Correspondence

Irradiation and choroidal melanoma

SIR, In their paper questioning whether irradiation is a justifiable treatment for choroidal melanomas Manschot and van Strik¹ base their conclusions on a thesis that has some major internal inconsistencies. They claim that dissemination of choroidal melanoma generally occurs after the tumour has grown to 7 mm or larger, that doubling times of uveal melanomas vary from 30 to 365 days, that death from metastasis occurs 30–40 doubling times after dissemination, and that tumour related deaths within three years after therapy are caused by pre-existing metastases. This is a reiteration of the views expounded a few years earlier by Manschot and van Peperzeel.²

In his Bowman lecture of 1980 Zimmerman pointed out why those concepts could not be logically used to advocate the need for early enucleation.³ Using their own views concerning the similarly slow growth rates of the primary and metastatic tumours and their own postulates, formulas, and tumour doubling times, some calculations were made and published as Table II. Reference to that table (reproduced here) shows that various combinations of data that would explain the peak occurrence of tumour deaths from melanomas measuring 15 mm in diameter within the first four postoperative years would require either that the tumours metastasised before they reached 4 mm in diameter, or that the primary tumours grew with such unrealistic rapidity as to give doubling times of 20–25 days. For the same reasons Manschot and van Strik cannot use their concepts to account for the data they presented in their Table 1, indicating no mortality in tumours less than 7 mm in diameter.

Table II* Implications of Manschot and van Peperzeel's model based on a melanoma measuring 15 mm at time of enucleation and 36 doubling times (Tds) from initial metastasis to death

Value of Td (days)	Years from enucleation to death	Tds from enucleation to death*	Tds from initial metastasis to enucleation*	Years from initial metastasis to enucleation	Size of uveal melanoma when metastasis began (mm)
200	2	3	33	18	< 0.01
200	4	7	29	16	0.02
200	>15	29	7	4	< 3.5
100	2	7	29	8	< 0.02
100	4	15	21	6	0.12
100	8	30	16	4	3.8
50	2	14	22	3	< 1.2
50	4	30	6	< 1	3.8
50	4.5	33	6	< 0.5	7.5
25	2	29	7	< 0.5	< 3.75
25	2.25	33	3	0.2	7.5
25	2.5	36	0	0	15
20	1	18	18	1	0.24
20	1.5	28	8	0.5	< 2.5
20	2	36	0	0	15

*From Zimmerman.³
Example: A patient died in the 2nd year after enucleation. If the doubling time for his tumour had been 100 days (Row 4), metastasis must have occurred when the primary was less than .02 mm in diameter. Row 4 also shows the elapsed interval from metastasis to enucleation would have been 29 doubling times, or 8 years

If, therefore, Manschot and van Strik insist that all tumour deaths occurring within three years after therapy are the result of dissemination prior to treatment, then they must acknowledge that such dissemination must have begun before the tumours had become symptomatic. Quite obviously, if that were the case, any debate concerning whether treatment should be by enucleation or irradiation would be irrelevant.

Let us make it clear that these calculations showing that dissemination must have begun when the tumours were minuscule were based entirely on the Manschot—van Peperzeel model,² which again provides the basis for the most recent article by Manschot and van Strik.¹ Obviously the model must be flawed and is clearly non-applicable, because early dissemination from tiny tumours is inconsistent with the generally accepted observation that deaths from metastasis are rare when tumours are treated before they have grown larger than 7 mm, as they indicated in their Table 1.

Manschot and van Strik then go on to insist that survival rates for less than four years after therapy are irrelevant in evaluating the efficacy of therapeutic regimens, and that our attention should be focused on survival rates of 10 years or more. We on the other hand are much more concerned about the fact that the greatest mortality occurs during the first several years after enucleation.⁴⁻⁷ The overall 15-year mortality is about 45% after enucleation, but two-thirds of these tumour deaths are within the first five years, with the peak occurring during the second year. Postenucleation mortality patterns remarkably similar to ours that were derived from cases treated in the USA have been reported by Benjamin *et al.*⁸ from London and by Jensen from the Danish Registry.^{6,9,10}

This curious mortality pattern, which Manschot and his colleagues have been unable to explain satisfactorily and which they recommend that we neglect by focusing our attention on tumour death rates after 10–15 years is in our

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view the major problem. It has been the broad experience of ophthalmologists, pathologists, and epidemiologists that deaths from untreated uveal melanomas are most unusual. Yet within the first few years after enucleation an appreciable mortality develops; then 6–7 years after enucleation the slope of the survival curve flattens out to an annual death rate of about 1–2%.

During the past two decades there has been a significant change in attitude concerning the management of uveal melanomas. Once considered to be lesions demanding enucleation as soon as possible after diagnosis, melanomas are now often left untreated until there is documentation that the tumour is growing and producing significant pathological effects on the eye. Manschot and others have feared that this change in attitude would significantly increase the tumour death rate, but to date there has been no documentation that this has occurred. Returning to the mortality pattern previously described, if as Manschot and his colleagues would have us believe, all tumour deaths within three years of treatment are the result of dissemination that began before treatment, then we would expect to see a similar mortality pattern among patients whose tumours were not diagnosed and treated promptly after they became symptomatic. We have been collecting cases of this type, but have not observed a similar peaking of mortality during the first few years after the untreated tumours became symptomatic.

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SIR, Thank you for allowing us the opportunity to reply to the letter by Drs Zimmerman and McLean. It is disappointing that this letter does not address the subject matter of our paper on irradiation of ocular melanoma.¹ Their letter is a reiteration by the same correspondants of a similar submission some eight years ago to another leading journal,² in which they criticised a paper by one of us (WAM) and H A van Peperzeel.³ It is probably for this reason that the 1988 letter does not cite any publications after 1980, apart from McLean *et al.* 1982.

Take the serious points in order:

Paragraph 1 ('Sir, in . . . diameter'): Zimmerman and McLean refer to a Bowman lecture⁴ in which Zimmerman argued that our concepts could not be used logically to advocate the need for early enucleation. The correspondents have failed since 1980—also in the 1980 Bowman lecture—to substantiate by decisive arguments that our concepts cannot be used to advocate early enucleation as the only justifiable treatment of choroidal melanoma. They never received any support for their opinion, but have, on the contrary, been contested themselves by especially those authors who have published calculated doubling times of choroidal melanomas.^{5,6} Zimmerman and McLean have ignored in their text our reply⁷ to their eight-year-old letter and have neglected the paper by Seigel *et al.*,⁸ who clearly demonstrated the pattern of a peak mortality in the early years after diagnosis in all tumour types studied. According to these authors there was no relationship between the increased risk of death after enucleation and the enucleation, which had also been emphasised in our paper.³

Paragraph 2 ('If, therefore, . . . irrelevant.'): We certainly insist that practically all tumour deaths occurring within three years after therapy are the result of dissemination prior to treatment, and that dissemination must have begun before the tumours had become symptomatic in those cases in which no prolonged patient's or doctor's delay had occurred. We find it hard to accept the statement made by Zimmerman and McLean: 'Quite obviously, if that were the case, any debate concerning whether treatment should be enucleation or irradiation would be irrelevant'. Enucleation of all eyes harbouring a melanoma of any size saves about 50% of these patients from tumour death. Today melanomas are generally detected at a much earlier stage than in former years, and the 10-year survival of 50% has been considerably improved in the meantime. The debate is far from irrelevant, because Zimmerman and McLean imply that irradiated melanomas cannot disseminate after treatment. Since fewer than 50% of melanomas studied microscopically after irradiation showed necrosis and 94% contained viable tumour tissue,⁹ it seems inevitable that some of the irradiated tumours will continue to shed tumour cell emboli.

Paragraph 3 ('Let us . . . Table 1'): Our model should be 'obviously clearly non-applicable, because . . . deaths from metastases are rare when tumours are treated before they have grown larger than 7 mm'. There is no acknowledgment that one of us (WAM) was the first to emphasise¹⁰ the critical importance of tumour size in small melanomas in prognosis. Analysis of two reports^{11,12} on the survival of patients with small enucleated melanomas in the <7 mm and the <10 mm diameter groups revealed that the tumour death rate in the two studies of 7–10 mm tumours was about

35% and 40% compared with nil % in the <7 mm groups. The authors of these two reports^{11,12} calculated 22.7% and 14.3% in the <10 mm groups, because they had not specially determined the death rates in the 7–<10 mm groups. Our model is, contrary to the opinion of Zimmerman *et al.*, fully applicable to the high tumour-related death rates in the 7–<10 mm group, because only a very small percentage of melanomas are enucleated before they have grown larger than 7 mm and because calculated doubling times of 36 out of 39 uveal melanomas^{5,6,13,14} appeared to vary from 60 to 540 days¹⁴ or even 900 days.⁵

Paragraph 4 ('Manschot ... Danish registry'): Zimmerman and McLean criticise our emphasis on survival data based on a 10-year follow-up. It has been emphasised above that the calculated doubling time of 36 out of 39 uveal melanomas was more than 60 days. Death by metastasis occurs 35–40 doubling times after dissemination.³ Thus we know that even survival rates up to more than six years after treatment (35×60 days=6.1 years) will be irrelevant in evaluating or comparing the efficacy of therapeutic regimens, because more than 90% of metastatic deaths must be due to dissemination prior to treatment.

Paragraph 5 ('This curious ... 1–2%'): This curious pattern of peak mortality has been repeatedly and exhaustively explained by us^{12,15} and others.⁸ We regret that Zimmerman and McLean find these explanations unsatisfactory, but we are consoled by the absence of any accurate basis for their criticism. We also have never recommended that this curious pattern be ignored, but have stressed that it must be accepted.^{3,15} The major problem which Zimmerman and McLean refer to in this paragraph would have been solved had they cited recent literature on doubling times.^{5,6,13,14} We are further perplexed, however, to read the unsubstantiated statement that 'It has been the broad experience of ophthalmologists, pathologists, and epidemiologists [all anonymous] that deaths from untreated uveal melanomas are most unusual'. It is noteworthy that Zimmerman and McLean had reported in 1979¹⁶ that they had collected 80 proved cases in which untreated uveal melanomas had metastasised. They then also acknowledged that much pertinent information is lost, because the cases usually do not come to the attention of ophthalmologists or ophthalmic pathologists.

Paragraph 6 ('During ... symptomatic'): For more than 15 years, irradiation of uveal melanomas has been a regular practice in many clinics in the USA and in Europe. So far only one clinic has reported survival rates and the functional results in *all* the treated patients after a mean follow-up period of 10 years.¹⁷ Survival figures for 27 patients treated by enucleation were compared with those of 21 patients who had been treated with cobalt-60 episcleral plaques in the same period. Of the enucleated patients 22% had died from metastases against 57% of the irradiated patients. The median survival after enucleation was 10 years; after irradiation it was 3.8 years. No other clinics have published the survival figures for all the treated cases for a follow-up period of 10 years or more. We are apprehensive that the

ophthalmological community will have to wait for a long time before definitive 10-year survival statistics for all patients treated by irradiation are made available by the majority of the radio-oncology clinics. A collection of anonymous, non-specified cases, as mentioned in the last sentence of the letter by Zimmerman *et al.*, is not very helpful to convince doubting colleagues.

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