Correspondence

Uveal melanoma management

Sir. Two important unresolved issues in uveal melanoma management are: at what stage in the natural history of the disease must intervention occur to avoid development of metastases, and what is the most effective means of treating this tumour? While there are no definitive data that demonstrate that either irradiation or enucleation is superior in preventing tumour-related mortality in uveal melanomas, Professors Manschot and Van Strik have made some false statements and inaccurate assumptions in their paper to marshal the argument that enucleation is better.

A number of assumptions about behaviour of uveal melanomas are backed by tenuous, if any, data. The doubling times of either primary or metastatic melanomas are uncertain. In primary eye tumours the doubling time may range from 30 to 360 days. As we and others have shown, measurement of doubling times is difficult and these data must be analysed cautiously. While Manschot and Van Strik are correct that Gass thought melanomas grow at a constant, slow rate prior to enucleation, our data showed a greater than exponential growth of tumour thickness in some uveal melanomas. In a few cases with simultaneous ocular and metastatic uveal melanoma, metastases often grow at strikingly greater rates than the primary neoplasm. It is difficult to support a central tenet of their argument that the shortest possible interval between dissemination of uveal melanoma and death from metastasis is three years, and that 'a period of less than four years' is irrelevant with regard to influence of ocular irradiation on survival. While it is possible that many patients who die in that interval already have metastatic disease, others may not, and there are no methods at the present time to separate the two groups.

We strongly disagree with a second central point in Manschot and Van Strik's argument that if any tumour cells are still present after irradiation the melanoma is still active. This is analogous to the statement that if there is a body still present, despite the absence of vital signs, it is not dead. The goal of successful radiation is to destroy the reproductive integrity of a tumour. In some tumours cells appear viable at the light microscopic level but have lost their reproductive integrity. Children who died of unrelated causes years after successful retinoblastoma irradiation can have viable appearing cells on histological examination of the treated eye. In some uveal melanoma eyes, enucleated because of radiation complications after helium ion irradiation, we have observed neither mitoses nor evidence of cell cycling using bromodeoxyuridine studies. The statement that 'only regression can save a patient's life if metastases were absent prior to treatment' is incorrect.

In support of their hypothesis Manschot and Van Strik cite the findings of a study which were shown to be invalid. It is true that unadjusted survival of enucleated patients in Gass's study was better than that of radiated patients. However, patients treated by radiation were more likely to have anterior tumours, a known prognostic factor for analysis. When these data were reanalysed using statistical methods which adjusted for this imbalance of prognostic factors, there was no longer any difference in survival between the two treatment types.

The statement that 'despite sufficient lapse of time, almost all survival statistics after irradiation are still based on follow-up periods of a few months to no more than three to four years' is incorrect. We published the first 128 patients treated consecutively with protons with a median follow-up of 5-4 years (range, 2.7–10.5 years). In this series the five-year survival data compare favourably with those of historical controls from previously published large series of patients who underwent enucleation. The statement that 'patients have the right to be treated by enucleation which eliminates any further dissemination' is unparsable. As the authors point out, there is a paucity of long-term data on large numbers of patients after irradiation of uveal melanomas. Short-term analysis of patients treated with either proton irradiation or cobalt plaques and compared with enucleation demonstrated no better survival with the latter technique when asymptomatic factors were adjusted for. We therefore believe that these authors fail to support their argument that enucleation is definitely better than irradiation. Although long-term follow-up studies are necessary for definitive answers, present data indicate that enucleation has no deleterious effect on the likelihood of the development of metastasis.

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Is irradiation a justifiable treatment of choroidal melanoma?

Sir, In reply to the letter by Drs Char et al., the answer to the question, ‘at what stage in the natural history of the disease must intervention occur to avoid development of metastasis,’ is: at the earliest feasible one, preferably before the 7 mm diameter stage (see paragraphs 3 of previous replies). The answer on ‘the most effective means of treating this tumour’ is: enucleation at the earliest feasible stage; this eliminates any (further) dissemination. Irradiation of melanomas has been a regular practice for about 15-20 years. The reason that ‘there are no definitive data that demonstrate that either irradiation or enucleation is superior in preventing tumour-related mortality’ is the surprising lack of reported ≥ 10-year survival results of irradiated patients. Only one clinic has published prospective 10-year comparative survival results of all primary enucleated and irradiated patients in the same period.

So far 39 calculated doubling times of uveal melanomas have been reported. Paragraph 4 of our reply to Drs Zimmerman et al. explains why it is warranted to assume that nearly all metastatic deaths within 6-1 years after treatment are a consequence of pre-existing dissemination. More than 50% of 153 microscopically studied irradiated melanomas did not reveal any necrosis, while 94% contained viable tumour tissue. One wonders that ophthalmic radiotherapists, not being trained pathologists, claim to be able to interpret better the viability of melanoma cells, which presumably they have not studied, than trained pathologists who have studied these tumours. Charet al. state that they have not observed mitoses in some irradiated melanomas. Other pathologists and we have observed mitoses in proton beam and in ruthenium irradiated melanomas. Besides, a body is legally dead because of the presence of signs of death, not because vital signs are absent.

The findings by Gass in his 10-year follow-up of all patients have never been ‘shown to be invalid’. The main criticism is the greater number of anteriorly located melanomas in the irradiation group. Many believe, for no reason, that anterior melanomas have a worse prognosis. Weinhaus et al. found that ‘patients with juxtapapillary melanomas had a worse prognosis than those with tumors in other locations’.

Our statement ‘almost all survival statistics after irradiation are still based on follow-up periods of a few months to no more than three to four years’ was correct at the time it was submitted (see paragraphs 7-9 of reply to Dr Oosterhuis et al.). Our statement that ‘patients have the right to be treated by enucleation which eliminates any further dissemination’ is progressively becoming more supportable. Death from metastases, disseminated after irradiation, cannot manifest itself before six years after therapy. ‘Short-term analyses’ of treated patients are irrelevant. Survival rates after enucleation, irradiation, and observation are identical during the first six post-treatment years if the selection conditions have been identical. Results more than six years after irradiation have been published only twice; both were highly unfavourable.

After enucleation any (further) dissemination is prevented. After irradiation major parts of the remaining tumour tissue (69% after a two-year follow-up period) continue their growth and will shed cell emboli, eventually causing metastatic death after more than six years.

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References

Familial exudative vitreoretinopathy (FEVR) and platelet dysfunction

Sir, Chaudhuri et al. reported abnormal platelet aggregation in patients from two families with familial exudative vitreoretinopathy (FEVR). However, Gole et al. reported no platelet aggregation defects in a patient with incontinentia pigmenti, a separate syndrome with a phenotypically similar proliferative retinopathy. These two conflicting findings are at odds with regard to association between FEVR and platelet function.