Is radiation a justifiable treatment of choroidal melanoma?

Sir, The paper by W A Manschot and R van Strik (Br J Ophthalmol 1987; 71: 348–52) is of value as it stimulates thinking about the controversies in melanoma treatment, but it lacks important relevant data.

The concept of tumour doubling time of the authors is an oversimplification, as they assume that there is only one growth potential of all tumour cells involved, whereas in fact a tumour consists of a heterogeneous group of cells of different growth potential.1

The statement that the tumour death rate of all patients with melanomas in the <7 mm diameter group is nil is incorrect. One patient out of 42 patients of Thomas et al.2 had metastases. Barr et al.3 mention metastatic death in one patient with a 7×7×2 mm melanoma. Davidofof and Lang4 had no metastatic deaths in their series of only 18 patients. Metastatic death occurred in three of the 22 patients with a choroidal melanoma up to 7 mm diameter and 2 mm in height, Tla according to the TNM classification, from the Leiden University Eye Clinic. Statistical evaluation may not be justifiable in these low numbers but it proves that even in Tla size tumours metastatic death occurs.

The authors state that tumour regression of 50% or 75% after radiation only delays metastatic death but that only total regression may save patients’ lives. This is not true, as, especially after irradiation of large melanomas, a totally necrotic residual mass may persist.5 Fig. 1 shows one of five cases of the University Eye Clinic in Essen. After ruthenium-106 application to a choroidal melanoma the height of the tumour regressed from 8-4 to 6-3 mm only. Because of a rather intense post-treatment inflammatory reaction attributed to tumour necrosis6 the eye having light perception only was enucleated three months after the irradiation. Histopathology, however, revealed a completely necrotic tumour mass without any viable cells (Figs. A, B).

The authors state that in almost all histopathologically studied eyes enucleated after radiotherapy viable tumour cells were present. The finding of viable tumour cells on histopathology in the enucleated eye after irradiation is what could be expected, as tumour growth after radiotherapy is one of the main reasons for performing enucleation. The fact that only in a few cases viable tumour cells could not be found indicates that in the postradiation follow-up patients have been carefully controlled and that hardly any errors have been made by mistakenly enucleating eyes with melanomas which have properly regressed. Moreover, after irradiation the tumour may be ‘sterilised,’ containing viable cells which, however, do not enter mitosis any more. This information has already been given to Manschot by Char’ in his answer to a letter to the editor by Manschot.6 ‘The major effect of radiation is to destroy the tumour’s reproductive integrity. In successfully radiated animal models, histologically normal intermitotic cells can remain in situ for a long period. DNA-induced errors result in cell death mainly after cell enters mitosis. After successful ocular irradiation, usually some residual necrotic or sterile cells remain.’

Concerning metastatic death the authors mention only unfavourable results of radiotherapy as compared with enucleation, but ignore all the more favourable results. They elaborate on the results of Gass,7 who found a much higher metastatic death after cobalt-60 irradiation than after enucleation, but omit to mention that the statistical reappraisal Gass had made of his results led to the conclusion ‘that after adjusting for both size and location, the treatments were almost significantly different using a likelihood ratio test. This leads to the conclusion that the issue of which treatment is better for the patient is still not settled.’8

The authors have failed to mention results of several other long-term studies with a follow-up period of more than four years as advocated by them. Augsburger et al.9 in an observational study of 237 patients with posterior uveal melanomas, 74-7% of whom were followed-up for five years or longer, 140 having been treated with enucleation and 97 with cobalt plaque radiotherapy, found after statistical adjustment for intergroup differences in risk factors that the difference in effect of enucleation versus cobalt plaque therapy on survival time was not statistically significant.

After cobalt-60 plaque irradiation of 123 patients Hungerford (personal communication, 1987) found no difference statistically in metastatic death from the comparable group of patients treated by enucleation after an observation period of 10 to 20 years.

Lommatzsch10 evaluated the results of 188 patients with choroidal melanomas treated with Ru-106 applicators followed up for more than five years with a mean period of 9-4 years. Of this group 18 (9-6%) had died from metastases. These results and the survival rate after irradiation of 79-5% (death only from metastases) after 10 years confirmed his earlier results11 that the survival rate after local beta irradiation is higher than after enucleation of tumours of a comparable size.11

Fig. 1A Overview of a histological section through a totally necrotic tumour in an eye after ruthenium applicator treatment performed in the University Eye Clinic in Essen. Intense post-treatment inflammatory reaction necessitated enucleation.
Gragoudas et al., studied metastatic death in their first 128 patients after proton beam irradiation for melanoma of the choroid and/or ciliary body; all patients but one had been followed up for more than four years, the mean follow-up being five years. Metastases developed in 26 patients (20-5%); according to the Kaplan-Muir curve the five-year survival rate is 80±5%. This compares favourably with the statistics after enucleation, as Jensen in his extensive study of tumours of all sizes found a five-year metastatic death rate of 37%. This difference is the more remarkable as more than half of the proton beam treated tumours were large, with a diameter of >15 mm, having a more unfavourable metastasis prognosis than the unselected material of Jensen.

The results of the long-term studies may not allow definite proof that the rate of metastasis is lower after irradiation than after enucleation, but the data obtained until now at least provide the reassurance that the long-term studies do not show a superiority of enucleation over irradiation as regards survival rate. Therefore irradiation of a choroidal melanoma is medically justifiable and a recommended treatment for patients with choroidal melanomas. We feel that every patient has not only the right to enucleation but also to radiotherapy within the limits of the different types of irradiation.

JENDO A OOSTERHUIS

PETER K LOMMATZSCH

ACHIM WESSING

Leiden, The Netherlands

Leipzig, GDR

Essen, FRG

Professor Dr J A Oosterhuis,
Oogheelkundige Kliniek,
Academisch Ziekenhuis,
2333 AA,
The Netherlands

References

Correspondence


Sir, Thank you for allowing us the opportunity to reply to the letter by Oosterhuis et al. Perhaps, we may answer, one by one, the consecutive paragraphs.

Paragraph 1 (The paper . . .): We would have appreciated an exact enumeration of the ‘important relevant data’ which our paper was said to be lacking. It is not possible to reply to undefined imputations.

Paragraph 2 (The concept . . .): We have never assumed ‘that there is only one growth potential of all tumour cells involved.’ We are familiar with the fact that a tumour generally consists of a heterogeneous group of cells of different growth potential. In basic oncology, however, tumour doubling time is defined as the time necessary for a tumour to double its volume; growth potentials of various tumour cells are not specifically distinguished therein.

Paragraph 3 (The statement . . .): We did not state that the tumour-death rate of all patients with melanomas in the <7 mm diameter group is nil. We stated that this rate had been nil in two American reports:12 we also specifically mentioned the one patient in the series of 42 patients of Thomas et al.,7 who had metastases, but had not yet died, and the patient described by Barr et al.8 who had died from metastases. We carefully concluded: ‘It seems reasonable to postulate that, in general, choroidal melanomas are unlikely to shed cell emboli before they have reached the 7 mm stage.’

Paragraph 4 with regard to the question of tumour regression and metastatic death. We in fact stated: ‘regression two years after irradiation of even 50% or 75% of the original volume can only delay metastatic death by one or two doubling times and cannot prevent eventual death from metastases. Only total regression can save a patient’s life, if metastases were absent before treatment.’ Oosterhuis et al. say that ‘this is not true’ and, surprisingly, substantiate their criticism with a histopathological report which actually had been made by one of us (WAM). The specimen concerned a blind, painful eye, which had to be enucleated within four months after a rhenium irradiation of a small uveal melanoma in the clinic of one of our critics (AW). The apparently excessive radiotherapy had caused severe necrosis of almost all intraocular tissue, including the melanoma. Oosterhuis et al. point specifically to the reported complete necrosis of the small melanoma, but they do not appear to be alarmed by the total loss of the eye.

Paragraph 5 (The authors state . . .): Taking credit for a necrotic melanoma in a subtotally necrotic inner eye appears equivalent to taking credit for the finding ‘that only in a few cases viable tumour cells could not be found’ in enucleated irradiated eyes. The major part of 27 most recently reported5 histopathologically studied irradiated eyes had not been enucleated because of continuing or relapsing tumour growth but because of postirradiation damage. The passage on the carefully controlled patients is a red herring. Tumour cells ‘sterilised’ by irradiation are, so far, an unsubstantiated fantasy for most of the irradiated patients. Moreover, ophthalmic pathologists are familiar with the fact that mitotic figures are also difficult to find in most non-irradiated melanomas. The ‘information (which) has already been given by Char1 on destruction by radiation of the tumour’s integrity’ is hypothetical, as appears from the only published mean 10-year follow-up report by Gass6 (next paragraph).

Paragraph 6 (Concerning . . .): More favourable results of radiotherapy as compared with enucleation, concerning metastatic death, have never been reported by any author who has presented a >5-year follow-up survival statistic of all irradiated patients. Again Oosterhuis et al. neglected to substantiate this crucial remark. Gass provided a mean 10-year follow-up survival rate for all 27 enucleated and 21 irradiated patients and revealed a 22% death rate after enucleation against 57% after irradiation, while the mean survival after enucleation was >10 years against 3-8 years after irradiation. These figures have not reached statistical significance as yet because of the small numbers of these patients; they are, however, highly impressive for the unbiased reader.

Paragraphs 7-9 with reference to reports of Lommatzsch and Gragoudas. We have not ‘failed to mention results of several other long-term studies with a follow-up period of more than four years . . .’ as Oosterhuis et al. state incorrectly. We have studied carefully the published reports, which were included in the bibliography. The papers by Augsburger et al.7 Lommatzsch,8 and Gragoudas et al.9 were published after our paper had been submitted. They cannot, therefore, be used in criticism of our paper. It is of interest that two of these papers present once again statistics on selected groups of patients instead of irradiated patients in toto. The third paper is based on a mean follow-up of 5-4 years. The readers will have noticed that our paper emphasises that after a 5-year follow-up some indications might be provided, but that 10-year or longer follow-up periods are needed to achieve decisive arguments. We have also stressed that tumour-related death after enucleation has appeared to decrease steadily to a low percentage in the second 5-year follow-up period. Tumour biology suggests, however, that after irradiation the remaining tumour tissue will either continue or restart its exponential growth. Then dissemination and death from metastases will tend to increase exponentially in the second 5-year follow-up period, as was shown by Gass.

Irradiation of uveal melanomas is still based on hypotheses and on too short follow-up periods in selected subgroups of patients, by which considerable selection artefacts have been incurred. Patients with uveal melanoma have the right to be treated by enucleation, which eliminates any further dissemination. Radiotherapy of uveal melanomas is justified only in patients with a short life expectancy and in patients who refuse enucleation.

W A MANSCHOT
R VAN STRIK
Erasmus University Rotterdam,
1Institute of Pathology,
2Institute of Biostatistics
References


Obituary

R B Harcourt, MA, MB, BChir, FRCS, DO

Mr Richard Brian Harcourt, consultant ophthalmic surgeon to the General Infirmary at Leeds, honorary senior clinical lecturer to Leeds University, and President of the Ophthalmological Society of the United Kingdom, died on 3 November 1987 aged 53.

Brian was born on 3 March 1934, the son of an engineer and the grandson of a surgeon, and was educated at Quarry Bank School, Liverpool, before studying medicine at Trinity College, Cambridge, and St Bartholomew’s Hospital, London. After national service in the Royal Air Force he chose ophthalmology as his specialty and undertook his training at the High Holborn branch of Moorfields Eye Hospital. Early in his ophthalmic career he showed a flair for paediatrics, and after spending a year as a Research Fellow in paediatric ophthalmology at the Hospital for Sick Children, Great Ormond Street, and the Institute of Ophthalmology he was appointed to the consultant staff of the General Infirmary at Leeds in 1968. He was made an honorary clinical lecturer to Leeds University and was promoted to honorary senior clinical lecturer in 1978.

At Leeds he developed his expertise in paediatric ophthalmology and in strabismus, so that in a very few years he had become one of the acknowledged experts in these fields. His many publications culminated in the book The Diagnosis and Management of Ocular Motility Disorders, written in collaboration with Miss Joyce Mein and published in 1986.

In addition to his extensive clinical practice, he was very active in national and international ophthalmic committees. He was elected a member of council of the Faculty of Ophthalmologists in 1970 and had been its honorary treasurer since 1979. He was a member of the General Optical Council, one of the British representatives on the Section of Ophthalmology of the European Union of Medical Specialists, and represented British ophthalmologists on the board of governors of Moorfields Eye Hospital. In addition to being a member of its court of examiners he had recently been appointed regional adviser in ophthalmology to the Royal College of Surgeons of England. In 1987 he was elected President of the Ophthalmological Society of the United Kingdom, an honour which he particularly appreciated, and he was looking forward with great pleasure to presiding over the annual congress of the society in Harrogate in April 1988.

In recent years he played a major part in developing the interests of ophthalmology, not least in his support for the proposed college of ophthalmologists, and was a wise and sympathetic adviser to his colleagues. He always displayed great charm and had an astute and inquiring mind.

In addition to his medical interests Brian Harcourt was a magistrate and a keen gardener, ornithologist, and sailor. He recently obtained his navigator’s certificate and had great pleasure in taking his family sailing during his last summer. Above all he was devoted to his family, who were most loving and supportive during his illness.

Brian will always be remembered as a dear friend and colleague, and his death at the height of his career will be a great loss to British ophthalmology.

He leaves a widow, Margaret, and two sons, one a medical student, and a daughter who is training to be an ophthalmologist.

Note

Case reports

Reports of single cases are more likely to be accepted if restricted to 600 words plus essential references and illustrations.