

Pre-enucleation irradiation of uveal melanoma

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SUMMARY The relative efficacy of various types of treatment in preventing metastatic uveal melanoma is unclear. We have performed a phase I-II non-randomised trial to determine if patients with large (>15 mm in diameter or > 5 mm in thickness) uveal melanomas would benefit from pre-enucleation irradiation. Twenty-eight patients were treated between 1978 and 1983 by means of 5×5 cm anterior wedge pair ports on a 4 me V linear accelerator. Each patient received five 4 gray (400 rad) fractions over a five-day period for a total of 20 Gy. Enucleation was performed by a single surgeon within five days after treatment. The mean follow-up of the patients was 24 months (range 7-54 months). All melanomas were histologically confirmed. Four patients (14%) have developed metastatic tumour with a mean interval between diagnosis and death of 25 months. No significant perioperative or long-term morbidity was observed.

There are some unresolved issues in the management of uveal melanoma. The relative efficacy of various types of treatment in preventing metastases is unclear. Some investigators have shown that patients treated by, variously, photocoagulation, radioactive plaques, and charged particle irradiation as alternatives to enucleation have a relatively low incidence of uveal melanoma metastases, but data from randomised prospective treatment trials are lacking.¹⁻³ Some authors have compared their results either with those from historic controls or with those from intra-institution non-randomised patients treated with alternative therapy or enucleation.^{3,4} Either method of comparison may be inaccurate. Changes in the definition of melanoma size have been made, and it is not clear what criteria were used to select alternative therapy versus enucleation in non-randomised studies from a single institution. The incidence of distant metastases may be changing as earlier diagnoses are made.

About five years ago we began a phase I-II non-randomised trial to determine if uveal melanoma patients with tumours greater than 15 mm in diameter or greater than 5 mm in thickness would benefit from pre-enucleation irradiation. In some cases of systemic malignancy preoperative irradiation was associated with decreased tumour-related mortality, and our initial investigation was a pilot study of morbidity and mortality prior to a random-

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ised prospective national trial to determine if pre-enucleation irradiation in cases of poor-risk uveal melanoma might decrease tumour-related mortality.⁵ This report presents our preliminary data. The relatively low incidence of short-term metastatic disease demonstrates the need for a randomised prospective study to determine what is the optimal therapy for patients with uveal melanomas.

Materials and methods

All patients were examined in the Ocular Oncology Unit, University of California, San Francisco between 1978 and 1983. The diagnosis of uveal melanoma was confirmed on the basis of clinical, ultrasonographic, photographic, and fluorescein angiographic criteria prior to therapy. Written and oral informed consent was obtained in all cases. Patients had a thorough physical examination, serum liver function tests (lactic dehydrogenase, alkaline phosphatase, and SGOT), and postero-anterior and lateral chest x-rays to detect possible metastases. If abnormalities were observed in any of these tests, a further examination was carried out.⁶

Pre-enucleation irradiation was performed on a 4 me V linear accelerator with 5×5 cm anterior wedge pair ports. All patients received five 4 gray (Gy) (400 rad) fractions of 4 meV photon irradiation on five consecutive days for a total of 20 Gy, and enucleation was performed by a single surgeon (D.H.C.) within five days after cessation of radiation

therapy. Enucleation was performed in a standard manner without cryoprobe, aqueous paracentesis, or other ancillary 'minimal touch enucleation manoeuvres.'

Tumour sizes were measured initially by clinical examination and both immersion B-scan and quantitative A-scan ultrasound. Tumour dimensions were confirmed both at the time of surgery, by corneal transillumination, and when eyes were examined in the eye pathology laboratory. All eyes were examined histologically and contained uveal melanomas; the tumours' cell types were classified in the standard manner.⁷ As outlined above, all patients have had serial evaluations for metastatic disease every three months.

Results

Twenty-eight patients with large (>15 mm in diameter or >5 mm in thickness) uveal melanomas received 20 Gy of conventional photon pre-enucleation irradiation. After a standard enucleation they have been serially followed up for 7-54 months (mean 24 months). No patients have been lost to follow-up.

All melanomas were examined and the diagnosis confirmed histologically. Six patients had spindle B tumours, 14 had mixed tumours with predominantly spindle B cells, six patients had mixed tumours, one patient had an epithelioid, and one a necrotic melanoma. No eyes had histological evidence of extraocular extension.

Four patients (14%) have developed metastatic melanomas, and these have been confirmed histologically. All four have died from metastases, death occurring 19-30 months (mean 25 months) after treatment.

No significant perioperative or long-term morbidity beyond that seen with standard enucleation was observed after this dose of pre-enucleation irradiation.

Discussion

We have demonstrated that pre-enucleation irradiation using five 4 Gy fractions can be performed with minimal perioperative or long-term morbidity. Less than 0.2 Gy is delivered to the contralateral lens, and we have observed no contralateral ocular, prosthesis/implant, or other cranial problems as a result of this adjunct therapy. Secondly, we have demonstrated that the short-term melanoma-related mortality in these treated patients with currently defined large melanomas is relatively low. Only four of 28 patients (14%) developed metastases; however, the five-year metastatic rate will undoubtedly be higher.

The observation of lower than expected mortality

in patients with large uveal melanomas treated by pre-enucleation irradiation may have several possible explanations. First, it suggests to us that the use of historic controls is inappropriate; some investigators have stated that large uveal melanomas have a five-year tumour-related mortality approaching 40%, but this level may no longer be correct. Secondly, it demonstrates the need for prospective randomised treatment trials to determine the relative efficacy of different forms of therapy in the prevention of uveal melanoma metastases, and to establish the metastasis rate for present day patients. Thirdly, it leads us to believe that pre-enucleation irradiation may have an effect on tumour mortality, and that it would be reasonable to mount a prospective national randomised study of this approach.

The objective of a randomised pre-enucleation irradiation study is to determine whether pre-enucleation irradiation at this dose and fractionation schedule would decrease the prevalence of metastases in patients with large (>15 mm diameter or >5 mm thickness) uveal melanomas.

There are several potential limitations. If patients with uveal melanoma develop only micrometastases prior to ocular treatment, this therapeutic approach would be ineffective. Secondly, most tumours in which pre- or perioperative irradiation has been successful have been those which have a propensity for local spread and involvement of regional lymph nodes; this is not the case for uveal melanomas.⁸⁻¹⁰ Thirdly, it is possible that the dose or fractionation schedule used in this study is not optimal.

The radiation parameters chosen for this study were based on four considerations. First, in some previous studies of other tumour sites this radiation dose has been effective.⁸⁻¹⁰ Secondly, melanomas may be more susceptible to high (4 Gy) than conventional (2 Gy) fractions.⁵ Thirdly, at this dose out-of-town patients can be treated in a timely manner; markedly to increase the radiation dose by conventional fractions would necessitate four to five weeks of therapy. Fourthly, this relatively low dose can be delivered safely and has a lower potential for untoward side effects. Fifthly, the rationale is to reduce systemic seeding of viable tumour cells at surgery; this radiation dose should reduce the percentage of viable cells by several log units.

The preliminary results with pre-enucleation irradiation appear promising. A randomised prospective treatment trial is needed. It can be effectively mounted to test the hypothesis within a reasonable length of time.

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