Reduced Melanoma-Related Mortality in Uveal Melanoma by Preenucleation Radiotherapy

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Background: Radiotherapy of an eye before enucleation, so called preenucleation radiotherapy (PER), of patients with uveal melanoma was initiated to reduce enucleation-induced systemic metastasis. Earlier studies with a short follow-up period have not demonstrated a significant effect on survival.

Objective: To study the effect of PER on melanoma-related mortality after more than 9 years of follow-up.

Design: In a prospective study, 167 patients with uveal melanoma were treated between 1978 and 1992 by irradiation with 800 rad (8 Gy) given in 2 fractions 2 days before enucleation. A group of 108 patients with uveal melanoma treated between 1971 and 1992 by enucleation only in the same hospital served as a historical control group. Patients were followed up until December 2002 or death.

Results: Melanoma-related death occurred in 32.3% of the PER-treated group and in 40.7% of the enucleation only group. Mean follow-up was 9.25 years. After 48 months of follow-up, a significant difference in survival became evident in favor of the PER group. The estimated 15-year survival rates for patients with melanoma in the PER group and enucleation only group were 63.7% and 51.0%, respectively. For patients dying of all causes, these percentages were 47.5% and 25.2%, respectively. In both groups, women had a better prognostic outcome than men.

Conclusion: This study suggests that PER improves long-term survival in patients with uveal melanoma.


UVEAL MELANOMA IS THE most common primary malignancy of the eye. Although radiotherapy has become the treatment of choice, primary enucleation of the tumor-containing eye is still indicated in 30% to 50% of the cases. Nearly half of all patients will die of distant metastasis in time.1 In the past, controversy occurred if early metastasis was due to the enucleation procedure or to undetectable micrometastases before enucleation.2,3 Spreading of melanoma cells has been detected during the enucleation procedure in animal models as a result of physical manipulation of the eye.4 One method to reduce the potential risk of enucleation-induced metastasis is preenucleation radiotherapy (PER), which proved to be effective in animal models.5-9 However, clinical application of PER has been abandoned, because no significant difference in survival could be demonstrated between PER and enucleation only (EO) groups.10,16 The mean follow-up time in these clinical studies ranged from 5 to 8 years. Based on theoretical models, clinically manifest metastases are likely to occur 5 or 6 years after onset of the systemic dissemination.3,17-20 For this reason, we extended our earlier study14 with a longer follow-up to study the effect of PER.

METHODS

DATA COLLECTION

All consecutive patients with a diagnosis of choroidal or ciliary body melanoma without clinical evidence of metastatic disease at presentation and who were treated by either EO or PER between 1971 and 1992 (Table 1) were entered into this study. All patients had their conditions diagnosed and treated at the Rotterdam Eye Hospital or the University Hospital Rotterdam.

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Eye Hospital or the University Hospital Rotterdam. Patients were extensively informed on the various treatment options, such as observation, EO, or PER. Between 1978 and 1982 patients were treated by PER or EO, depending on personal preference of their ophthalmologist in...
the hospital. From 1982 until 1992 all patients were treated by PER as a standard protocol unless there were contraindications. From April 1992 on, PER was discontinued because interim analysis showed no beneficial effect on survival. The PER was delivered 48 and 24 hours before enucleation by 2 fractions of 400-rad (4-Gy) electron beams (16 MeV) by means of a 5 × 5-cm anterior field on a linear accelerator. The present study includes the same patients with uveal melanoma treated between 1971 and 1990 whom we previously described14 plus all consecutive patients with uveal melanoma treated until December 1992. The control group consisted of all patients treated by EO between 1971 and 1992 (Table 1). All patients were followed up until death or December 2002.

Patients had a complete physical examination before surgery, including chest x-ray films and liver function tests; from 1978 on, liver ultrasonography was routinely added. Patients with clinical evidence of metastatic disease before surgery were excluded. Patients were followed up twice a year in the first 2 postoperative years; after that, annual checkups were performed. The follow-up program included ophthalmoscopy of the remaining eye, inspection of the socket, palpation of preauricular and submandibular lymph nodes, and liver enzyme tests. Follow-up data on patients who did not keep their appointments were obtained by contacting their general practitioners, local ophthalmologists, or both. To verify the date and cause of death, the files from the general practitioner, hospital, or both were recovered. Melanoma-related death was diagnosed in case of histopathologic confirmation of metastases or by clinical evidence (laboratory and radiodiagnostic) of metastatic disease. Otherwise, the patients were considered to have died of other causes.

The following patient and histopathologic data were recorded: date of enucleation, age at date of the enucleation, sex, location of the tumor (ciliary body, choroid), largest tumor diameter and tumor thickness, cell type (epithelioid or nonepithelioid), extrascleral growth, follow-up time, and eventual cause of death. An ophthalmic pathologist (C.M.M.) reviewed all histopathologic data from each tumor, at least 10 consecutive slides were examined.

### DATA ANALYSIS

The χ² test was used for comparison of sex, tumor location, cell type, and extrascleral growth in the PER and control group. We used the 2-sample t test to compare largest tumor diameter and age. Univariate survival analysis was performed by Kaplan-Meier curves accompanied by the log-rank test to study the effect of PER. To investigate whether PER had a different effect on late follow-up compared with early follow-up, the log rank test was performed separately for both periods. A cutoff period of 48 months was chosen, because for this time point the likelihood of our statistical model was maximal. The Cox regression model was used for multivariate analyses. In this model, the effect of PER was allowed to differ between the periods before and after 48 months of follow-up, using 2 time-dependent covariates defined as follows: the first, representing the effect of PER in the first 48 months, was defined as being equal to 1 at follow-up times before 48 months for patients with PER and equal to 0 otherwise. The second, which represented the PER effect after 48 months, was defined as being 1 after 48 months for patients in the PER group and 0 otherwise. We checked on the linearity assumption of each of the continuous covariates in the model by looking at whether adding its square made the model significantly better. We also checked on the proportional hazards assumption by testing the significance of the interaction of each covariate with the logarithm of follow-up time. All survival analyses were performed for both melanoma-related death (other causes of death censored) and death from all causes.

### RESULTS

Between 1971 and 1992 a total of 275 patients were treated of whom 167 patients received PER (Table 1). Seven cases received no PER because of acute angle-closure glaucoma (n = 1), unexpected melanoma in a phthisic eye (n = 1), and a period of breakdown of the radiation equipment (n = 5) and were included in the EO group. Mean follow-up was 114 months in the PER group and 111 months in the EO group. In the PER group, 4 patients were lost to follow-up after 115 to 234 months; in the EO group, 1 patient was lost to follow-up after 24 months. Six patients in the PER group and 10 in the EO group received postoperative radiation therapy (2800-3200 rad [28-32 Gy] in fractions of 400 rad [4 Gy]) because of extrascleral tumor extension. Data on age, sex, tumor location, tumor size, cell type, and extrascleral growth for the PER and the EO groups are given in Table 1. The 2 groups differed significantly (P = .006) in age. No statistically significant difference occurred between both groups in sex, tumor location, largest tumor diameter, cell type, and extrascleral growth. In 54 (32.3%) of 167 patients treated with PER and in 44 (40.7%) of 108 patients treated with EO, melanoma-related death occurred. All-cause death was specified in 90 (53.9%) of 167 patients treated with PER and 81 (78.8%) of 108 patients treated with EO. The estimated Kaplan-Meier 5-, 10-, and 15-year survival rates in the patient group with melanoma-related death were 76.5%, 69.8%, and 63.7%, respectively, in the PER group and 71.2%, 57.2%, and 51.0%, respectively, in the EO group (Figure 1A). No difference in survival rates between the PER and EO group was found with the log rank test (P = .09) for the whole period of follow-up. Also in the early follow-up, the period before 48 months, no significant difference (P = .71) between the 2 groups could be demonstrated by the log rank test. However, survival was better (P = .003) after 48 months in the PER group.

### Table 1. Clinical and Histopathologic Data

<table>
<thead>
<tr>
<th></th>
<th>Enucleation Only (n = 108)</th>
<th>P Value</th>
<th>Prenucleation Radiotherapy (n = 167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1971-1977</td>
<td>53</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1978-1981</td>
<td>31</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>1982-1992</td>
<td>24</td>
<td>146</td>
<td></td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>62.5 (16-89)</td>
<td>0.006</td>
<td>57.8 (21-92)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td>.39</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>64 (59.3)</td>
<td>90 (53.9)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44 (40.7)</td>
<td>77 (46.1)</td>
<td></td>
</tr>
<tr>
<td>Posterior location, No. (%)</td>
<td>98 (90.7)</td>
<td>.26</td>
<td>144 (86.2)</td>
</tr>
<tr>
<td>Largest tumor diameter, mean (range), mm</td>
<td>12.2 (4-20)</td>
<td>.15</td>
<td>11.6 (2-22)</td>
</tr>
<tr>
<td>Prominence, mean (range), mm</td>
<td>7.0 (1-20)</td>
<td>.25</td>
<td>6.4 (1-20)</td>
</tr>
<tr>
<td>Epithelioid cell type, No. (%)</td>
<td>61 (56.5)</td>
<td>.67</td>
<td>90 (53.9)</td>
</tr>
<tr>
<td>Extrascleral growth, No. (%)</td>
<td>29 (26.6)</td>
<td>.11</td>
<td>39 (23.4)</td>
</tr>
<tr>
<td>Follow-up, mean, mo</td>
<td>111</td>
<td></td>
<td>114</td>
</tr>
</tbody>
</table>
group. The estimated 5-, 10-, and 15-year survival rates in the patient group dying of all causes were 71.3%, 57.5%, and 47.5%, respectively, in the PER group and 62.7%, 40.2%, and 25.2%, respectively, in the EO group (Figure 1B).

Melanoma-related death was associated with older age (P < .001), male sex (P = .03), larger tumor size (P < .001), and epithelioid cell type (P = .006) in the univariate analysis. No association was found for the year of treatment (P = .16). To adjust for the potential confounding prognostic variables, such as year of enucleation, age at enucleation, sex, tumor location, tumor size, and cell type, on the effect of PER, a multivariate Cox regression was used (Table 2) for melanoma-related death. In the first period of 48 months, no significant effect of PER (P = .479) was seen on survival, whereas after 48 months a significant association was noted (P = .006). The estimated adjusted hazard ratio (PER vs EO) for melanoma-related death after 48 months was 0.39 (P = .006). Similar Cox regression was also used for death due to all causes (results not shown). The estimated adjusted hazard ratio (PER vs EO) for all-cause death was 1.21 before 48 months (P = .476) and 0.50 after 48 months (P = .003). In the EO group metastases seemed to occur more often in men than in women (P = .07), whereas in the PER group the percentages were not significantly different (P = .99). A significant difference was demonstrated in the effect of PER on survival between men and women (P = .03) when the interaction between sex and PER was added in the multivariate analysis.

### Comment

In this study, we observed a beneficial effect on long-term survival of PER by 2 fractions of 400 rad (4 Gy) compared with EO. The effect became apparent after 48 months of follow-up. This dose should be sufficient to eradicate most (<90%) of the tumor cells and induce a reduction in proliferation activity of melanoma cells as has been demonstrated in in vitro and experimental studies.9,21,22

Preenucleation radiotherapy did not decrease the number of short-term melanoma-related deaths.12,15,23 Likewise, no beneficial effect of PER on survival was found in an uncontrolled prospective study of 80 patients with primary choroidal and ciliary body melanoma12 or in an uncontrolled retrospective study of 26 patients with choroidal melanoma.11 Moreover, preoperative radiation with 5 fractions of 400 rad (4 Gy) had a worse prognosis in a series of 41 nonrandomly selected patients.10 Auggsburger et al13 found a nonsignificant cumulative 5-year survival probability of 63.9% for 29 patients in the PER group vs 57.9% for 29 patients in the EO group. The Collaborative Ocular Melanoma Study trial16 reported an estimated 5-year survival rate of 62% in the PER group and 57% in the EO group. In our earlier report, we found a cumulative 7.5-year survival probability of 75.9% in the PER group and 72.1% in the EO group,14 which was not significantly different. However, in the present extended study, we observed a reduction in the risk in the PER group after a period of 48 months (P = .006). This finding suggests that a longer follow-up is needed to confirm differences.

Death in the first 48 months is therefore probably mainly due to micrometastatic spreading of tumor cells before initiation of the treatment.17,20 Preoperative spreading is most likely responsible for a significant part of the melanoma-related deaths after 48 months and could be prevented by irradiation before enucleation.

The positive effect of PER is more evident in the 15-year all-cause survival rates (PER group vs the EO group, 47.5% and 25.2%, respectively) in our study, whereas these melanoma-related survival rates were 63.7% in the PER group and 51.0% in the EO group. All-cause survival is considered to be important, since the disease does not appear to increase the risk of death from other causes. Survival after treatment depends on tumor parameters and the
expected survival of the patients independent of the melanoma.

In our Cox proportional hazard analysis, melanoma-related death was associated with age, tumor size, and cell type as previously described by others.\textsuperscript{21-25}\textsuperscript{26-28} Although no significant difference was observed in several previous studies between men and women,\textsuperscript{18,23,25,26,28,29} we found that women had a better prognostic outcome than men. This difference in prognosis remained after adjusting for irradiation, age, tumor size, tumor location, cell type, and year of treatment. This confirms the finding by Folberg et al\textsuperscript{27} of a more favorable outcome for women, and more recently it was postulated that women with a history of childbearing had an even better survival compared with nullipara women and men.\textsuperscript{30} Also in studies with cutaneous melanoma, women have a better prognosis than men.\textsuperscript{31,32}

Compared with other studies, our study has a large sample size and a long follow-up with little dropout. Patients in the EO and PER groups were not treated during the same period, which could be considered a shortcoming of our study. However, the effect of year of treatment, studied in a multivariate analysis, showed no significant association with melanoma-related death ($P = .16$). A significant difference in age was observed between the PER group and EO group. The average ages in EO and PER groups were 62.5 and 57.6 years, respectively. The older age in the EO group could have a negative influence on survival in this group. This might be a reason for the difference in the Kaplan-Meier survival estimate in favor for the PER group. After adjusting for this prognostic covariate in the multivariate analysis, the difference was still present. We cannot tell if this difference in age between the EO and PER groups was due to earlier tumor detection or shorter observation time of smaller tumors before the recommendation of enucleation was given.

In conclusion, we found a long-term beneficial effect on survival after 2 fractions of 400-rad (4-Gy) PER. Life expectancy in women was more favorable than in men. Even though our study has a long-term follow-up after PER, it would be interesting to see if longer follow-up in similar studies would lead to the same conclusion.

### Table 2. Influence of Treatment and Possible Confounders on Melanoma-Related Death

<table>
<thead>
<tr>
<th>PER vs EO</th>
<th>β*</th>
<th>SE</th>
<th>$P$ Value</th>
<th>HR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 48 mo</td>
<td>.22</td>
<td>.31</td>
<td>.479</td>
<td>1.25 (0.67-2.31)</td>
</tr>
<tr>
<td>After 48 mo</td>
<td>-.94</td>
<td>.34</td>
<td>.006</td>
<td>0.39 (0.20-0.76)</td>
</tr>
<tr>
<td>Age (1-y increase)</td>
<td>.04</td>
<td>.01</td>
<td>&lt;.001</td>
<td>1.03 (1.02-1.06)</td>
</tr>
<tr>
<td>Sex (women vs men)</td>
<td>-.48</td>
<td>.21</td>
<td>.03</td>
<td>0.62 (0.41-0.95)</td>
</tr>
<tr>
<td>Tumor location (anterior vs posterior)</td>
<td>.63</td>
<td>.25</td>
<td>.01</td>
<td>1.88 (1.14-3.10)</td>
</tr>
<tr>
<td>Largest tumor diameter (1-mm increase)</td>
<td>.12</td>
<td>.03</td>
<td>&lt;.001</td>
<td>1.13 (1.07-1.19)</td>
</tr>
<tr>
<td>Cell type (epithelioid vs spindle)</td>
<td>.62</td>
<td>.23</td>
<td>.006</td>
<td>1.86 (1.19-2.90)</td>
</tr>
<tr>
<td>Year of treatment</td>
<td>.03</td>
<td>.02</td>
<td>.16</td>
<td>1.03 (0.99-1.07)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EO, enucleation only; HR, hazard ratio; PER, preenucleation radiotherapy.

*The β coefficient is the natural logarithm of the HR.
†An HR, for instance, of 0.62 for sex means that at each time during follow-up women have a chance of dying within 1 month equal to 0.62 times the chance of dying within 1 month for men.

### References

14. Luyten GP, Mooy CM, Eijkenboom WM, et al. No demonstrated effect of pre-