Following enucleation. Also, although of lesser concern with radiotherapy for many such tumors. The dilemma was exacerbating life. However, because of the retrospective nature of the comparisons and differences in the characteristics of patients and tumors selected for 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 studies 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.

**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 possibilities remaining uncertain regarding the best course for their patients.

**The Investigators’ Perspective on the Collaborative Ocular Melanoma Study**

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sibly being large nevi. Furthermore, neither enucleation nor eye-conserving radiotherapy was deemed acceptable for these small lesions. Thus, design of a randomized trial for small choroidal melanoma was tabled.

The primary trial of interest was designed to compare enucleation with eye-conserving radiotherapy for a majority of patients with ocular melanoma defined to be medium-sized who would be suitable candidates for either treatment. Brachytherapy was selected for the radiotherapy arm in this trial because of the small number of facilities equipped to deliver charged particles. The second randomized trial was designed to evaluate radiotherapy as an adjunct to enucleation with the goal of improving the survival rate among patients with large choroidal melanoma for whom most ophthalmologists would recommend enucleation. An observational study of small melanoma was designed with the goal of determining how such tumors were being managed, the number available for enrollment in a clinical trial, and survival rates with the goal of later designing and initiating a randomized trial of the most frequently used management approaches.

A review and meta-analysis of the published literature suggested that the 5-year mortality rate among patients treated with enucleation was 30% when the tumor was medium-sized, 50% when the tumor was large, and 15% when the tumor was small. With 2 treatment arms in each of the clinical trials and the goal of excellent statistical power to detect or rule out a relative treatment difference of 25% with high probability, sample sizes of 2400 and 1000, respectively, were projected for a trial of brachytherapy vs enucleation for medium-sized tumors and a trial of preenucleation external beam irradiation vs enucleation alone for large tumors. A decision was made to focus the clinical trials on choroidal melanoma because of the worse prognosis for anteriorly located uveal melanoma. Because uveal melanoma is a relatively rare primary cancer, with only 6 to 8 cases per million population per year diagnosed in the United States, it was recognized that a large number of participating clinical centers would be required and that it would be necessary to modify referral patterns to the major radiotherapy centers that had been established during the previous decade. Furthermore, with 5-year mortality as the projected outcome of primary interest, patients would have to be followed up for at least 5 years, requiring a long-term study to recruit and follow up a sufficient number of patients.

OTHER ISSUES AND DECISIONS

To permit the COMS steering committee and data and safety monitoring committee to monitor the feasibility of enrolling a sufficient number of patients in the COMS clinical trials within a reasonable period, the COMS design included reporting of basic data for each patient diagnosed with choroidal melanoma at a participating COMS center during the accrual period. As required by the COMS protocol, detailed baseline data were collected and reported for enrolling patients. In addition, a small number of demographic data items and tumor dimensions and location were reported for both patients judged by the local COMS ophthalmologist to be ineligible for a COMS trial and patients judged to be eligible but who did not enroll. Reasons for ineligibility or not enrolling were reported, as appropriate, along with the treatment selected for each of these patients.

Review of the information provided for all patients with choroidal melanoma permitted evaluation of the effect of individual eligibility and exclusion criteria on patient accrual and consideration of aspects of the protocol that could be modified to increase participation. As noted earlier, a major goal of the trial of brachytherapy vs enucleation was to include a majority of patients diagnosed with choroidal melanoma. In 1991, it became apparent that many otherwise eligible patients with tumors smaller than the lower-height criterion and larger than the upper-height criterion originally adopted for this trial were being treated with brachytherapy and enucleation outside the COMS. After discussing the ramifications of expanding the size criteria with the data and safety monitoring committee and the study investigators, the criteria were modified to be more inclusive.

Investigators at the Radiological Physics Center (Houston, Texas), who were providing expertise to a number of radiotherapy trials in cancer, and an experienced radiation oncologist collaborated with the participating ophthalmologists to design a standard brachytherapy protocol that could be implemented at many institutions and monitored centrally. The brachytherapy protocol adopted for the COMS included delivery of radiation by means of a gold-shielded episcleral plaque with a Silastic insert in which iodine 125 (125I) seeds were embedded. The plaques were designed to be reused by replacing the Silastic insert and radioactive pellets so as to achieve the protocol radiation dose to the prescription point and prescribed dose rate for each tumor. The plaques were provided in 5 sizes to accommodate a range of tumor diameters. A detailed protocol for dosimetry, verification of 125I seed activity, training of radiation physicists, and other aspects of brachytherapy administration was developed and implemented. This protocol was part of the detailed COMS Manual of Procedures in which protocols for other procedures for screening, enrollment, treatment, and follow-up were included.

A quality assurance committee was established to coordinate training of all study personnel in the procedures required by individual study roles and to oversee adherence to the COMS protocols. Members of this committee visited each clinical center prior to approval to initiate enrollment of patients in the COMS and periodically thereafter. The quality assurance committee adopted early on procedures for documenting that each member of the COMS team at each clinical center, including the ophthalmologists and oncologists, had the experience, training, knowledge, facilities, and ability to perform the assigned study role. Initially, the Radiological Physics Center investigators waived such requirements for the participating radiation physicists. However, after observing the process for other COMS team members, they recommended similar procedures for the radiation physicists.

Other quality assurance mechanisms implemented in the COMS included central review of eligibility by personnel at the COMS Coordinating Center (Baltimore, Maryland) before a random treatment assignment was made for each patient enrolled; central review of echograms and pho-
SUMMARY OF STUDY QUALITY AND PRIMARY OUTCOME FINDINGS

As is well known, the COMS was funded by the National Eye Institute and conducted at more than 50 institutions. Accrual to the trial of $^{125}$I brachytherapy vs enucleation ("medium-tumor trial") began in January 1987 and ended in July 1998 at the recommendation of the data and safety monitoring committee. Accrual to the trial of preenucleation irradiation vs enucleation alone ("large-tumor trial") began in November 1986 and ended in December 1994 when the target sample size was achieved. The result of the quality assurance methods adopted was a very high-quality study in which:

- Few randomized patients were found to be ineligible after enrollment: 7 of 1003 enrollees in the large-tumor trial, and 12 of 1317 enrollees in the medium-tumor trial (ie, <1%).
- Almost all patients received the assigned treatment within 4 weeks after enrollment: 99% in the large-tumor trial, and 98% in the medium-tumor trial.
- Follow-up for mortality and clinical outcomes was excellent (>99%); vital status known 5 years after enrollment for 998 of 1003 large-tumor trial enrollees and 1313 of 1317 medium-tumor enrollees.
- Adherence to the radiotherapy protocols was exceptionally good: 93% of patients treated with preenucleation irradiation in the large-tumor trial and 91% of patients treated with $^{125}$I brachytherapy in the medium-tumor trial received radiotherapy "per protocol."
- Both trials were completed successfully.

In 1997, the COMS data and safety monitoring committee approved publication of interim mortality findings from the trial for large tumors. In 2001, that committee also approved publication of interim mortality findings from the trial for medium-sized tumors. In both clinical trials, survival rates were essentially equivalent in the 2 treatment arms, with neither a clinically nor statistically significant difference in mortality at any time after enrollment and treatment. Thus, the issue of whether enucleation or eye-conserving radiotherapy led to earlier death than the alternative treatment was resolved for patients with medium-sized choroidal melanoma, assuming that they met COMS eligibility criteria and were treated and followed up clinically as in the COMS. Quality-of-life findings also revealed little difference between enucleation and $^{125}$I brachytherapy over 5 years. Thus, patients who prefer to have the cancer removed from their bodies even though removal means losing the affected eyes and those who prefer to retain their eyes despite the likelihood of loss of vision can choose their treatments without fear that they would have a longer or better life with the other treatment. However, the COMS investigators were disappointed that, among patients with large choroidal melanoma, preenucleation irradiation did not reduce mortality compared with enucleation alone, suggesting that clinically undetectable metastasis at the time of diagnosis was responsible for many deaths of patients with large choroidal melanoma.

EFFECT ON CLINICAL PRACTICE

A major outcome of the COMS was that radiotherapy delivered in a standard fashion became available at multiple locations convenient for most patients diagnosed with choroidal melanoma as a result of the standard design of the reusable gold-shielded plaques and the standard brachytherapy protocol developed for the COMS. In addition to the institutions and practices that participated in the study, COMS procedures for $^{125}$I brachytherapy have been adopted by many institutions and practices worldwide. Standardization was particularly important because a majority of patients with choroidal melanoma judged to be medium-sized by COMS criteria are believed to be treated with $^{125}$I brachytherapy at the present time. On the other hand, few patients with large choroidal melanoma now undergo the expense and inconvenience of preenucleation irradiation as a result of the COMS.

However, the most significant result of the COMS may be that 5-year mortality rates among COMS patients in both trials were 10% lower than were estimated from published data when the COMS was designed. Although COMS findings are believed to be generalizable to patients with choroidal melanoma who satisfy COMS eligibility criteria, those criteria excluded patients with clinically detectable melanoma metastasis and most other primary cancers as well as those with other life-threatening conditions. The COMS criteria also incorporated carefully defined specifications regarding tumor size and location and central review of the diagnosis and tumor height as well as central monitoring of radiotherapy protocol adherence. Patients whose tumors were contiguous with or very close to the optic disc were excluded from the trial for medium-sized tumors as a consequence of the decision to adopt a radioactive plaque to deliver radiation. Other methods of delivering eye-conserving radiotherapy to that subgroup of patients may yield results similar to those from the COMS trial but have not been evaluated in randomized trials with respect to their effects on long-term survival.

IMPLICATIONS FOR FUTURE RESEARCH

Clearly, better methods of detecting metastases at the time of diagnosis of choroidal melanoma are needed. Furthermore, effective treatments for metastasis from choroidal melanoma are needed. Several investigators are pursuing research in these areas. Epidemiologists have investigated a number of potential risk factors for choroidal melanoma with the goal of identifying those that may be modifiable. These investigations are difficult because of the rarity of the condition in the population, requiring...
that they be conducted at centers where a sufficiently large number of patients with choroidal melanoma are diagnosed and treated but resulting in the potential for selection bias. It is not feasible to follow up large samples from the population prospectively to evaluate predictors of choroidal (or uveal) melanoma.

Other issues in the management of uveal melanoma remain and suggest possible multicenter randomized trials that would provide useful information to physicians and patients (eg, a trial of enucleation alone vs enucleation and adjuvant chemotherapy for large [high-risk] uveal melanoma, a trial of early vs deferred eye-conserving radiotherapy of small suspected choroidal melanoma, and a trial of charged particle irradiation of peripapillary medium-sized choroidal melanoma). However, patients with uveal melanoma compose a very small fraction of all cancer cases. As a cause of vision loss, these ocular tumors are overshadowed by other more prevalent ocular conditions. Thus, it is difficult to identify sponsors of research who have large enough budgets that a portion can be devoted to uveal melanoma.

CONCLUSIONS

The COMS arguably was the most challenging of the multicenter clinical trials sponsored by the National Eye Institute since the Diabetic Retinopathy Study. Nevertheless, the multidisciplinary collaboration required to conduct the COMS was exemplary. The primary questions addressed by the study were answered with data of good quality. More than 30 articles from the COMS Group have been published in peer-reviewed journals to report primary and secondary outcomes and to evaluate methods used in the COMS. Many ancillary studies were conducted; publication of their findings also has contributed to the methods of randomized trials and the epidemiology and treatment of choroidal melanoma. More than 20 years after its initiation in a climate of controversy, an objective observer must conclude that the COMS was a success.

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Trial Registration: clinicaltrials.gov Identifier NCT00000124.

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