Improved iodine-125 plaque design in the treatment of choroidal malignant melanoma

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Abstract

The use and development of iodine-125 plaque therapy for choroidal malignant melanoma are described. Since 1975 experience has led to changes in plaque design and insertion techniques. Twenty-one patients were irradiated with local episcleral iodine-125 plaques. Three patients required a second plaque for tumour recurrence. Four eyes were enucleated because of continued tumour growth and a further eye was removed because of glaucoma secondary to radiation retinopathy. Two patients (9·5%) died of metastases. The remaining 19 patients are alive and clinically clear of metastases, with a mean follow up time of 73·1 months (range 43–142 months).

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Radiation therapy has become an established form of therapy for posterior uveal malignant melanomas.[1 2] Interest in this modality has increased since Zimmerman and co-workers[3-5] suggested that enucleation may be detrimental to the patient because of the sharp increase in the incidence of death from metastases which occurs after the operation. Though external radiotherapy in the form of proton beam irradiation[6] and helium ion therapy[7] are being used they are only available in a few centres. The application of local radiotherapy administered by radioactive episcleral plaques has gained widespread acceptance.

Radon seeds were introduced by Moore[8] in 1930. In 1966 Stallard reported the use of cobalt-60 plaques in a large number of patients with choroidal malignant melanomas,[9] and several other studies have since been published.[10-15] Because of the inherent problems encountered with this high energy source various attempts have been made to use low energy radioactive sources. Lommatzsch[16] used ruthenium-106 but did not recommend its use for tumours thicker than 5 mm. Rotman *et al*[17] mentioned the use of iodine-125 and in 1976 Sealy *et al*[18] first reported the use of this isotope in three patients with ocular tumours including one with a choroidal melanoma. Subsequently Stannard *et al*[19] reported the use of iodine-125 plaques in the treatment of retinoblastoma. The low energy rays of iodine-125 permit easy screening of nearby structures. The radiation is 99·9% absorbed by a sheet of gold 0·2 mm thick which compares favourably with cobalt-60 which requires an 11 mm block of lead to attenuate it by 50%.[18 20 21] The isotope emits *x*-rays with an energy of 27 to 35 keV, and has a relative biological effectiveness (RBE) of 1·5 relative to cobalt-60.[22] Moreover it has recently been reported that the oxygen enhancement ratio for iodine-125 is less than that of iridium-192 and the RBE is especially high for hypoxic cells.[23] For the purpose of plaque therapy the tissue penetration is good and similar to high energy isotopes over short distances.[24] The tissue half value layer is 20 mm which allows large choroidal melanomas to be treated.

Iodine-125 is supplied, absorbed onto silver rods or resin beads, in the form of seeds measuring 4·5 mm in length and 0·75 mm in diameter. The short half-life of iodine-125 (60 days compared with 5·26 years for cobalt-60) is a disadvantage but, as the seeds are commercially available and can be re-used several times during this period, this does not constitute a major

Table 1 Summary of patient data and treatment

Patient	Age	Sex	Eye	Size (mm) (L×W×H)	Position	Proximity to optic nerve (mm)	Date of plaque	Follow up (months)	Initial VA	Final VA	Dose apex TDF (Gy)	Repeat plaque	Notes
GO	58	F	R	15×15×7	ST	0	20/3/75	139	CF	E	170 (110)	N	Recurrence
QL	59	F	R	10×9×8	IT	7	19/4/78	142	6/12	E	90 (50)	N	RD, RR, glaucoma
MB	67	F	L	13×16×6	T	4	8/5/78	105	6/24	E	105 (50)	N	Recurrence
HL	59	M	L	11×12×5	IN	0	9/6/80	114	6/12	6/12	164 (112)	N	Cataract
JH	67	M	L	10×10×6	ST	5	9/10/81	43	6/9	6/24	144 (126)	Y	RD, recurrence, Mets
BG	72	F	L	12×15×4	SN	2	23/9/83	76	6/6	6/6	115 (61)	N	
MW	20	M	R	20×19×5	SN	1	3/2/84	74	6/24	E	174 (81·4)	Y	RD, recurrence
RG	44	M	L	10×10×8	IN	5	17/2/84	78	6/6	CF	164 (80)	N	RD, cataract
LA	42	F	R	6×8×5	T	3	12/3/84	72	6/12	CF	166 (80·6)	N	RR
KB	60	F	R	10×10×5	ST	2	19/4/84	71	6/9	6/18	165 (80)	N	
AA	45	M	L	12×10×6	IN	5	24/9/84	68	6/5	6/18	152 (44)	N	RD, RR, cataract
WG	73	M	L	11×11×8	IN	1·5	3/10/84	58	6/60	HM	153 (48·2)	N	RR
DM	62	F	L	8×8×4·9	IN	0	23/11/84	65	6/6	6/12	149 (47·7)	N	
MH	57	M	R	12×12×4·3	IT	2	14/1/85	64	CF	CF	158 (43·7)	N	
AH	47	F	R	6×6×4·6	T	5	11/2/85	53	6/9	6/24	150 (44·8)	N	RR
EP	25	M	R	12×9×7·6	IT	6	19/2/85	61	6/9	E	150 (45·4)	N	Recurrence
VJ	55	L	R	9×7·5×5·2	IT	1	25/6/85	60	6/12	CF	150 (45·4)	N	RR, Vit hx, cataract
DS	39	F	L	11×9×7·5	I	2	9/7/85	53	6/9	HM	145 (40·7)	N	RR, cataract
NG	58	M	R	16×15×10·2	T	6	11/2/86	47	6/12	CF	154 (66)	N	RR, Vit hx, Mets
LK	32	F	L	12×12×8·2	IN	0	8/8/86	46	CF	HM	152 (78·6)	N	RD, RR
MC	69	F	R	9×9×7·8	IT	2	30/9/86	46	6/24	6/9	99·5 (57·5)	Y	Recurrence

VA=visual acuity; CF=count fingers; HM=hand movements; E=enucleation; RD=pre-operative retinal detachment; RR=radiation retinopathy; Vit hx=vitreous haemorrhage; Mets=died of metastatic disease; ST=superotemporal; IF=inferotemporal; SN=superonasal; IN=inferonasal; S=superior; I=inferior.

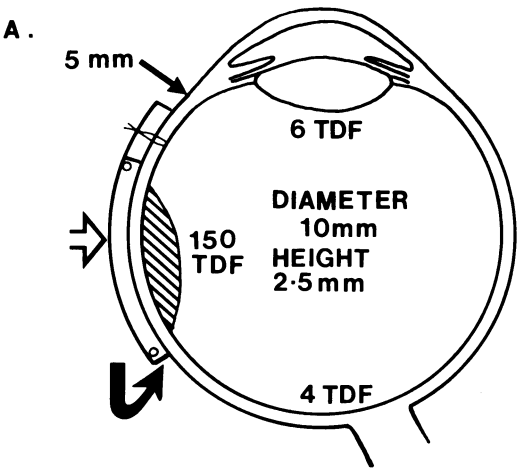

Figure 1A

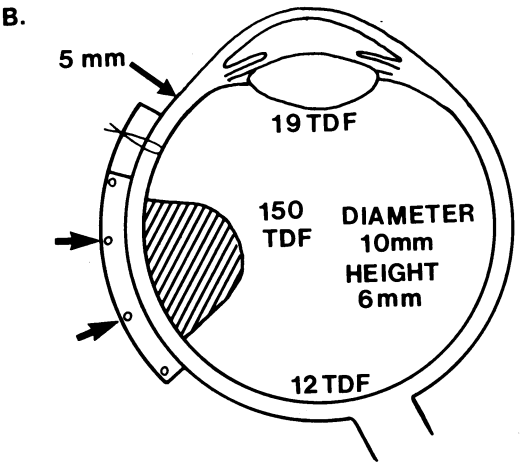

Figure 1B

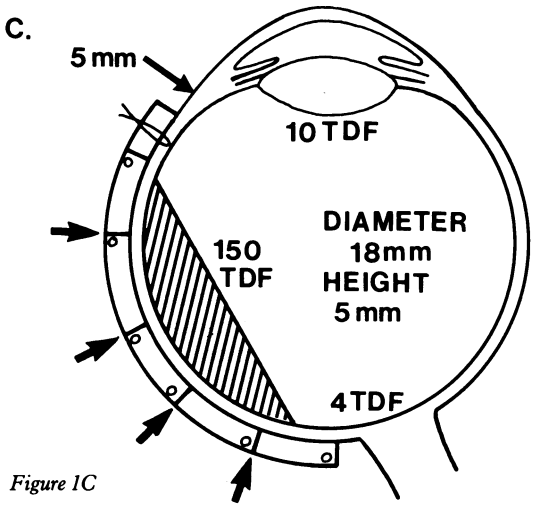

Figure 1C

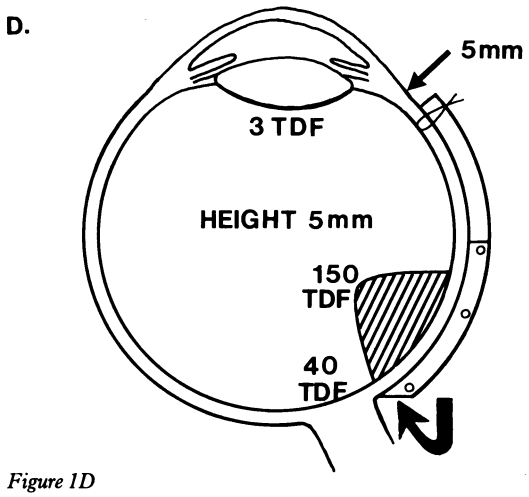

Figure 1D

Figure 1 Diagrammatic representations of various plaque designs for tumours of different sizes and position. (A) Standard plaque. Small rather flat lesion. No shielding other than returned edge (arrow) and backing (open arrow) needed. (B) Extra sources (arrows) added to ensure an adequate dose to apex and to base of tumour. (C) For larger lesions with many sources, it is necessary to place sources against ridges (arrows) to protect adjacent structures. These extra sources are needed to ensure a homogeneous dose to the base. Note returned edge protects optic nerve. (D) The tumour reaches the optic nerve but does not invade it. The returned edge is angled outwards at 45° (arrow) to throw the beam wider at this point, the oblique beam passing over the optic nerve.

problem. The excellent screening characteristics, good tissue penetration, low oxygen enhancement ratio, and high RBE make iodine-125 an ideal source for local radiotherapy treatment of choroidal melanomas and other tumours in and around the eye. Recently iodine-125 was selected for use in the Collaborative Ocular Melanoma Study.[25] This paper presents our experience with this isotope for the treatment of choroidal malignant melanomas and discusses the change in plaque design since our earlier communications.[18 26]

Patients and methods

Twenty-one patients with choroidal malignant melanomas were treated with radioactive iodine-125 plaques during the period 1975 to 1986. Eleven females and 10 males are included in this series with a mean age of 52·6 years (range 20–73 years) (Table 1). All patients were jointly assessed in a combined ophthalmology-radiotherapy clinic. A full clinical examination was performed together with a full blood count, erythrocyte sedimentation rate (ESR), serum chemistry and liver enzymes, chest *x*-ray and, on most patients, a liver ultrasound examination. All the patients were free of metastases at the time of operation. Ophthalmic assessment included direct and indirect ophthalmoscopy (and fundus contact lens when indicated), fundus photography, fluorescein angiography, ultrasonography, and transillumination. The tumour dimensions were measured clinically and tumour height in later cases was obtained by B-scan ultrasonography. On occasions an examination under anaesthetic was performed especially with anterior tumours. This permitted accurate delineation of the anterior edge and in particular the posterior extent of the lesion could be judged when retinal detachment was present, by performing conjunctival peritomy followed by gentle posterior indentation and transillumination. Ultrasonography and computed tomography (CT) scans were used to help delineate the posterior edge when retinal detachment was present. Recently we have also used magnetic resonance imaging (MRI) scans.[27]

According to Shields's classification[1] seven tumours treated in this series were classified as medium sizes and 14 as large (Table 1). The

Table 2 Calculated radiation doses to optic disc and lens, showing the importance of returned plaque edges

Plaque dimensions			Dose to optic disc		Dose to lens	
Sagittal (mm)	Coronal (mm)	Plaque position	Without edge (Gy) (TDF)*	With edge (Gy) (TDF)	Without edge (Gy) (TDF)	With edge (Gy) (TDF)
10	10	Centred on equator	10·2 (19)	6·2 (10)	13·0 (27)	8·3 (14)
10	25	Centred on equator	15·4 (33)	7·6 (13)	19·5 (46)	10·0 (19)
20	10	Abutting optic nerve	76·7 (292)	27·2 (72)	11·0 (21)	8·1 (14)
20	25	Abutting optic nerve	78·0 (299)	14·3 (30)	15·1 (32)	8·4 (15)

*Time-dose factor (TDF) values are shown in parentheses and assume an RBE of 1·5. Tumour height is taken as 5 mm, tumour apex TDF dose is 150, and treatment time is 4 days in each case.

mean dimensions of the tumours treated (length ×width×height) were 11·2×11·1×6·35 mm (range 6–20×6–19×4–10·2 mm).

Plaque design

All plaques are designed and made on an individual basis by the radiotherapist, the medical physicist, and technical staff. If optimum shielding is to be obtained 'standard' plaques cannot be used because of variations in tumour size and height and the variable relationship of tumour to the optic nerve, macula, lens, and ciliary body. The position of the tumour is drawn on a model eye with coordinates marked on it as described by Stannard *et al.*[19]

The manufacture of the gold backing and returned edge is similar to that described previously.[26] The returned edge prevents radiation being emitted sideways from the plaque. This reduces the dose to adjacent normal tissues provided the edges are straight and the seeds are placed adjacent to the edge (Fig 1). Ridges within the plaque control the distribution of the radiation (Fig 1C). Table 2 gives theoretical examples of radiation doses received by the lens and nerve head for various sizes of plaque in different positions, with and without the returned edge. The effective shielding of these structures allows lesions close to the optic nerve to be irradiated more safely. Large high tumours are difficult to treat by other types of plaque as effective radiation doses cannot be given to the apices of the tumours without excessive radiation to other ocular structures. With our system the physical practical limit of the radioactive surface area of the plaque is about 400 mm² (20×20 mm). The design of the radioactive element of the plaque is calculated by a physicist, the number of seeds used is adjusted to allow an adequate dose of irradiation to the apex of the tumour within an acceptable time of 3–5 days. A range of doses and dose rates have been used in this series and the dosimetry has now been standardised for different dose rates using the TDF (time-dose factor) concept.[28] The mean TDF was 146 (range 90–174) taking the RBE of iodine-125 to be 1·5. The mean duration of time the plaque remained in situ was 103·2 hours or 4·3 days (range 62–144 hours). Seed activity is usually about 4 mCi but seeds with 20 mCi activity can be used if an asymmetric dose distribution is required. The seeds are placed accurately in the plaque in their predetermined position and held in place with Tensol cement and, when dry, covered with a layer of thick acrylic solution. Loading time is about 1 hour.

The original plaques[18 26] were made to cover the tumour with a 3 mm margin. Scleral sutures were placed at the edges of the plaque; however insertion was technically difficult, especially with posterior lesions. This problem has been overcome by incorporating an anterior inactive extension to the plaque. The front edge of the plaque is then sutured to the sclera 5 mm posterior to the limbus, as depicted in Fig 1.

During insertion a sector limbal conjunctival peritomy is performed and the necessary external ocular muscles are detached. The radioactive plaque is introduced and sutured to the sclera, with the anterior edge 5 mm from the limbus, using the suture holes provided. There is thus no suturing or manipulation deep in the orbit except for transillumination or indentation along the edge of the plaque to check the relative positions of the plaque and tumour. The detached muscle(s) are temporarily attached to stainless steel loop(s) added to the outside of the plaque. There is excellent staff protection during the insertion of the plaque and the procedure takes approximately 30 minutes.

Results

The patients in this series were followed for a mean period of 73·1 months (range 43 to 142 months) (Table 1). Fifteen patients showed cessation of tumour growth. Five of these had almost complete tumour regression and in 10 the tumour decreased in size and especially in height. Six patients had recurrent or continued growth of their tumours. Three of these patients then underwent enucleation at 3, 54, and 60 months respectively after the plaque therapy. The other three patients received a second iodine-125 plaque: 4, 9, and 15 months respectively after the first application. One of these patients had the eye enucleated 13 months after the first plaque because of continued growth while the other two had cessation of growth. Two patients died of metastatic disease 43 and 46 months following plaque therapy: one was locally clear of disease and the other had had a successful retreatment with a second plaque. The remaining 19 patients are alive without evidence of metastases.

Four (28·6%) of the 14 patients who presented with useful vision of 6/12 or better retained useful vision. Four patients retained vision of 6/18 to 6/60. Three patients presented with visual acuities of less than 6/60 and a further 10 eyes lost vision to this level including patients undergoing enucleation. The overall trend was for patients to lose vision with time (Fig 2).

Complications are shown in Table 1. Five patients developed posterior subcapsular lens

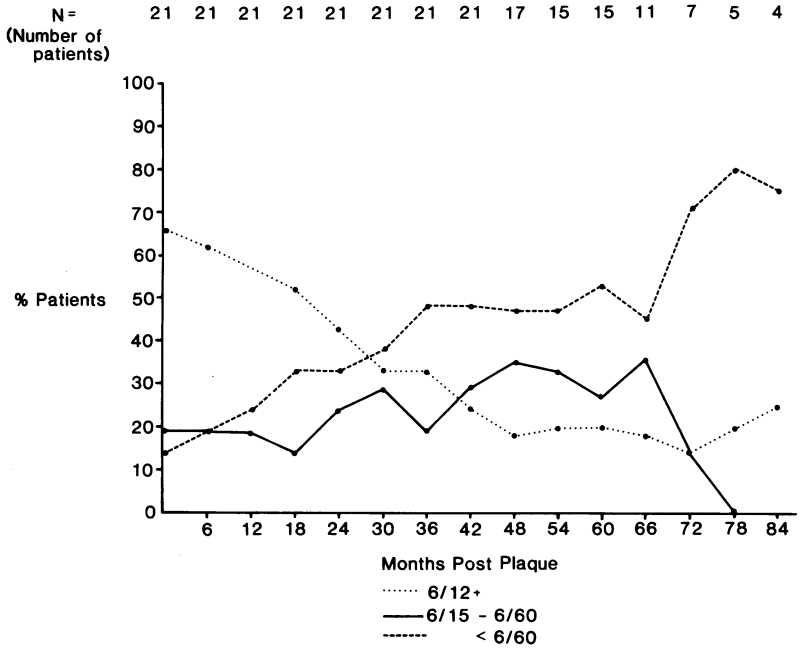

Figure 2 Graphs to show percentage of eyes with vision in the three acuity groups against time.

opacities following irradiation; four eyes have subsequently undergone successful lens extraction. Two eyes developed vitreous haemorrhage which was surgically cleared in one patient and has virtually resolved in the other. Nine patients showed evidence of radiation retinopathy with the occurrence of exudates and/or retinal haemorrhages. In three patients the exudative retinal detachment present before treatment extended soon after plaque therapy and resulted in further loss of vision. One eye developed neovascular glaucoma and was enucleated. No cases of optic atrophy, ocular hypotension, scleral necrosis, or dry eye occurred in this series.

Discussion

In this series two patients (9·5%) developed metastases and subsequently died. The other 19 are clinically free of metastatic disease. The mean follow up is 73·1 months. The number of patients treated in our study is small but the mortality rate is comparable to other studies: 5–12% with cobalt-60 plaques,[12 13 15] 17% with iodine-125 plaques.[29] All our patients had medium or large tumours with documented growth and would have been offered enucleation if radioactive plaques had not been available.

Though only four patients (19%) retained useful vision of 6/12 or better 16 patients (76%) retained their eye and thus avoided the psychological and cosmetic trauma of enucleation. With the passage of time the trend is for patients to lose vision following plaque therapy (Fig 2). Five patients in this study required enucleation, four for recurrent tumour growth. Two were among the earliest we treated with iodine-125 plaques: one patient's tumour was inaccurately localised because of a large serous retinal detachment and the other patient had recurrence at the tumour edge because of poor plaque placement. The new plaque design allows accurate placement of the plaque by aligning it to the limbus, and correct placement is confirmed by scleral indentation or transillumination along the side of the plaques. Another patient who had an enucleation for tumour recurrence was treated twice with iodine-125 plaque. His tumour was one of the largest tumours treated in the study measuring 20×19×5 mm; in addition a large retinal detachment was present on initial examination.

In this series there was a wide range of radiation doses and dose rates. Those patients receiving a higher TDF did not have an improved response. We now aim to deliver a TDF of approximately 150 to the apex of the tumour within 3–4 days provided that the doses to the optic nerve, ciliary body, and lens do not exceed the tolerance of these tissues.

The ability to screen the radiation from iodine-125 by gold foil ensures protection of staff and allows us to confine most of the radiation to the treated area thereby reducing the dose to surrounding sensitive structures, unlike cobalt-60 plaques where damage extends beyond this area.[30] It has also permitted us to treat tumours close to the optic disc with few complications. With cobalt-60 plaque therapy a 5 mm distance between plaque and optic disc is recommended.[31]

The tumours responding to irradiation demonstrated variable response. Five tumours showed good regression with marked diminution of tumour mass. The other 11 patients showed partial regression. Though reassuring to both patient and doctor total tumour regression is not necessary to ensure a good prognosis for either life or vision. Provided tumour growth can be curtailed the prospects of the patient retaining the eye and remaining free of metastases appear good.

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