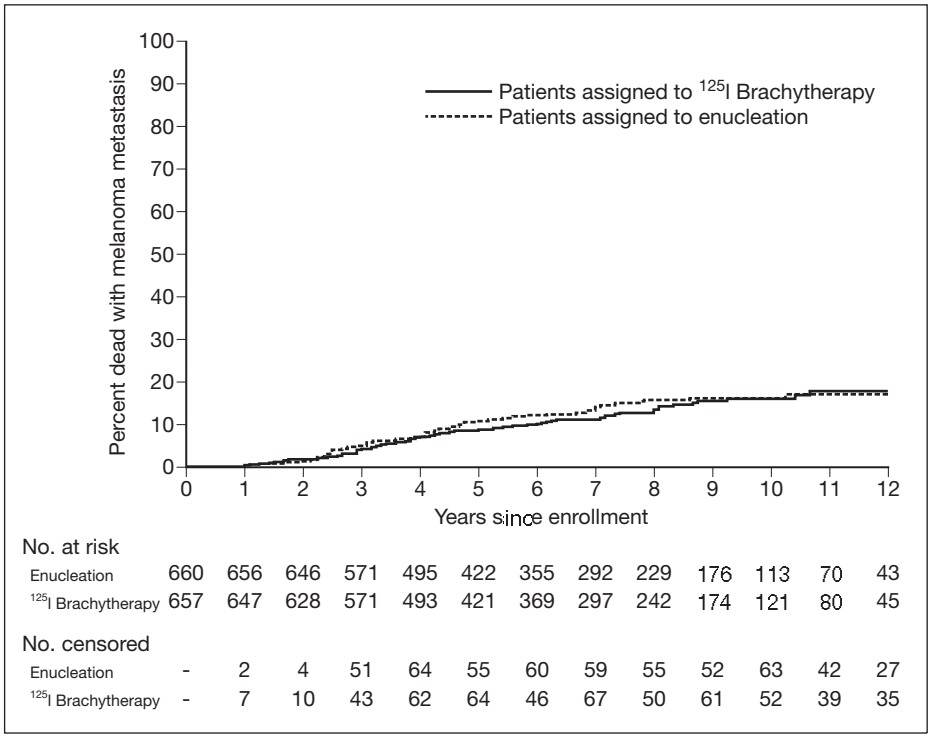

Fig. 44-4 The cumulative percentage of patients in the COMS randomized trial of I-125 brachytherapy who had died with metastatic melanoma by the specified times after enrollment. Blue line: patients assigned to brachytherapy. Red line: patients assigned to enucleation. The numbers of patients at risk of death and numbers censored, based on date of enrollment, are given at annual anniversaries of enrollment by random treatment assignment. Event is death with histologically confirmed metastatic melanoma. (Reproduced from Collaborative Ocular Melanoma Study Group. Arch Ophthalmol 2001; 119:969–982. Copyright © (2001) American Medical Association. All rights reserved.)

FINDINGS FROM THE NONRANDOMIZED PROSPECTIVE STUDY OF SMALL CHOROIDAL MELANOMA

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Sixteen patients were treated shortly after enrollment; 20 additional patients were treated after the melanoma grew to medium or large size (COMS criteria) and the patients were enrolled in one of the COMS randomized trials. As of June 1996, an additional 47 patients had been treated during follow-up.[22,23]

By June 30, 1996, 27 patients had died. Survival findings are summarized in Fig. 44-5. The estimated 5-year all-cause mortality rate was 6% (95% CI: 3% to 9%).[23] Of 188 patients who were not treated at time of enrollment, 44 had tumors that had grown to medium or large size by February 1997, based on COMS criteria. The estimated 5-year proportion of initially small tumors that grew was 31% (95% CI: 23% to 39%).[22] No further follow-up of this group of patients is anticipated.

HISTOPATHOLOGIC FINDINGS IN ENUCLEATED EYES

The COMS Group has one of the highest rates of diagnostic accuracy ever documented.[24,27] Of 1532 eyes enucleated in the COMS by June 1996, 994 from patients enrolled in the randomized trial for large choroidal melanoma and 536 from patients enrolled in the trial for medium choroidal melanoma, 1527 (99.7%) were confirmed histopathologically by the Pathology Review Committee to harbor choroidal melanoma.[27] A detailed description of the characteristics of the 1527 confirmed cases has been published.[27] Key findings include documentation of local tumor invasion: rupture of Bruch's membrane in 88% of eyes, invasion of emissary canals in 55%, retinal invasion in 49%, tumor cells in the vitreous in 25%, invasion of tumor vessels in 14%, and vortex vein invasion in 22% of eyes with vortex veins. Scleral invasion was present in 56% of eyes and extrascleral extension in 8%. Histopathologic review confirmed that pre-enucleation radiation significantly reduced mitotic activity.[15]

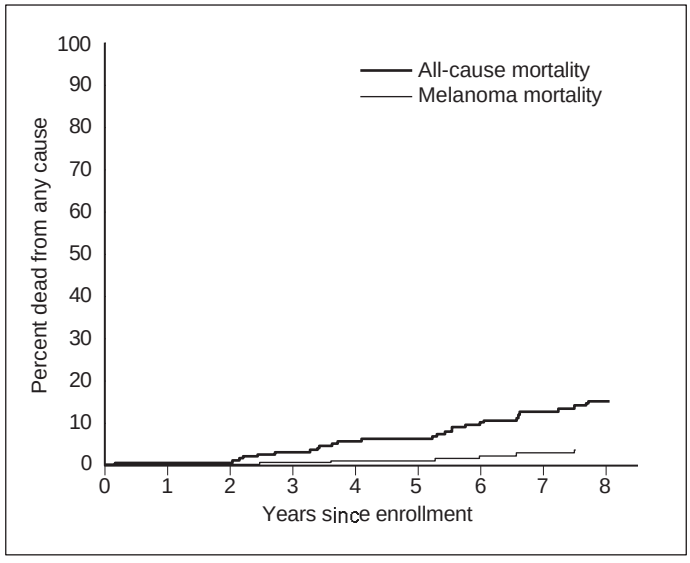

Fig. 44-5 Cumulative percentage of patients in the COMS nonrandomized, prospective study of small choroidal melanoma who had died by the specified times since enrollment. Thick line: death from any cause. Thin line: death from metastatic melanoma. (Reproduced from Collaborative Ocular Melanoma Study Group. Arch Ophthalmol 1997; 115:1537–1544. Copyright © (1997) American Medical Association. All rights reserved.)

In other published histopathologic investigations of enucleated eyes of COMS patients, silver-stained nucleolar organizer region scores have been evaluated as predictors of later metastasis, transillumination and histologic measurements of tumor dimensions have been compared,[28] and a clear cell variant of choroidal melanoma has been identified.[29] Other investigations of this unique tissue bank are nearing completion.

OTHER PUBLISHED FINDINGS

The multicenter organization of the COMS has facilitated referral to a COMS clinical center of cases of choroidal melanoma from most of the United States and from a large part of eastern Canada. The large number of patients screened for the COMS and judged to have choroidal melanoma (totaling 8712 as of July 31, 1998, when accrual halted) provide the largest group of patients with this diagnosis for whom data have been collected systematically at time of presentation in accord with a common protocol. Trends in size of choroidal melanoma and treatments over time have been published.[30] The COMS Group has reported the only published cases of choroidal melanoma in Native Americans.[31] This large database permits comparison of tumor characteristics at time of screening and diagnosis among different racial subgroups. This information may provide clues for future investigation in epidemiologic and genetic studies of choroidal melanoma.

The COMS Group also has published information on surgical and postsurgical complications among the largest group of patients whose eyes have been enucleated because of choroidal melanoma and who have been examined in accord with a common follow-up protocol,[16] documenting the low rates of serious complications following enucleation for this condition. Comparisons of tumor dimensions measured clinically, echographically, and histopathologically have been published.[28] The importance of liver function tests and other tests for metastasis have been evaluated; those findings have been published in the oncology literature. Also, 10-year changes in fellow eyes of patients enrolled in COMS randomized trials have been reported.[32] In addition to publications from the COMS Group that have important clinical information, several articles have been published that deal with research methodology.

SUMMARY

The COMS Group successfully enrolled sufficient numbers of eligible patients with choroidal melanoma so that valid comparisons between treatments could be made for mortality and other important clinical outcomes and, in the case of the trial for medium tumors, also on important patient-centered ("quality of life") outcomes. Major findings already have been published; others are expected to be published during the next few years.