Encleation 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. 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.

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. 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, that radioactive plaque brachytherapy incurs worse survival than enucleation, and that radioactive brachytherapy was as effective as enucleation in preserving life. 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.

**Purpose**

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.

**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. 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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Small</th>
<th>Medium</th>
<th>Large</th>
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<tbody>
<tr>
<td>Meta-analysis</td>
<td>&lt;3 mm height and &lt;10 mm diameter / &lt; 300 mm³</td>
<td>10–15 mm diameter</td>
<td>&gt;15 mm diameter or &gt;5mm height</td>
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<tr>
<td>1966-1988</td>
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<tr>
<td>COMS</td>
<td>1.5–2.4 mm height 5–16 mm diameter</td>
<td>2.5–10 mm apical height and &lt;16 mm diameter</td>
<td>&gt;10 apical height and &gt;16 mm diameter</td>
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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.

Results

- Of small choroidal melanomas initially managed by observation, 21% demonstrated growth by 2 years and 31% by 5 years.

- Patients with medium sized choroidal melanomas have similar survival rates for two alternative treatments for primary eye cancer—radiation therapy and enucleation.

- Patients with large eye melanomas had similar five-year survival rates regardless of whether they were treated with radiation prior to removal of the eye or had their eye removed without prior radiation therapy.

Conclusion

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. (3) The fact that preenucleation radiation does not confer any survival advantage over standard enucleation argues against the hypothesis by Zimmerman et al 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.

Limitations

A major criticism of the COMS is that its primary findings essentially confirm what strongly suspected but never proven 15 years ago was — 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 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.

Table 2: All-Cause and Tumor-Related Mortality Rates

<table>
<thead>
<tr>
<th>COMS</th>
<th>Large</th>
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<tbody>
<tr>
<td>5-yr</td>
<td></td>
<td></td>
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<tr>
<td>all-cause mortality</td>
<td>43% (38-48%) a</td>
<td>19% (16-23%) c</td>
<td>6% (2.7-9.3%)</td>
</tr>
<tr>
<td>5-yr tumor-related mortality</td>
<td>28% (24-32%) a</td>
<td>11% (8-13%) c</td>
<td>1% (0-2.5%)</td>
</tr>
</tbody>
</table>

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. 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).

Long-term follow-up will determine if this trend becomes clinically important.

The results of the COMS confirming that the centuryold 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. Research into the early detection and treatment of micrometastases needs to be given the highest priority.

References