Management of intraocular melanoma

Prompt enucleation of the eye has been the conventional management of intraocular melanoma for at least 50 years. In spite of the radical nature of the surgery no follow-up study has shown any clear benefit in terms of improved patient survival. Indeed many studies have demonstrated an increased mortality during the first two years after enucleation — for example, the study of Benjamin et al reported in 1948.1 Zimmerman and colleagues2 were the first to suggest that enucleation might have an adverse effect on survival and claimed that dissemination of tumour cells during enucleation might predispose to subsequent metastatic death.

There is no doubt that the behaviour of intraocular melanoma is very variable, some tumours leading to early metastatic death while others behave in a relatively benign fashion. But even a prolonged tumour-free period after enucleation does not rule out the possibility of late metastatic death, for secondary tumours developing as long as 35 years after enucleation have been described.3 It has been suggested that most intraocular melanomas shed malignant cells into the circulation from an early stage and probably when active growth is clinically detectable, and there is a consensus that in ways not at present understood the immune system may prevent the majority of such cells from developing into frank metastases.

Previously when the diagnosis of intraocular melanoma was made purely on clinical grounds mistakes were made in up to one-fifth of eyes enucleated.4 Now that numerous ancillary investigations are available (fluorescein angiography, echography, CT scanning, magnetic resonance imaging, immunoscintigraphy, and surgical biopsy) mistakes are rare and in centres specialising in ocular oncology occur in less than 1% of eyes removed for suspected melanoma. It is generally agreed that enucleation of an eye for melanoma should not be undertaken without a full diagnostic appraisal, and where doubt exists the patient should be seen in a centre experienced in the management of this tumour.

Zimmerman's suggestion that enucleation might have an adverse effect on survival in patients with melanoma has led to an increased interest in more conservative forms of management. The simplest form of conservative management is to keep the tumour under observation. Observation alone has, however, been followed by growth of the tumour in a significant proportion of cases,5,6 and patients whose tumours grow may subsequently develop metastases (17% in one study7).

The major options for preserving the eye while eradicating the tumour lie between various forms of radiotherapy and local surgical resection of the tumour.

Melanoma is a radioresistant tumour requiring for its eradication a dose of radiation in excess of that which can be tolerated by many normal ocular tissues. To be used in the management of ocular melanoma radiotherapy has to be concentrated in the tumour and the dose to other radiosensitive ocular tissues minimised. Two main approaches have been used. Firstly the use of radioactive plaques containing such isotopes as "cobalt,8 10iodine9 (both of which are γ ray emitters), or "ruthenium/rhodium10 (which is mainly a β ray emitter). An alternative treatment is by a beam of charged particles (protons or helium ions) accelerated in a cyclotron11,12. This procedure requires an expensive and sophisticated technology but can concentrate the radiotherapy within the tumour, with marked sparing of surrounding tissues, by making use of the physical characteristics of high energy particles. "Cobalt plaque therapy, first used by Stallard13 in the management of intraocular melanoma, has been shown to be followed by a high incidence of late postirradiational vascular damage in the eye,14 and none of the methods used for the radiotherapy of intraocular melanomas is entirely free from possible adverse irradiational side effects.

The other major form of treatment is local surgical resection, a method used for some 20 years in Glasgow15 and now gaining acceptance in a number of other centres. The local resection of even sizeable tumours contiguous with the optic disc is possible, and indeed the results of treating posteriorly situated tumours by this technique are somewhat better than in the case of tumours involving both choroid and ciliary body.15 The advantages of local resection in addition to the immediate elimination of the tumour are that histological confirmation is obtained, and information of prognostic significance is provided, such as the type of cells present in the tumour. The disadvantages are that immediate morbidity is higher than with radiotherapy, though interestingly the long term visual outcome may be better after successful local surgical resection than after radiotherapy, for a progressive loss of vision of the order of 10% per annum has been noted among eyes treated by radiotherapy.16

Although the preservation of vision is a commendable aim, the primary goal of treatment of uveal melanoma is the prevention of subsequent metastatic death. So far the published statistics of radiotherapy or of surgical resection have shown no benefit of one method as against another or indeed of conservative management as against enucleation. Subsequent metastatic death appears to be determined mainly by whether or not there are epitheliod cells in the tumour and to less extent by such factors as the location of the tumour (anterior tumours having a poorer prognosis than posterior), the volume of the tumour, and the presence or absence of extrascleral spread. In relation to the last, some studies have shown by multivariate analysis that extrascleral spread is not a particularly important risk factor on its own, merely that it points to an adverse cell type in the tumour.17

At present we thus have at our disposal a number of methods for the control of the local disease. The choice of treatment is greater for smaller than larger tumours, all forms of management being suitable for tumours of up to 10 mm in diameter and up to 4 mm in thickness (laser photocoagulation, surgical resection, plaque therapy). For tumours in the range 10–15 mm in diameter local surgical resection, plaque therapy, or proton beam therapy may be indicated, while for larger tumours surgical resection or proton beam therapy may be employed, though enucleation is still required for very large tumours not susceptible to conservative management.

No treatment seems to be of value in improving survival, and the assumption has to be that most patients with an adverse cell type in the tumour already have micrometastases at the time of diagnosis. At present the goal of the ocular oncologist is to devise methods aimed at destroying sub-
clinical micrometastases in the hope of improving survival, and secondly to improve techniques for the local control of the tumour to achieve the lowest morbidity and best visual acuity in both the short and the long term. Although the evidence so far suggests that various forms of conservative management of uveal melanoma are comparable to enucleation in terms of subsequent survival, the absence of any really firm data has prompted the establishment of a cooperative multicentric trial in the United States to compare the results of local plaque delivered radiotherapy and enucleation in terms of survival. Many aspects of this study have been criticised, but there is no doubt that useful information will eventually be obtained — though the cost at some $20 million is high. Though excellent techniques are available to control the local disease, there is still some controversy about which size or location of tumour is best suited to one or other of the available methods of treatment. New techniques such as ultrasound or microwave induced hyperthermia in the tumour and photochemotherapy are being assessed, as is the use of chemotherapy, including the theoretical possibility of linking cytotoxic drugs or suitable radionuclides to monoclonal antibodies against melanoma antigens in the hope of increasing the specificity of tumour destruction.

As matters stand at present, enucleation of the eye for melanoma is now regarded as an infrequent and 'last ditch' method of treatment.

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