

Collaborative Ocular Melanoma Study (1986-1998)

Purpose

- Primary research questions:
 - To evaluate therapeutic interventions for patients who have choroidal melanoma and to assess the potential life-preserving as well as sight-preserving role of radiation therapy.
 - To determine which of two standard treatments, removal of the eye or brachytherapy, is more likely to prolong survival of eligible patients with medium-sized choroidal melanoma.
 - To determine whether preoperative radiation prolongs life for patients whose eyes with large choroidal melanoma are enucleated.
- Primary outcomes:
 - All-cause and tumor-related mortality
- Perceived clinical importance:
 - Little was known about the difference in patient survival between enucleation (removal of the eye) versus radiation therapy as treatments for choroidal melanoma.

Background and Context (1-3)

- Choroidal melanoma is the most common primary eye cancer affecting adults. In the United States, 1500 new cases are reported yearly. There is a 10%-30% 5-year mortality rate due to systemic metastasis, varying by tumor size.
- Enucleation (removal of the eye) has been the standard treatment for choroidal melanoma for over 100 years.
- In 1978, evidence suggested that enucleation increased the risk of tumor metastasis.
- In 1980s, radiation therapy was becoming the alternative treatment that could potentially preserve the eye and retain some vision.
- Data on patient survival comparing enucleation or radiation was limited at the time and in light of the suggestive evidence that enucleation might increase mortality, meetings commenced between ophthalmologists and oncologists to initiate a

prospective multicenter clinical trial to assess the overall mortality difference between the two treatments at the National Eye Institute in 1983.

- In 1985, the Collaborative Ocular Melanoma Study (COMS) was established. COMS consisted of two multi-center randomized, controlled clinical trials. It was the first set of RCTs implemented in order to compare enucleation and radiation with respect to relative success in prolonging survival of choroidal melanoma (medium & large-size) patients.
 - Two RCT trials within COMS
 - Medium Tumor Trial
 - Large Tumor Trial
- Main issues surrounding the merits of COMS at the time (4), included:
 - Financial justification for COMS: Choroidal melanoma was not a national problem.
 - Clinical relevance: Observational data suggested no difference in mortality rate due to enucleation versus radiation therapy. Evidence suggested that no significant difference in mortality would be found between the two treatments compared.
 - Ethical issue: Leading ocular oncologists questioned the ethics of the study design: removal of eyes with medium-size melanomas and 20/20 vision acuity.

Date and Place Conducted:

- Multi-center randomized controlled trials
- Locations: United States & Canada
 - 43 clinical centers in major population areas
- Recruitment:
 - Medium Tumor Trial: Nov. 1986 to July 1998
 - Large Tumor Trial: Nov. 1986 to Dec. 1994

Principal Investigators:

- Collaborative Ocular Melanoma Group
- Stuart L. Fine, MD (Chairman); Barbara S. Hawkins, Ph.D. (Director)

Sponsored by/source of funding:

- Supported by the National Cancer Institute and the National Eye Institute, National Institutes of Health, Bethesda, MD.

Size and Design:

- *Design:* Two multicenter randomized clinical trials:
 - Medium Tumor Trial (N=1,317)

"The Randomized Trial of I-125 Brachytherapy for Medium Choroidal Melanoma"

- Medium-size tumor: 3mm ≤ apical height < 8mm
- Patients with medium-size tumors were randomized to enucleation or radiotherapy (I-125)

- Large Tumor Trial (N=1,003)

"The Randomized Trial of Pre-Enucleation Radiation for Large Choroidal Melanoma"

- Large-size tumor: apical height of ≥ 8mm
- Patients with large tumors were randomized to enucleation alone or to enucleation preceded by irradiation (pre-enucleation with radiation)

- All randomized patients followed for 5-15 years or until death
- The Mortality Coding Committee: to ensure accurate assessment the cause of death in each case to judge whether or not this was related to underlying choroidal melanoma.
- The Data and Safety Monitoring Committee: an independent group that monitored the progress of the trial, recommended continuation or discontinuation of accrual and follow-up, and approved release of data when appropriate.
- *Eligibility:* Men and women eligible for the study had to be 21 or older, have primary choroidal melanoma in only one eye, and have no evidence of metastatic disease. Patients must have best-corrected visual acuity in the fellow eye of 20/200 or better. Required accurate estimation of tumor thickness by echography. Informed consent obtained from all participants.
- *Exclusion:* Patients with tumors adjacent of the optic disc, predominantly ciliary body melanoma, and additional primary cancer
- *Statistical analysis:*
 - Intent-to-treat analysis strategy employed: All patients were analyzed with the treatment arm to which they were assigned randomly at time of enrollment, regardless of subsequent findings or treatment received.
 - Product-limit method of Kaplan and Meier was used to estimate time to death.
 - Cox proportional hazards model was used to analyze time to death, adjust for baseline covariates.

Results:

- Medium Tumor Trial (2, 5):
 - Published in 2001, with 11½ -year accrual period
 - Mortality: All causes or deaths due to melanoma metastasis
 - Mortality rates did not differ between the enucleation arm (N=660) and radiation therapy arm (N=657).
 - Unadjusted estimated 5-year survival rates for enucleation vs. radiation was 81% and 82%, respectively (p = 0.48)
 - Considerably better than the projected 70% 5-year survival rate at the study's inception
 - Adjusted risk ratio for radiotherapy vs enucleation: 0.99 (95% CI: 0.80-1.22)
 - Adjusted 5-year mortality rate: 0.91 (95% CI: 0.66-1.24)
 - Visual loss occurred gradually in the radiotherapy arm compared to immediate visual loss in the enucleation arm (5).
 - 63% with visual acuity of $\geq 20/200$ by 3 years of treatment
 - 85% retained their eyes for ≥ 5 years
- Large Tumor Trial (6-8):
 - Published in 1998, with 5 year follow-up time (8)
 - Mortality rates did not differ between enucleation arm (N=506) and pre-enucleation radiation (N=497)
 - 5-year survival rates for enucleation vs. pre-enucleation with radiation was 57% and 62%, respectively (p = 0.32)
 - Adjusted 5-year mortality rates: 1.03 (95% CI: 0.85-1.25)
 - Fewer perioperative complications were reported for patients in the pre-enucleation radiation arm.
 - Published in 2004, with 10 year follow-up time (6)
 - Mortality rates did not differ between enucleation arm and pre-enucleation radiation arm. Confirmed previous report.
 - Adjusted 10-year all-cause mortality rates for enucleation arm and pre-enucleation radiation arm were 61% and 62%, respectively
 - Adjusted risk ratios for pre-enucleation radiation vs. enucleation were 0.91 (95% CI: 0.75-1.11) and 1.00 (95% CI: 0.85-1.18) for first 5-year after treatment and 10 follow-up period, respectively.

General Outcome:

- There is no survival advantage attributable to radiotherapy vs. enucleation (Medium Tumor Trial) or to pre-enucleation radiation vs. enucleation (Large Tumor Trial).
- Observed 5-year survival rates for enucleation treatment was considerably better than the projected survival rate in 1983 at the time COMS was implemented.
- Patients in the pre-nucleation radiation arm experienced fewer local complications.

Impact

- COMS represents a landmark study of large scale proportion for choroidal melanoma. The study was the first, and likely the last, of its kind to examine the survival benefit of radiotherapy against the standard enucleation treatment. Radiation therapy allows the preservation of the eye as well as possible vision, thus is attractive to patients afflicted with choroidal melanoma.
- COMS investigators relied on the recommendations of the COMS Data and Safety Monitoring Committee on the direction of the trial (e.g. continuation of accrual) and were not informed of mortality rates by treatment arm until March 2001.
- COMS garnered considerable controversies. Some ophthalmologists opposed to COMS and questioned the merits of conducting an expensive RCT (approximately \$62 million) on a rare disease that lacks national impact (4). Additionally, detractors of COMS questioned the study's ability to find significant differences between the treatment arms and implied that the outcome might have already been known. For those who believed the issue was already settled in favor of radiation, a study of enucleation was unethical.
- As the result of COMS, patients suffering medium-size choroidal melanoma might factor quality of life (preservation of the eye and some vision) more prominently in their decision.

Unresolved issues

- Findings from COMS revealed that there is no benefit or harm between enucleation and a) pre-enucleation radiation (for large-size tumor) and b) radiotherapy with I-125 brachytherapy (medium-size tumor).
- Questions remain on how to apply these findings to assist patients in their decision-making with regards to which treatment is best.
- The question of whether enucleation might alter the natural history course of choroidal melanoma remains unanswered (1).
- Some experts raised the question of why COMS was not stopped sooner given the earlier indications that there was no survival difference, particularly the randomization of medium-size tumor patients into enucleation or radiotherapy (4). Did the COMS' Data and Safety Monitoring Committee recommend the trial's continuation without carefully considering the null findings?

Summary

COMS was initiated to determine whether radiation therapy would prolong survival in patients with choroidal melanoma as well as enucleation, the standard treatment. Two trials were conducted simultaneously: a trial comparing treatments in medium size tumors and one in large tumors. In the medium size tumor trial, radiation therapy (I-125 brachytherapy) was as effective as enucleation in prolonging survival, while preserving some vision for five years in 85% of the patients. In the large tumor trial, there was no survival advantage for patients assigned to pre-enucleation radiation. The COMS study was controversial among ophthalmologists already convinced of radiation's advantage; the DSMB's policy of not communicating interim results to the investigators was criticized for similar reasons. For others, COMS demonstrated the possibility of a treatment which prolonged vision in patients with choroidal melanoma.

References:

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