

## CORRESPONDENCE

### Risk factors for residual and recurrent and metastatic uveal melanoma after trans-scleral local resection

EDITOR,—Damato *et al*<sup>1,2</sup> suggest a great potential for bias in their two papers. Reports on metastatic death rate after management of uveal melanomas require a survival rate of at least 10 years of all patients.<sup>3</sup> Follow up periods in their two studies varied from 7 days to 20.9 years with a median of 33 months. Only 24 out of 332 patients had a follow up of  $\geq 10$  years.

The paper on risk factors for residual and recurrent melanoma<sup>1</sup> is based on an irrelevant simplification of a mostly impossible differentiation between these two 'types' of remaining melanoma. The only criterion was the point of time separating the 40th and the 41st postoperative day. Both types represent failure of the management. Eighty one of 310 patients (26%) retained intraocular melanoma; 46% of these eyes had to be enucleated.

The described drastic surgical approach often has severe consequences. I quote: 'Incomplete tumour removal follows retinal detachment as the commonest cause of visual loss and enucleation (p 102). Forty eight patients received adjunctive plaque radiotherapy. Ocular depression by pars plana vitrectomy was performed in 147 patients (p 104). External plombage and/or internal tamponade with gas or silicone were used to prevent retinal detachment if a large retinal defect was created (p 103). Now, adjunctive plaque radiotherapy, laser photocoagulation, and/or cryotherapy are applied irrespective of histological clearance. All patients should receive additional therapy if possible. The placement of a radioactive plaque at the end of a resection may be difficult or impossible... Furthermore, radiotherapy may cause radiational optic neuropathy, maculopathy, or cataract (p 107)'.

The drastic therapeutic modality causes much depression, as do the remaining functional results which are poor. The vision in the operated eyes at the time of surgery was  $\geq 6/12$  in 58.6% and  $\leq 6/60$  in 17.8% of cases (their Table 1).<sup>2</sup> Moreover, 1 year after surgery vision was  $\geq 6/12$  in 23% and  $\leq 6/60$  in 62% of cases (Table 4).<sup>2</sup> A recent review<sup>4</sup> shows that 3 years after radiotherapy, using any modality, vision had decreased to  $\leq 6/60$  in about 50% of cases. A further decrease of 10% per annum was noted by others.<sup>5</sup> Vision was also measured with pinhole aperture, which is not representative of the quality of life.

Furthermore, the paper on risk factors for metastatic uveal melanoma<sup>2</sup> lacks introductory basic oncological knowledge. Metastatic death occurs 35–40 doubling times after dissemination. Out of 39 calculated doubling times of uveal melanomas, 36 appeared longer than 60 days.<sup>3</sup> Thus, metastatic death generally occurs at least  $35 \times 60$  days = 6 years after dissemination; actually it is 6 to even 50 years thereafter. In a series of 12 cases<sup>6</sup> of primary enucleated uveal melanomas, five patients died of metastasis 47, 45, 30, 28, and 27 years respectively after enucleation. A statistically significant difference in impact on survival by an analytical comparison of treatment modalities on the uveal primary cannot be established within the first 7–8 years

after treatment, because all metastatic deaths in that period are caused by pretherapeutic metastases. All published reports on comparison of death rates after various managements of uveal melanomas substantiate this postulate.<sup>3</sup> Damato *et al*<sup>2</sup> suggest that this might not be true with regard to adjunctive plaque radiotherapy after trans-scleral local melanoma resection (p 114). Their follow up periods after this adjunctive therapy have, however, been much too short and are, therefore, irrelevant.

Proof of the statistical invalidity of their studies is the conclusion in the abstract (p 109)<sup>2</sup> that 'metastatic death was not significantly associated with (i) incomplete tumour excision or (ii) small residual/recurrent tumour treated by enucleation'. On p 102<sup>1</sup> the authors state, on the contrary, that 'incomplete tumour removal is also associated with an increased incidence of metastases'! Also invoking a question mark is the statement (p 109): 'Sight conserving treatment...does not influence survival in patients with medium sized and large tumours because fatal tumour dissemination has already occurred by the time the patient first presents'. Generally, ophthalmic surgeons do not feel justified in advising sight conserving treatment in patients with known metastatic melanoma. In case of doubt of metastasis, their first duty is always to eradicate completely the uveal melanoma to prevent future metastases. The first ethical command of the medical profession still is Hippocrates' oath: 'I will never do harm to anyone, nor will I give advice which may cause his death'.<sup>7</sup> Every treatment modality of uveal melanoma which risks leaving behind vital melanoma stem cells may cause metastatic death. Every day, mortal emboli can be disseminated if the primary is not eradicated completely. Damato *et al* left vital melanoma behind in at least 81 of 310 patients (p 102); this means for at least 81 of their patients an avoidable increase of lethal risk. A future 10 year follow up of all their operated patients will regretfully justify this fear. Jensen<sup>8</sup> proved after 25–35 years of follow up of 99.8% of 302 patients, that primary enucleation of posterior uveal melanoma in 1943–52 had saved 49% of these patients from metastatic death after 25–35 years. The figure of 49% should be improved markedly with modern diagnostic facilities.

Moreover, the impact of enucleation on the quality of life appeared to be insignificant in vision dependent activities as working, driving, reading, and television viewing.<sup>9</sup> Fifteen years after enucleation 90% (18/20) still could drive and 96% (25/26) still could read. Another postenucleation study on the same activities<sup>10</sup> reported that 94% (48/51) noted no change in any of these activities after a mean follow up of 89 months.

The results reported by Damato *et al* should demand that they be reluctant to realise the further therapeutic experiments considered (p 107). The quality of life after primary enucleation generally is much better than after their 'sight conserving' experimental therapy. After primary enucleation there is no anxiety about harbouring a malignancy which might cause a much feared metastatic death. Moreover, these privileged patients do not suffer from the physical and psychological stresses caused by the frequent re-examinations and retreatments of recurrences and by the various surgical or radiological complications.

W A MANSCHOT

Erasmus University, Institute of Pathology,  
Rotterdam, Netherlands

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### Reply

EDITOR,—We note Manschot's comments on our two recent articles on trans-scleral local resection of uveal melanoma.

Manschot criticises our studies because few patients have been followed up for more than 10 years. We have included all 332 patients treated since 1969 in accordance with conventional statistical methods of analysing outcomes after treatment of cancer. Our follow up times (96 patients more than 5 years) are long enough for us to have demonstrated statistically significant results with respect to known risk factors for tumour behaviour. We certainly hope to repeat these studies when more patients have longer follow up times, so that we can continue to assess to what extent survival is influenced by factors such as residual tumour, clinical local tumour recurrence, and adjunctive plaque radiotherapy.

Although Manschot considers incomplete tumour excision to be 'failed management', our results parallel those obtained following local resection and adjunctive radiotherapy of breast cancer,<sup>1</sup> which is no longer regarded a medical experiment but which has become accepted practice worldwide. Because of the theoretical risk of metastases from residual or recurrent tumour we now advise adjunctive photocoagulation and plaque radiotherapy in all cases, although well aware that the latter may compromise the visual result in some patients in the long term.

With respect, we feel that Manschot exaggerates the 'drastic' nature of local resection and its various components. The local resection itself usually takes between 2 and 3 hours, including the time for performing a limited vitrectomy (10 minutes), inserting a ruthenium plaque (10 minutes), and performing binocular indirect laser photocoagulation (15 minutes). Removal of the ruthenium plaque 1 or 2 days later takes about 30 minutes and patients are allowed home the following day. The extent of these interventions alone is greater than that of plaque radiotherapy, which is why we only resect tumours that we consider to be unsuitable for plaque or proton beam radiotherapy.

Manschot's comments on psychological wellbeing after local resection can only be speculative, because as a pathologist he could not have met many patients treated conservatively, let alone by local resection. Loss of an eye is a significant psychological trauma for most patients and recent studies indicate that quality of life after plaque radiotherapy is superior to that after enucleation, despite the need for follow up (Y Brandberg, E Kock, S Seregard, A F Trampe, Psychological consequences of choroidal melanoma, JERMOV 1995, personal communication). Our patients have selected local resection in preference to enucleation after being fully informed of all the risks and expected outcomes and are therefore highly motivated. Our impression is that very few of these patients express regret about taking this decision, even when complications occur. Nevertheless, formal quality of life studies are necessary and, indeed, are in preparation. These will take into account not only visual acuity but also the visual field, which is often more useful if the fellow eye is healthy.

B DAMATO  
St Paul's Eye Unit,  
Royal Liverpool University Hospital,  
Prescot Street, Liverpool L7 8XP

J PAUL  
Clinical Trials Unit, Beatson Oncology Centre,  
Western Infirmary, Glasgow G11 6NT

W S FOULDS  
Ross Hall Hospital, 221 Crookston Road,  
Glasgow G52 3NQ

1 Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. *N Engl J Med* 1995;333:1444-55.

### Indications for trans-scleral local resection of uveal melanoma

EDITOR.—In his recent editorial,<sup>1</sup> Shields criticises us for not including our indications and contraindications for local resection of uveal melanoma. Our indications and contraindications are, indeed, different from his and we thought it would be useful to itemise them as follows:

(1) A large tumour thickness and secondary retinal detachment complicate radiotherapy but facilitate local resection. Ruthenium plaque radiotherapy is contraindicated for tumours more than 5 mm thick and, with larger tumours, iodine plaque radiotherapy and charged particle radiotherapy have a high complication rate.<sup>2,3</sup> Our main indication for local resection, therefore, is a tumour size deemed excessive for radiotherapy.

(2) A tumour is not inoperable just because it has a large basal diameter (>15 mm). Statistical studies show that large diameter is not an independent risk factor for visual loss.<sup>4</sup> There is an increased risk of local tumour recurrence, however, so that special precautions, such as wide clearance margins and adjunctive treatment, are necessary.<sup>5</sup> Although there is an increased probability of metastatic disease,<sup>6</sup> this is no worse than after enucleation.<sup>7</sup>

(3) Tumour extension to within one disc diameter of the optic disc is not a contraindication. Although the risks of local tumour recurrence,<sup>5</sup> and retinal detachment are increased, both of these complications are usually preventable and treatable, unlike

radiational optic neuropathy, which causes severe visual loss and neovascular complications.

(4) Tumour proximity to the fovea is not a contraindication, because although central visual loss may be inevitable, this is also the case with any other form of treatment. Preservation of the temporal field of vision is worthwhile even if central vision is good in the fellow eye. For many patients, preservation of both eyes is important not only for self esteem, but also for social and occupational reasons.

(5) Retinal invasion is not a contraindication, because it is usually possible to preserve an intact retina, prevent retinal detachment by external plombage and photocoagulation, and prevent local tumour recurrence by photocoagulation and plaque radiotherapy. Retinal perforation by tumour causes problems not only with local excision but also after radiotherapy, and if there is vitreous seeding enucleation is the safest option.

(6) Extraocular extension, if small, is not a contraindication, because it can be excised en bloc, with the full thickness scleral defect closed using a lamellar graft from another part of the same eye.

(7) Old age is not in itself a contraindication to local resection despite the use of hypotensive anaesthesia for controlling haemorrhage. If anything, old age facilitates haemostasis because during hypotensive anaesthesia bleeding stops at a higher pressure than is the case in younger patients. We have operated on patients older than 75 years of age without incurring systemic complications and, statistically, old age is not a risk factor for visual loss.<sup>4</sup>

(8) Diffuse melanomas are very aggressive, and best treated by enucleation.

(9) Involvement of more than a third of ciliary body or angle creates difficulties not only for local resection but also radiotherapy, and is an indication for enucleation unless the patient is extremely reluctant to lose the eye, when some form of combination treatment may be attempted.

(10) Optic disc involvement is usually a contraindication, although in some cases it is possible to peel the tumour away from the disc and treat the area by photocoagulation.

(11) Systemic contraindications to systemic hypotensive anaesthesia vary from anaesthetist to anaesthetist, and include any significant circulatory, cardiac, pulmonary, hepatic, or renal insufficiency. Diabetes mellitus is not a contraindication.

(12) As with any surgical procedure, local resection (which includes vitrectomy as an integral part of the procedure) should be performed only by surgeons who have a sufficient competence in the technique and the ability to deal with recurrent tumour. Incomplete excision and local tumour recurrence are not associated with an increased incidence of metastatic disease<sup>6</sup>; however, adjunctive plaque radiotherapy seems to improve the chances of survival<sup>8</sup> so that it is now difficult to justify local resection without additional treatment.

Unlike Shields, we do not consider local resection to be 'a time consuming procedure which requires more complicated postoperative care'. The procedure is usually completed within 3 hours, depending on the size of the scleral flap, and this is comparable with many vitreoretinal procedures. Patients return to a general ophthalmic ward after about 2 hours in a recovery suite. They are mobile on the first postoperative day and are allowed home on the third postoperative day. Subsequent

follow up is the same as for any other form of conservative therapy for uveal melanoma.

B DAMATO  
St Paul's Eye Unit,  
Royal Liverpool University Hospital,  
Prescot Street, Liverpool L7 8XP  
W S FOULDS  
Ross Hall Hospital, 221 Crookston Road,  
Glasgow G52 3NQ

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### Reply

EDITOR.—In their response to my editorial, Damato and Foulds state that I criticised them for not publishing their indications for local resection of uveal melanoma. I re-read the editorial and I do not believe that I was critical. I am sure that Drs Damato and Foulds are aware of my admiration for their pioneering work. However, since they had not mentioned their indications, I felt it would be appropriate to summarise for the readers of the *BJO* what I believe to be the current relative indications and contraindications for local resection, based on personal experience. In the editorial I stated that my comments regarding the indications 'represent a personal viewpoint that may differ somewhat from that of Damato and associates'. I also stressed that our indications and contraindications were relative ones and there are no absolute rules.

I find that our differences are minor but they do warrant further comment, based on our personal experience.<sup>1</sup>

(1) My colleagues and I agree that tumours with greater tumour thickness and secondary retinal detachment can be successfully resected and that retinal detachment may actually facilitate the procedure. However, we do not agree that thicker tumours in the peripheral choroid and ciliary body have such a high complication rate following plaque radiotherapy. The main complication is cataract but the ophthalmologist can remove a cataract with restoration of vision, provided that there is no significant posterior radiation retinopathy. Cataract is certainly a common problem after local resection as well. We have treated with plaques many patients with ciliary body tumours greater than 3 clock hours with satisfactory results and we are generally happy that we did not attempt to resect the tumours. After plaque radiotherapy for peripheral melanomas, the visual acuity usually remains