

THE TREATMENT OF CHOROIDAL MELANOMA USING
IRIDIUM-192 EYE PLAQUES

A Thesis

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ABSTRACT

There are many methods used in the treatment of choroidal melanoma ranging from observance of the tumor to bombardment by proton beam irradiation. The method of using iridium-192 wire(s) in eye plaques was investigated and compared to the other treatment regimes currently in use. Of the published data on this subject, iodine-125 seemed to be the most popular radionuclide. Because of the fact that iridium-192 is a relatively powerful isotope, the problem of shielding has surfaced. A modification of the present eye plaque used for iridium-192 has been proposed. Parameters for computer generated isodose plans using iridium-192 have been discussed. Some computer plan examples using different size iridium rings with different linear activities are illustrated. The development of a plaque that can completely bracket and irradiate malignant melanoma of the choroid could provide an alternative to enucleation. This method is still in the preliminary stages but is well worth investigating especially if vision could possibly be preserved.

INTRODUCTION

Melanomas are a malignant, pigmented tumor that develop from melanocytes which are the cells that are responsible for forming melanin. Melanin is the pigment which gives color to hair, skin, the substantia nigra of the brain (grey matter), and the choroid of the eye (7). Melanocytes are derived from the neural crest cells in the embryo which migrate to the skin, eye, central nervous system, and occasionally elsewhere during fetal life (1). Thus, malignant melanomas may arise from the skin, eye, brain, and spinal cord. This paper deals only with the melanomas that affect the choroidal layer in the globe of the eye.

The choroid is the brown vascular coat of the eye located between the sclera and retina (Figure 1). It consists of blood vessels united by connective tissue containing the melanin cells.

There are a large variety of neoplasms that can affect the eye and associated intraocular structures. (Table 1.0). Choroidal melanoma is the most frequent primary intraocular tumor (1). Benign intraocular tumors occur infrequently. There are two principal malignant intraocular tumors: retinoblastoma and choroidal melanoma.

Even though choroidal melanoma is the most common intraocular malignancy, it is estimated to occur in only about 0.05% of the total eye-patient population (1).

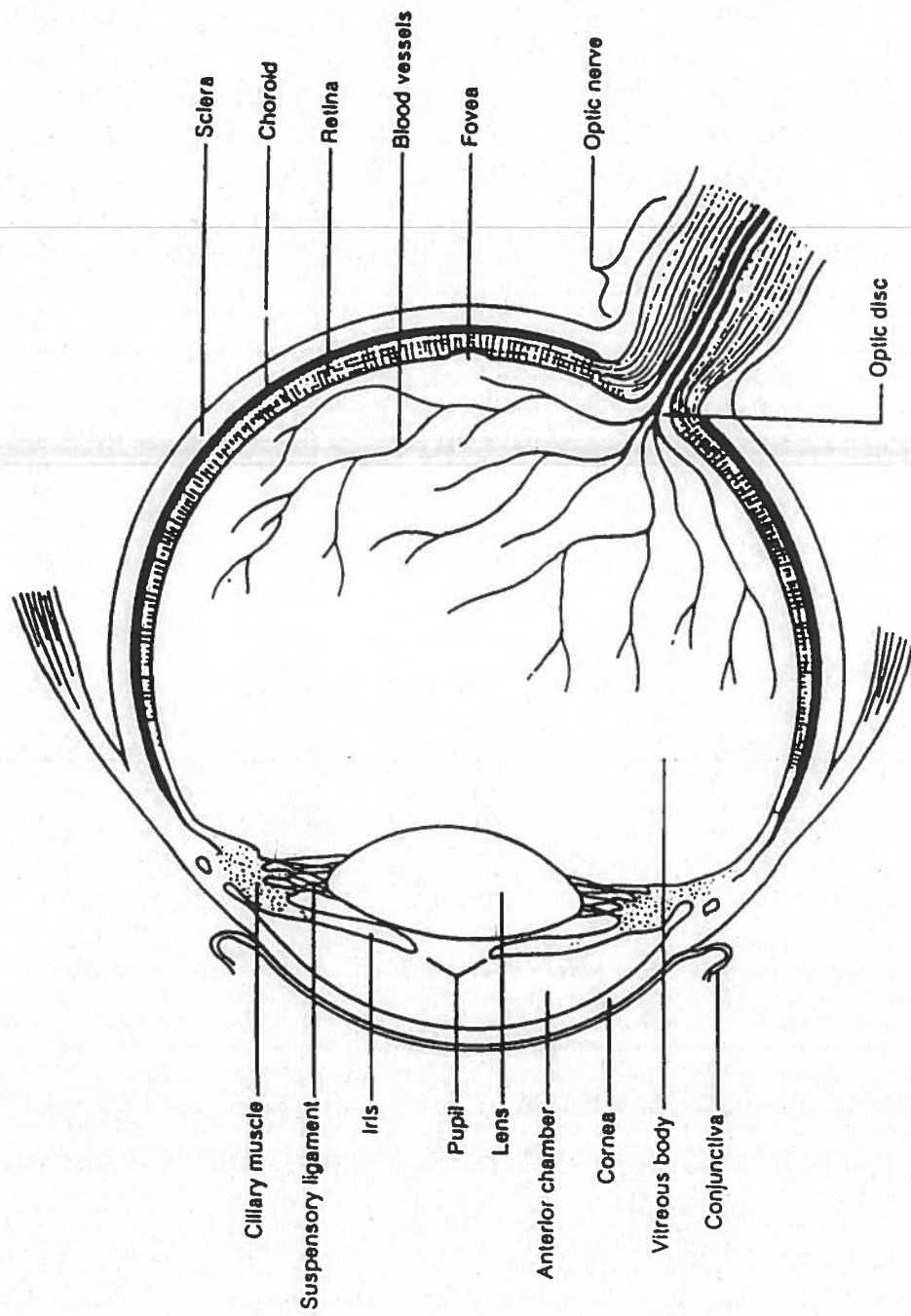


Figure 1.0 Anatomy of the Human Eye

THE MOST COMMON TUMORS OF THE EYE

Site	Adults				Children		
	Tumor Type	Sign	Visual Loss	Tumor Type	Sign	Visual Loss	
Lid	Basal cell carcinoma	Scabbing ulcer	None	Hemangioma	Red strawberry mass	Closed eyelid	
Conjunctive	Squamous cell carcinoma	Fleshy lesion	None	Leukemia	Raised, inflected mass	None	
Intraocular	Melanoma	Black to brownish elevated area in choroid	Scotoma	Retinoblastoma	White reflex	Blindness	
Intraorbital	Lymphoma	Mass, displacement of globe	Diplopia	Embryonal rhabdomyosarcoma	Mass, displacement of globe	Diplopia	
Metastatic	Breast (lung)	Raised area in retina	Scotoma	Neuroblastoma	Proptosis, ecchymosis, pain	Diplopia	

Table 1.0 Reference #1

This tumor affects adults with an average age of 50 years; is most common in whites; and is responsible for most enucleations second only to trauma. It is very rarely associated with other melanomas, like that of the skin. When present it is almost always a primary tumor with only a few reported cases of a primary cutaneous melanoma metastasizing to the eye (2).

In the past, the only method for treating choroidal melanoma was enucleation. There are two exceptions to this rule, however: Melanoma of the iris and anterior portions of the ciliary body. The reason is because these tumors are slow growing, relatively benign, and rarely metastasize (1,43). The enucleation procedure has been questioned by many as to whether or not it may promote distant metastasis (1,3,24,28). On some selected cases the mortality rate before enucleation is low (1% per year), however, this rate had increased abruptly after enucleation (1).

Table 2 shows the histopathologic classification of choroidal melanoma and their survival rates after enucleation. Spindle A cells are small spindle-shaped cells with small nuclei and are the most benign cell type. The five year mortality rate tumors containing spindle A cells is less than 5% (1). The spindle B type cells are larger and contain a more prominent nucleoli. This cell type is moderately aggressive with a 5 year mortality rate of 14%. The fascicular cells are more closely packed together. The mortality rate of this group of tumors is about 30%. Necrosis is rare in melanomas and occurs in

MELANOMA AFTER ENUCLEATION				
	5-Year		10-Year	
	Number of Patients	Survival (%)	Number of Patients	Survival (%)
Spindle A	63	89	31	81
Spindle B	337	77	159	64
Fascicular	52	71	25	56
Necrotic	83	46	48	29
Mixed	502	37	320	22
Epithelioid	27	33	15	0
	—	—	—	—
Total	1,064	55	598	38

Table 2.0 Percent survival of patients with choroidal melanoma after enucleation for different cell types

only about 7% of the tumors (1). Half of the melanomas of the eye represent a mixed cell type (1). Even the dangerous epitheloid cell type usually presents itself as a mixed tumor. These mixed tumors demonstrate a 51% - 5-year mortality rate (1).

Malignant melanomas are considered radioresistant (1,10). Figure 2 shows a typical survival curve for melanoma cells derived from a mouse. The cells were grown in culture and irradiated by 250 kV x-rays (5). This survival curve looks similar to mammalian cell cultures with the exception of the high extrapolation number (4). The curve begins with an initial D_0 of about 230 cGy and continues with a broad shoulder and finally extends to a steep slope with a D_0 of about 85 to 90 cGy in the terminal exponential region. Extrapolation of this terminal line to the ordinate gives an extrapolation number of 25. The terminal D_0 is found to be within the range of a wide variety of normal and malignant mammalian tissues (65 cGy to 195 cGy) for fully oxygenated cell cultures (6). Therefore, there does not appear to be any inherent radioresistance if the choroidal melanoma cells are fully oxygenated. The high extrapolation number would suggest, in theory, that an average of 25 targets must be hit for cell inactivation (6). This would indicate that at small doses many cells would recover from the sublethal injury as indicated by the broad shoulder region, the initial high D_0 , as well as the high extrapolation number. If this is any indication that most of the cells of choroidal melanoma

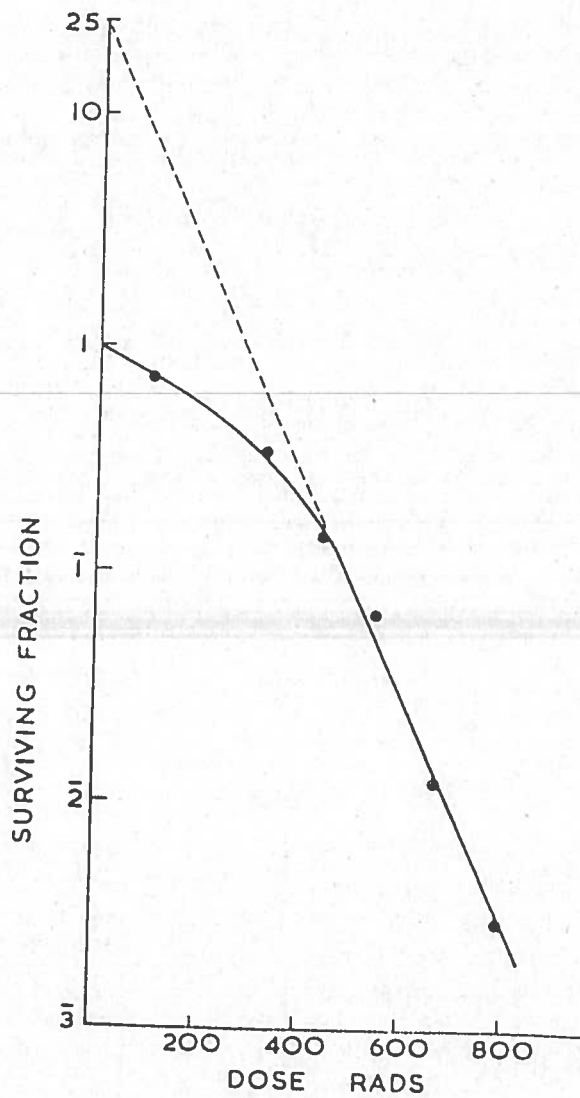


Figure 2.0 The survival of melanoma cells growing in culture after irradiation by 250 kV, X-rays in air. The cells were derived from a mouse.

are hypoxic, then irradiation using very large numbers of small fractions (i.e., continuous irradiation or interstitial implants) could offer potential advantages in the treatment of choroidal melanoma: 1) interstitial implants used to irradiate choroidal melanoma use low dose rates (3). It has been demonstrated in experimental animals that hypoxic cells become rapidly reoxygenated, and, therefore, more radiosensitive when exposed to low dose rate continuous irradiation (4). 2) a theory suggest that hypoxic cells are less protected against single hit killing, a characteristic of low dose rate irradiation (4). 3) since the repair mechanisms of hypoxic cells may be slowed down or absent, unrepaired sublethal injury occurring from low dose rates may even kill hypoxic cells. Therefore, interstitial or intracavitary techniques deliver the necessary high dose volume needed for tumor control, plus the combined potential advantages of low dose rate irradiation as mentioned, as well as the rapid fall off of dose within a few centimeters from the source make this type of irradiation for choroidal melanoma a good alternative for those who wish not to have there eye enucleated.

The current radiotherapeutic options in the management of choroidal melanoma are many (10-38). These include proton beams (23), heavy charged particles (34), cobalt plaques (25-28), ruthenium-106/rhodium-106 (33), and iodine-125 plaques (29-31). To date, there are no published data for treating choroidal melanoma with iridium-192. Other methods of treating small choroidal

melanomas include photocoagulation i.e., the use of ordinary light rays or a laser beam to alter the proteins in tissue. Photocoagulation is also utilized in the management of retinal detachments and hemorrhage. Radon seeds, gold grains, and hyperthermia have also been used to treat retinal tumors (32,35,38). Cryotherapy has been investigated for destroying small melanomas (36). Chemotherapy is used when widespread metastatic disease has occurred. Some chemotherapeutic agents have been used to treat systemic melanoma but not ocular melanoma (14). Each of these methods offer promising results, however, the management of choroidal melanoma is complex and depends on the size of the tumor (39). Sometimes enucleation cannot be avoided if the tumor is very large (diameter greater than 16 mm or tumor height greater than 8 mm) or if vision has already been lost. Radioactive eye plaques offer selected cases an alternative in the management of choroidal melanoma.

The objective of today's treatment of choroidal melanoma is twofold: First, and foremost is to save the patient's life. Second, and if possible, to save the function of the eye as well. Since choroidal melanoma is radioresistant and the contents of the globe are radiosensitive, careful treatment planning is critical for optimal results.

The purpose of this thesis is: i) to outline a protocol in the treatment of choroidal melanoma, ii) to discuss plaque design and construction, iii) to perform computerized isodose distributions of these eye plaques.

METHODS OF PROCEDURE

DIAGNOSTIC PROCEDURES:

There are several procedures currently available to establish an accurate diagnosis, size, and location of choroidal melanomas. In the past, there was a 10-20% incidence of false positive diagnoses (1). The current approaches to the diagnosis of choroidal melanoma have shown to improve clinical accuracy and are listed below:

- 1) Obtaining patient history
- 2) Medical evaluation
- 3) Examination of the opposite eye
- 4) Indirect ophthalmoscopy
- 5) Transillumination
- 6) Fluorescein angiography
- 7) Phosphorus-32 uptake studies
- 8) Ultrasound
- 9) Fundus photography
- 10) CT and MRI scans
- 11) Visual field examinations

With further investigation, other diagnostic procedures may be developed for clinical use that will improve the diagnostic accuracy even more. With those mentioned above, however, most of the diagnostic problems involving choroidal melanoma have been solved. Melanomas located in the anterior portion of the eye are usually detected earlier, diagnosed, and treated easier if they are not too large.

Melanomas located in the posterior portion of the eye are not accessible to biopsy and therefore are harder to diagnose, as well as, more difficult to treat using radioactive implants. Usually posterior tumors that are large and less accessible are treated with finely collimated external beams (3,4,24) (figure 3).

Phosphorus-32 uptake studies have been useful in distinguishing benign from malignant tumors (8). The phosphorus-32 is concentrated in rapidly growing tumor cells during DNA replication (1)

Fluorescein angiography is often used as an aid in the differential diagnosis of posterior fundus lesions, specifically, choroidal melanoma (37). Three milliliters of fluorescein sodium in sterile water is injected rapidly into the antecubital vein. This solution provides a yellowish-green fluorescence which appears readily in the extracellular fluid and gains access only to viable cells. This fluorescence distinguishes the area under observation from adjacent areas. It is used as a diagnostic aid in ophthalmic angiography including examination of the fundus, evaluation of the iris vasculature, distinction between viable and non-viable tissue, and differential diagnosis of malignant and non-malignant tumors. Serial fluorescein photographs of malignant melanoma will show a striking appearance of the dye in the pigmented area in the early arterial phase with a continuation of the dye in the tissue after the late venous phase. However, this

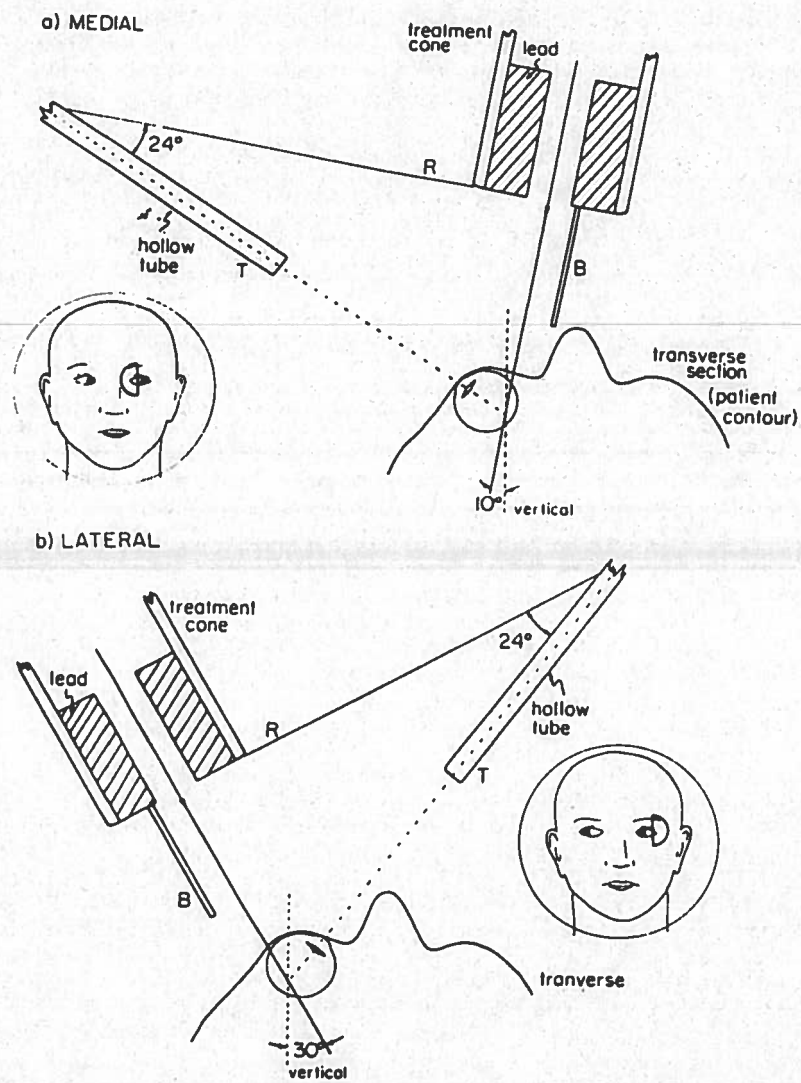


Figure 3.0 Treatment arrangement for malignant melanoma at the optic disk using Cobalt-60. (a) medial and (b) lateral directions; the hollow localization tube, T, is supported by a rod, R, attached to the lead block. The 24 degree angle can be varied according to the ability of the patient to look in the extreme lateral direction (ref.#24).

procedure cannot be solely relied upon as a positive test for malignant tumors because benign hemangiomas will present themselves in a similar fashion. Other eye lesions, however, can be ruled out including metastatic tumors and inflammatory conditions. Fluorescein angiography can also be used in follow-up studies to determine the extent of the viable tumor cells after a completed course of radiation therapy.

Fundus photography is useful in obtaining a permanent record of the patient's fundus and offers the ophthalmologist a good diagnostic tool. The pupils are usually dilated and the fundus is examined by indirect ophthalmoscopy and photographed. Maximal and minimal basal diameters can be estimated clinically which is essential for the design of eye plaques.

Computerized tomography (CT) and magnetic resonance scans are very useful as an accurate means of localizing and determining the configuration of the tumor within the orbit.

Ultrasound scans are an important diagnostic aid in measuring the base diameter (LxW) of the tumor and the tumor thickness (height), especially when visualization of the tumor is not possible. This information is very important in order to select the proper size eye plaque to be used in the treatment of choroidal melanoma.

Visual field examinations are useful in follow-up whether the form of treatment is observation or

radioactive eye-plaques.

Once the diagnosis of choroidal melanoma has been established, all patients should be evaluated for metastatic disease prior to treatment. This should include a complete physical examination, blood tests, liver enzyme test, chest x-ray, radioisotope scans of the liver, bone and brain (29). In melanoma, the favorite site of metastasis is the liver. Radioisotope scans of the liver and brain can be substituted with CT scans. Distant metastasis could occur if: 1) extrascleral extension is present 2) a large tumor is present 3) the tumor contains epitheloid type cells 4) recurrent disease in the orbit (30).

ANATOMY:

The uvea is the second or middle layer of the eyeball lying immediately beneath the sclera. It consists of the iris, ciliary body, and choroid. The uvea forms the pigmented layer, is highly vascular (especially the choroid), and contains no lymphatic channels. Systemic metastasis occurs via hematogenous routes. Melanomas of the uvea tract may spread by local extension through Bruch's membrane (separates the choroid from the retina) to involve the retina, or by extension through the sclera or optic nerve into the orbit. Most uveal melanomas involve the choroid - choroidal melanomas. Thus this paper is concerned only with choroidal melanomas. As mentioned, iris melanomas are relatively benign, slow

growing and rarely metastasize. As the tumor gets closer to the choroid, i.e., posterior ciliary body melanomas and choroidal melanomas, they become more malignant and metastasize more frequently (43).

STAGING OF CHOROIDAL MELANOMAS:

The following information was obtained from reference 43.

If histologic verification of the disease cannot be obtained, these cases must be reported separately. The 3 categories used in staging this disease are: 1) Primary tumor (T), 2) regional lymph nodes (N), 3) distant metastases (M). The regional lymph nodes are the preauricular, submandibular, and cervical lymph node chains.

PRETREATMENT CLINICAL CLASSIFICATION (cTNM)

Primary tumor (T)

TX Primary tumor cannot be assessed.

TØ No evidence of primary tumor.

T1 (small tumor) Tumor having a base diameter of up to 10 mm, and/or a height not more than 3 mm.

T1a Tumor not more than 7 mm in base diameter and with a height not more than 2 mm.

T1b Tumor with a base diameter between 7.1 mm and 10 mm and with a height between 2.1 mm and 3 mm.

T2 (medium tumor) Tumor having a base diameter greater than 10 mm but less than 15 mm and with a height greater than 3 mm but not more than 5 mm.

T3 (large tumor) Tumor more than 15 mm in base diameter or with an elevation of 5 mm or more.

T4 Tumor with extraocular extension. (Metastases may be present).

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed.

N0 No evidence of regional lymph node involvement.

N1 Evidence of involvement of regional lymph nodes.

Distant metastases (M)

MX Distant metastases cannot be assessed.

M0 No evidence of distant metastases.

M1 Evidence of distant metastases.

POSTSURGICAL HISTOPATHOLOGIC CLASSIFICATION (pTNM)

Histopathologic grade (G)

GX Grade not assessed.

G1 Spindle cell melanoma.

G2 Mixed cell melanoma.

G3 Epitheloid cell melanoma.

Venous invasion (V)

VX Venous invasion not assessed.

V0 Veins do not contain tumor.

V1 Veins in melanoma contain tumor.

V2 Vortex veins contain tumor.

Scleral invasion (S)

SX Scleral invasion not assessed.

S0 Sclera does not contain tumor.

S1 Intrasccleral invasion of tumor.

S2 Extrascleral extension of tumor.

Stage Grouping for Choroid

Stage I T1, N0, M0

Stage IA T1a, N0, M0

Stage IB T1b, N0, M0

Stage II T2, N0, M0

Stage III T3, N0, M0

Stage IVA T4, N0, M0

Stage IVB Any T, N1, M1

Small tumors usually have a better prognosis than larger tumors. The largest tumor diameter is the single most important clinical and pathological prognostic indicator (9,22,39). Figure 4 shows the actual survival rates according to the largest tumor diameter (LTD). When the LTD is 10 mm or less, the prognosis is fairly good and becomes worse as the tumor exceeds 10 mm. In one study, the mortality rate was 13% if the LTD was 10 mm or less and 70% when the it exceeded 12 mm (39).

CANIDATES FOR RADIOACTIVE EYE PLAQUES:

The aim of the ophthalmologist and radiotherapist in the treatment of choroidal melanoma is to first save the patient's life and second to preserve useful vision of the affected eye. Some authors feel that all primary intraocular malignant tumors with the exception of retinoblastoma, are best treated by surgical techniques (14). Surgical management has resulted in a 50% five-year survival rate and 35% ten-year survival rate (14).

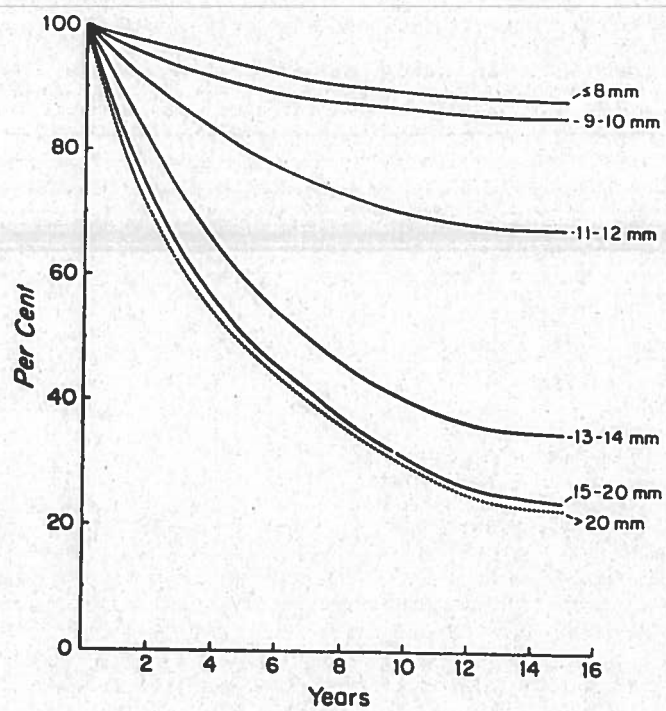


Figure 4.0 Survival rates according to the largest tumor diameter (ref.#39).

Stallard, who used radon seeds and later cobalt-60 plaques reports a 75% five year survival in a series of 100 patients treated with this technique (14). Despite the successful irradiation of the tumor using cobalt-60 plaques, the high energy from cobalt-60 (average gamma energy of 1.25 MeV) has led to a large number of adverse affects, including loss of vision, which negates the benefits of irradiation (28).

Thus, the decision to treat choroidal melanomas using eye plaques is based on several factors:

- 1) Size and location of the tumor - this is a very important factor. The larger the tumor, the smaller the number of treatment options available. For small tumors, this range of options include: observation, radiotherapy, photocoagulation, local resection, and enucleation. Small tumors sometimes remain dormant for years without affecting the patient, thus observation until growth documentation is usually considered, but not always recommended. For medium and large tumors, either local resection or radiotherapy are about the only two alternatives to enucleation. For very large tumors, enucleation is almost inescapable. The location of the tumor also plays an important part in deciding which mode of treatment is optimum. Tumors that are close (5.0 mm) to the optic nerve or macula make the use of eye plaques very difficult. Treatment using eye plaques in this area can cause many complications, i.e., radiation retinopathy

which can lead to loss of vision. In some studies (17), eyes receiving a radiation dose in excess of 50 Gy to the fovea and/or optic disc commonly lose a substantial amount of vision within 2 to 3 years. But the visual prognosis appears to be good for eyes receiving a dose of less than 50 Gy to these sites.

Usually, small and medium tumors which are accessible and situated away from the macula, optic nerve, and lens, are good candidates for radioactive implants (3). Again, posterior tumors that are larger and less accessible may be treated with small, finely collimated cobalt-60 external beams. If enucleation is the only method of choice, pre-op irradiation can be administered to decrease the size of the tumor and to cut down on the chances of metastasis (4,16,17,18) (figure 5).

2) Active growing tumors.

3) Visual acuity - if vision before treatment is such that no improvement can be expected then enucleation may be the only choice.

4) The only functional eye - if the affected eye is the patients only remaining functional eye then some form of treatment other than enucleation should be tried first to spare the eye.

In summary, radiotherapy is offered if tumor shrinkage and preservation or recovery of vision can be anticipated or if the patient refuses enucleation.

CONSTRUCTION OF EYE PLAQUE:

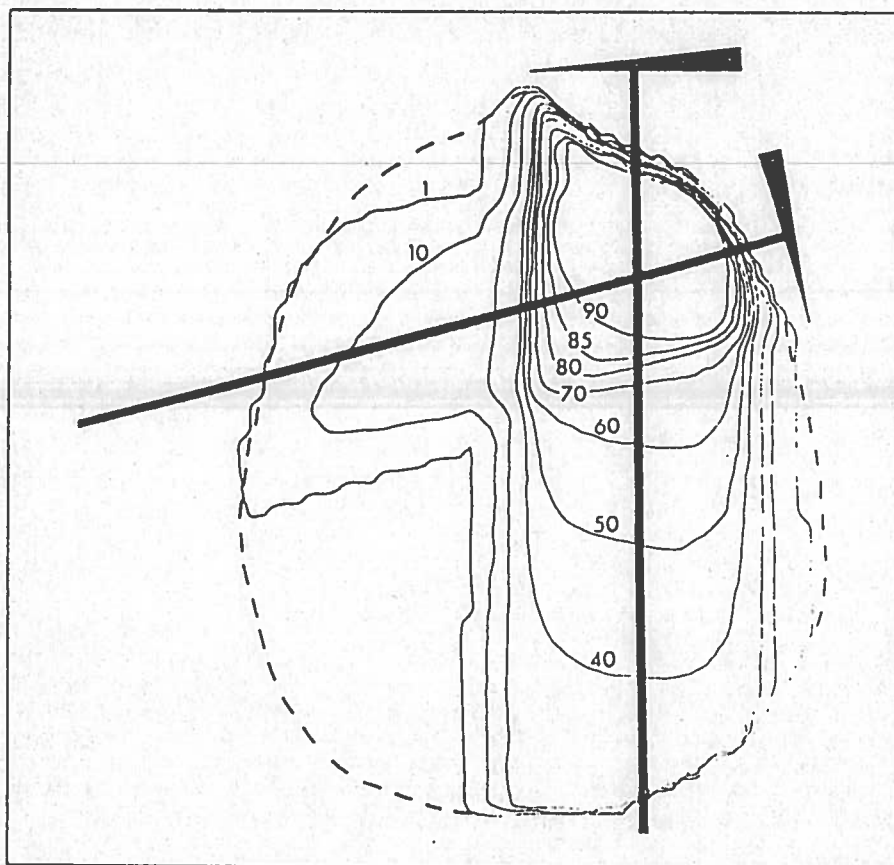


Figure 5.0 Anterior wedge pair radiation fields in pre-operative enucleation of choroidal melanoma (ref.#18).

The plaque can be made by either a dentist or jeweler who possess the tools necessary to make accurate plaque designs. The eye plaque is "tailor-made" according to the tumor size and shape obtained clinically. The dimensions of the plaque should be sufficient enough to encompass the tumor base plus a 2 to 3 mm "tumor-free" margin. This is to ensure that the tumor is well covered including viable tumor cells that cannot be observed but are known to occur. A 1.0 mm extension beyond the specified diameter of the plaque is included for the placement of suturing holes. At least three suture holes are necessary to anchor the plaque in place, however, multiple holes should be employed to give the surgeon more options to choose from. The suture holes should be about 0.4 mm in diameter and drilled around the plaque periphery. A "lip" should be made around the periphery of the plaque (about 1.0 mm high) so that the iridium-192 wires never protrude above the surface. This minimizes any side scatter of radiation. A space of about 1 mm should be between the radioactive source and the sclera. This increases the percent depth dose and also prevents the sclera from getting over exposed. The eye plaque should have a radius of curvature of 25 mm to approximate the radius of curvature of the eye. The plaque can be 3 mm thick (and possibly more) with a total height of 4 mm. Many gold weights can be used, the most common being the 18 to 24 karat (fig.6).

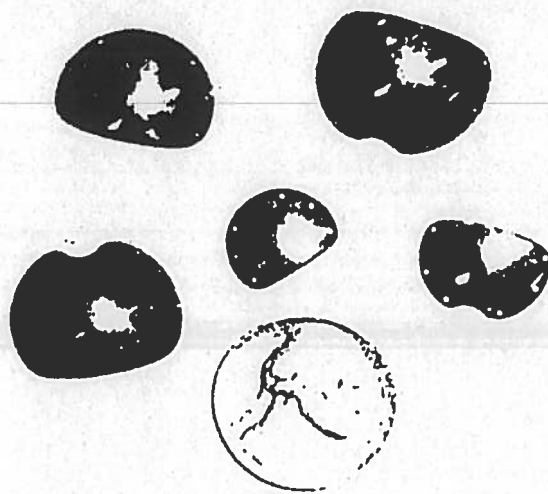


Figure 6.Ø A schematic representation of eye-plaques of different shapes and sizes. The indented edges on some represent where they abut against the optic nerve. Note their size in relation to a U.S. nickel.

OTHER IRIIDIUM-192 EYE PLAQUE DESIGNS:

At the Ontario Cancer Institute, Toronto, Ontario, they employed using a mold composed of three to four concentric rings of iridium wire glued between two heat molded plastic cups. The lengths of the wire corresponded to the circumference of the desired tumor and the iridium-192 wires were cut and formed into circles. Thin plastic was heat molded into cups of radius 12.5 mm approximating the radius of the eye. The rings were attached to the outside of the cup using Crazy glue.

A second layer of plastic was put over the rings and suture holes were made in the edge of the plastic. Typical examples of the sizes of the three rings that may be used are: 13 mm, 15 mm, and a 18 mm diameter. The iridium-192 wire procedure is not used anymore at the Ontario Cancer Institute because of the severe eyelid reaction and epilation of the eyelashes (40). However, using plastic molds to encase the iridium-192 wire would provide hardly no attenuation and thus normal tissues may get over-exposed.

At the Medical College of Wisconsin, they also used iridium-192 wire plaques for the treatment of choroidal melanoma. The plaques consisted of two gold plated copper shells about 0.5 mm thick each with iridium-192 wires glued between them. The iridium-192 wire is about 0.4 mm in diameter so the total thickness was about 1.4 mm thick. Three sets of suture holes would hold the shells together.

The attenuation is about 5.0% with these plaques so again there is a high percentage of normal tissues getting irradiated. Follow-up visits were not long enough to give any reliable data, however, at the time of conversation, the follow-up for iridium-192 eye plaque users was about the same as for the iodine-125 patients (41).

Both hospitals no longer use iridium-192 wires for the treatment of choroidal melanoma for several reasons:

- 1) They both report severe eye lid reactions using iridium-192.

- 2) Dose distribution using iodine-125 is good.

- 3) Less radiation exposure to hospital personell and surgeon using iodine-125.

- 4) Patient does not have to be isolated during treatmet with iodine-125.

- 5) Making the small circles in the plaque is easier with seeds than with wires and iridium-192 seeds are difficult to get.

PROPOSED IRIDIUM-192 EYE PLAQUE DESIGN:

Iridium-192 is a relatively powerful radioisotope with an average gamma energy of 380 keV. If a plaque could be made thick enough to effectively shield most of the gamma irradiation and still be useful to place in the eye, then iridium-192 may be used. To shield this high radiation intensity radioisotope, a solid gold plaque with 1 or 2 half-value-layers (HVL) may be used. In calculting the HVL (the thickness of absorber material that will

reduce the incident radiation intensity by a factor of two) for iridium-192 and gold plaques, it would take at a thickness of about 1.7 mm of gold to equal to 1.0 HVL.

$$d_{1/2} = 0.693 \times \frac{\text{gram}}{0.216 \text{ cm}^2} = 3.21 \text{ gram/cm}^2$$
$$= 3.21 \text{ gram/cm}^2 \times \text{cm}^3/19.32 \text{ gram} = 0.17 \text{ cm or } 1.7 \text{ mm}$$

The plaque could only be about 2 HVL's thick or 3.5 mm at its thickest part. This would attenuate 75% of the radiation which may be enough to prevent major damage to the surrounding tissues. This, however, has not been tried. Another concern is the fact that the tissue HVL penetration for iridium-192 is about 5.0 cm. The opposite retina or lens could get a substantial dose if directed in that region and measures were not taken to reduce the exposure to the normal eye.

VERIFICATION FILMS:

This implant procedure precludes the use of orthogonal films to view the iridium-192 wires since the gold plaque completely attenuates the x-ray beam and there-by obscuring the wires. Therefore, to obtain orthogonal views of the wires in the plaques in order to perform the necessary computer dose calculations, another technique has to be utilized. With the wires already in place in the gold plaque, project the z,-z image on the

wall or graph paper using any projector. The wires can then be traced and the magnification factor can be determined. Careful radiation safety precautions must be adhered to while doing this procedure.

This graphic view of the wires can be broken up into "seeds" for the computer and thus located in a lateral view. By knowing the height and chord length of the plaque, the radius of curvature can be calculated. Then one can accurately draw a representative plaque in cross section. The wires can be drawn in by knowing the diameter of each ring in the +Y, -Y direction. This diameter can be "fitted" on the radius of curvature of the plaque drawn in cross section.

THE PLACEMENT OF IRIDIUM-192 WIRES IN PLAQUES:

The wires are cut and formed into circles corresponding to the desired circumference and is attached to the eye plaque in one of two ways: 1) It can be glued using ordinary Crazy glue but the disadvantage here is that when the glue dries, getting the wire out of the plaque to save the plaque for a possible future use can be tedious and difficult. 2) another method is to use silicone rubber caulk. This material adheres well to the plaques and can be removed with minor effort. Usually a layer of caulk about 2 mm thick is applied to the inside of the eye plaque and the wire can then be pressed down into the caulk in the desired pattern determined by computer generated isodose curves for a particular tumor

geometry. Then the remaining caulk can be smoothed over the wire(s) and after the caulk has cured the plaque can be autoclaved or sterilized by chemicals.

IMPLANTATION PROCEDURE:

In the operating room, the pupil is dilated and the eye rotated so that the area of the base of the tumor is exposed. The conjunctiva is dissected away from the sclera and the muscles retracted. By using trans-illumination, the tumor's dimensions are marked on the sclera by a diathermy probe. At this point a dummy plaque is placed over the globe, encompassing the marks, and stitched to the sclera. For every plaque that is made, a dummy plaque needs to be made in an exact replica. This dummy plaque is used to reduce the radiation exposure to operating room personnel while the surgeon puts the stitches in the sclera to hold the plaque in place. Ideally, the dummy plaque needs to be a transparent plastic replica so that the diathermy marks can be seen easily while the plaque is adjusted to the desired position. The dummy plaque is then removed and replaced by the treatment plaque. The muscles are then returned to their position on top of the implant and the conjunctiva reattached. The plaque stays in place for up to seven days. After the plaque is removed, ultrasound can be used to monitor any tumor shrinkage.

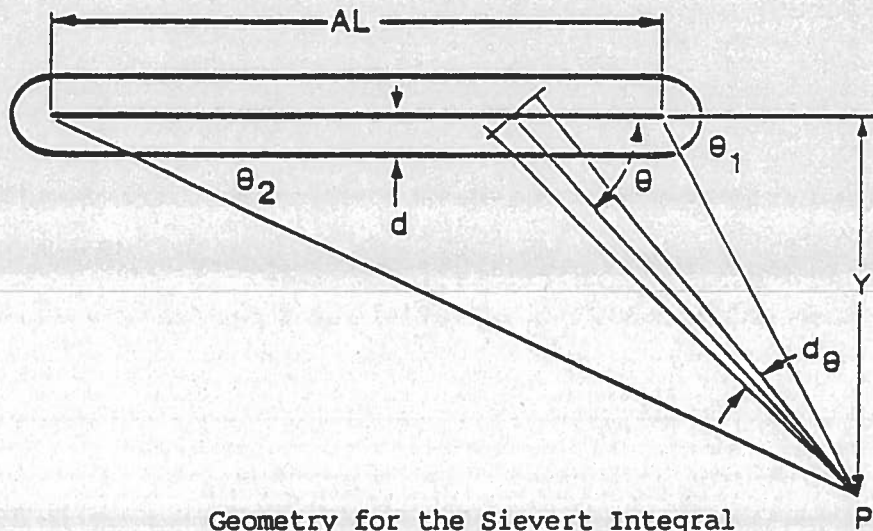
COMPUTER GENERATED ISODOSE DISTRIBUTIONS:

The following radiation distributions were calculated

using Atomic Energy of Canada, Ltd., THERAPLAN L. computer system, (version-3). The programs used in these treatment plans were SORDAT and ISODOS. Program SORDAT creates a table of dose rates around a specified linear or seed source of unit activity. Program ISODOS accepts the specified source activity and interpolates or extrapolates the tabular data generated by program SORDAT.

For the linear sources, the exposure rate to a point from a filtered uniform line source can be calculated using the Sievert integral (fig. 7), however, a correction to the computed exposure rate would have to be made for the effect of gamma ray self absorption by the source and filter material. Figure 8 shows the increased error at increased distances from the source end due to oblique filtration. The method of calculation of dose to a point is accomplished by using Sievert's integral to calculate the dose in four geometric zones around a linear source. The Young and Batho method is used, in which the linear source is divided into several small increments (1 mm), and the attenuation of the filter and self-absorption is calculated for each line element. Then applying the Meisberger, et al, correction factor, the exposure rate is corrected for absorption and scattering in the surrounding medium (considered to be equivalent to soft tissue) at various distances.

The dose rate is calculated by the equation



The dose rate, D , at the point P is obtained by:

$$D = M\tau/(AL.Y) \int_{\theta_1}^{\theta_2} e^{-\nu d \sec \theta} d\theta$$

where: M is the radium content of the source in mg.
 τ is the specific gamma ray constant for radium.
 AL is the active length of the source.
 Y is the perpendicular distance from the point to the line of the source.
 d is the thickness of platinum filtration.
 ν is the effective absorption coefficient for platinum.

Figure 7.0 Courtesy of A.E.C.L., Ltd., Ottawa, Canada

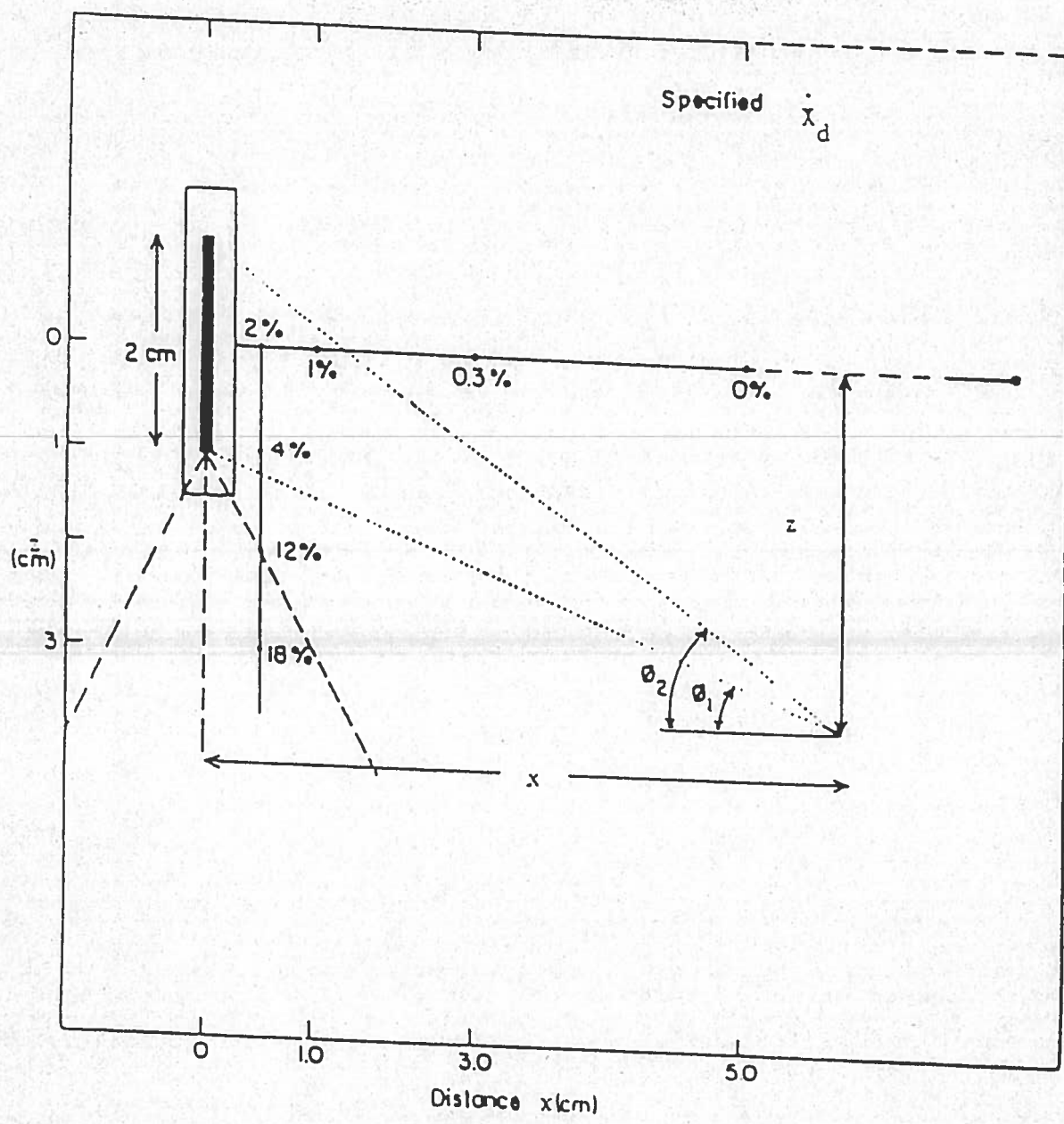


Figure 8.0 Sievert's integral for a line source showing increased error due to source and filter attenuation.

$$\dot{D}_P = (f \cdot \Gamma \cdot A / N) \times \sum_{i=1}^N [\exp(-\mu_f t_{fi} - \mu_s t_{si}) \cdot a(d_i)] / d_i^2,$$

where \dot{D}_P = dose rate at point P, f = roentgen-to-rad conversion factor, Γ = specific gamma-ray constant, A = unit activity of the source (mCi, Bq, or mg-radium equivalent), N = number of increments, μ_f = linear absorption coefficient of filter material, t_{fi} = path length in filter from i th increment to point P, μ_s = linear absorption coefficient of source material, t_{si} = path length in source from source center to point P, d_i = distance from i th increment to point P, and $a(d_i)$ = function accounting for attenuation in surrounding medium.

In program SORDAT, the data is stored as the product of the dose rate and the square of the radial distances on a quadrant polar grid (fig. 9). This product varies less rapidly than dose rate alone, hence, the accuracy of the interpolation is increased. The entries in the table include thirteen radial distances for each of the eleven different angles (fig. 10). The angular increments are 11 equal intervals of the sine of the angle relative to the source axis. Thirteen radial increments are calculated, increasing in exponential fashion from 0.1 to 6.4 cm from the origin.

Most of the computer generated isodose plans were

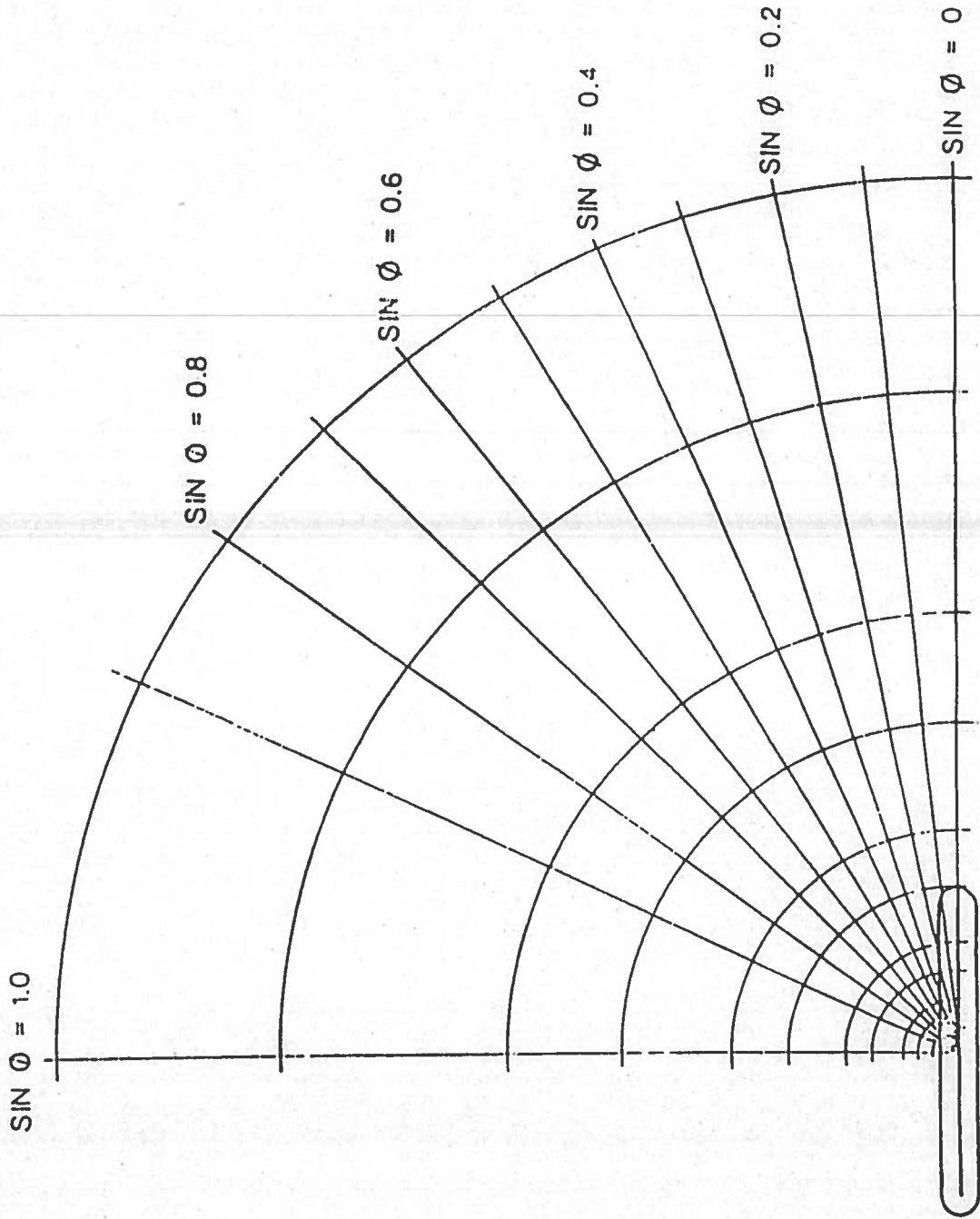


figure 9.0. Quadrant grid showing how dose rate is calculated in A.E.C.L. THERAPLAN L computer system (42).

	I											
	angle	1	2	3	4	5	6	7	8	9	10	11
		0.0	5.7	11.5	17.5	23.6	30.0	36.9	44.4	53.1	64.2	90.0
J	R											
1	0.10	999.0999	999.0999	999.0999	999.0999	0740.5566	66.8461	61.6392	8344.7307	3		
2	0.15	999.0999	999.0618	6517.2418	4340.4282	4239.7207	9183.8164	2				
3	0.20	181.3177	1178.4180	4171.5158	7145.1132	3120.7110	5101.2					
4	0.30	49.7	49.3	53.4	56.5	58.2	58.1	57.0	55.3	53.3	51.1	48.6
5	0.40	23.7	23.6	26.5	28.2	29.6	30.2	30.3	30.1	29.7	29.0	28.2
6	0.60	9.3	9.3	10.8	11.5	12.2	12.7	12.9	13.0	13.0	13.0	12.8
7	0.80	4.9	5.0	5.9	6.3	6.7	7.0	7.1	7.2	7.3	7.3	7.3
8	1.20	2.1	2.2	2.5	2.8	2.9	3.1	3.1	3.2	3.2	3.3	3.3
9	1.60	1.2	1.2	1.4	1.5	1.6	1.7	1.8	1.8	1.8	1.8	1.8
10	2.40	0.5	0.5	0.6	0.7	0.7	0.8	0.8	0.8	0.8	0.8	0.8
11	3.20	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5
12	4.80	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
13	6.40	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Figure 10.0 Computer printout showing the 11 sine angular intervals and 13 distances, R, used in the calculation of tissue doses relative to the source axis.

calculated using the point source technique or the seed program QSEEDS. The dose around a seed is proportional to the inverse square of the distance to the calculation point and a function of absorption and scatter in the medium surrounding it. No correction for filter and source absorption is needed. The seed program was easier to work with and just as accurate as the linear source program.

The parameters used for iridium-192 wire that were entered into the treatment planning system for the linear sources are: $f = 0.967$, $\Gamma = 5.243$ (R mCi⁻¹ h⁻¹ at 1 cm), $A =$ mCi, filter and source filtration linear absorption coefficient = 4.45 cm⁻¹, filter radial wall thickness = 0.1 mm, active core diameter = 0.2 mm, $T_{1/2} = 1771.95$ hours. For the seed program, filter and source correction factors were not needed and the specific gamma-ray constant, Γ , was changed to the standardized value of 4.9 R h⁻¹ cm² mCi⁻¹. The actual iridium-192 wire specifications used in this experiment was based on the manufacture's specifications of Rads S.L. Inc., Lake Charles, Louisiana.

Figure 11 shows how the wires on a 25 mm diameter sphere would look. The following isodose plans were computed using this format. The three rings, a, b, and c were positioned so that they were coaxial along their centers but offset along their common axis x, -x.

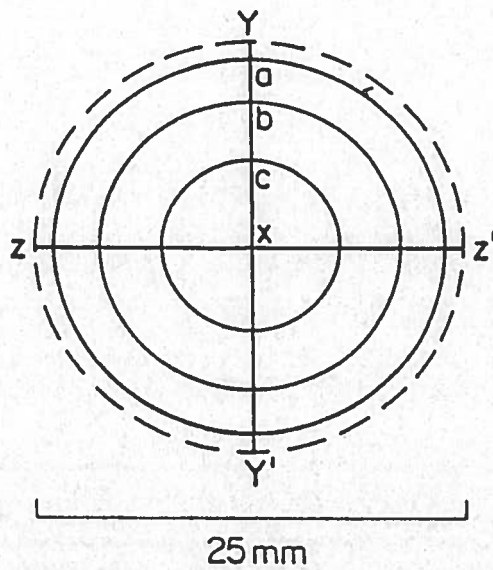
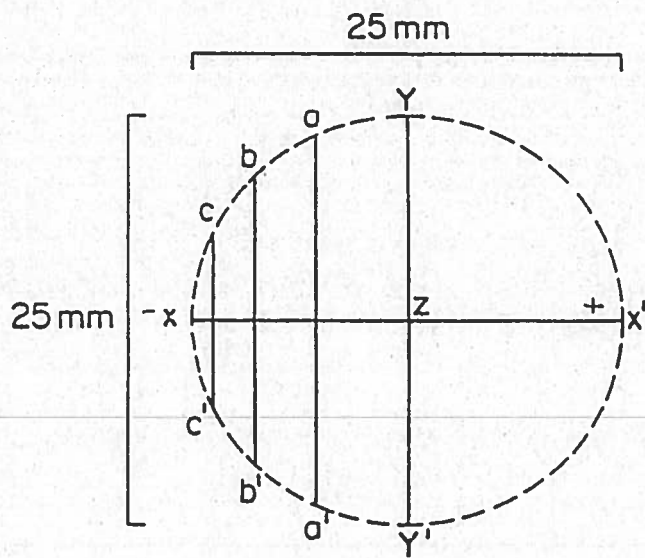


Figure 11.0 Two orthogonal views of Iridium-192 wire rings a, b, and c.

In figure 12, a computer calculation using the linear source program for a single wire ring is shown. The ring is 2.0 cm in diameter and has a circumference of 6.28 cm. It was divided into 20 sources, each being 0.31 cm active and total length with 0.1 mm platinum filtration. Each source was corrected for filter and source filtration. The linear activity used was 1.0 mg radium equivalent per cm or 0.5 mci per source. The dose rate at about 1.0 cm from the base of the sphere is 40 cGy/hr.

Figure 13, is a typical tumor model showing a 8 mm high and 15 mm diameter tumor in the eye with a 2 mm separation between the Ir-192 eye plaque and the base of the tumor. The following computer generated dose distributions uses this tumor model and shows how different diameter wires with different activity weightings can alter the outcome of a plan.

Figure 14 shows 4 rings, 2.0 cm, 1.5 cm, 1.0 cm, and 0.5 cm in diameter. The seed program was used on these dose distributions for two reasons: 1) simplicity 2) results were equal to the linear program. When working with circles it was much easier to make the circle a composite of many point sources rather than many linear sources. The rings were divided up into the appropriate number of "seeds" depending on their radius and hence, their circumference. All the seeds in figure 14 had the same activity (0.8 mci each), therefore, all the activities were considered linear. The isodoses are in

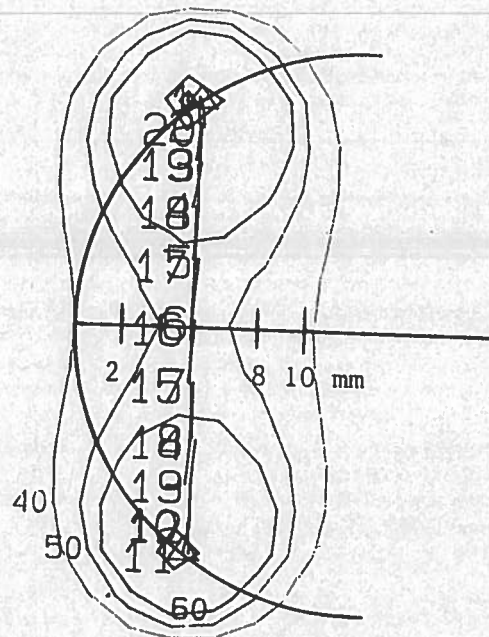
Isodoses

200

60

50

40



2.0 CM DIAMETER RING W/20

SOURCES 0.31 ACTIVE & TOTAL

Figure 12.0 Computer calculation of the dose distribution for a single iridium-192 wire ring.

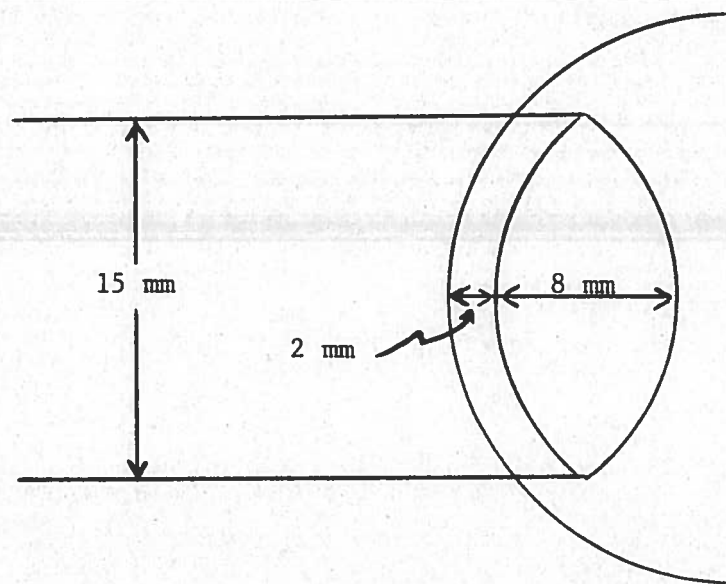


Figure 13.0 Tumor configuration relative to the plaque shell

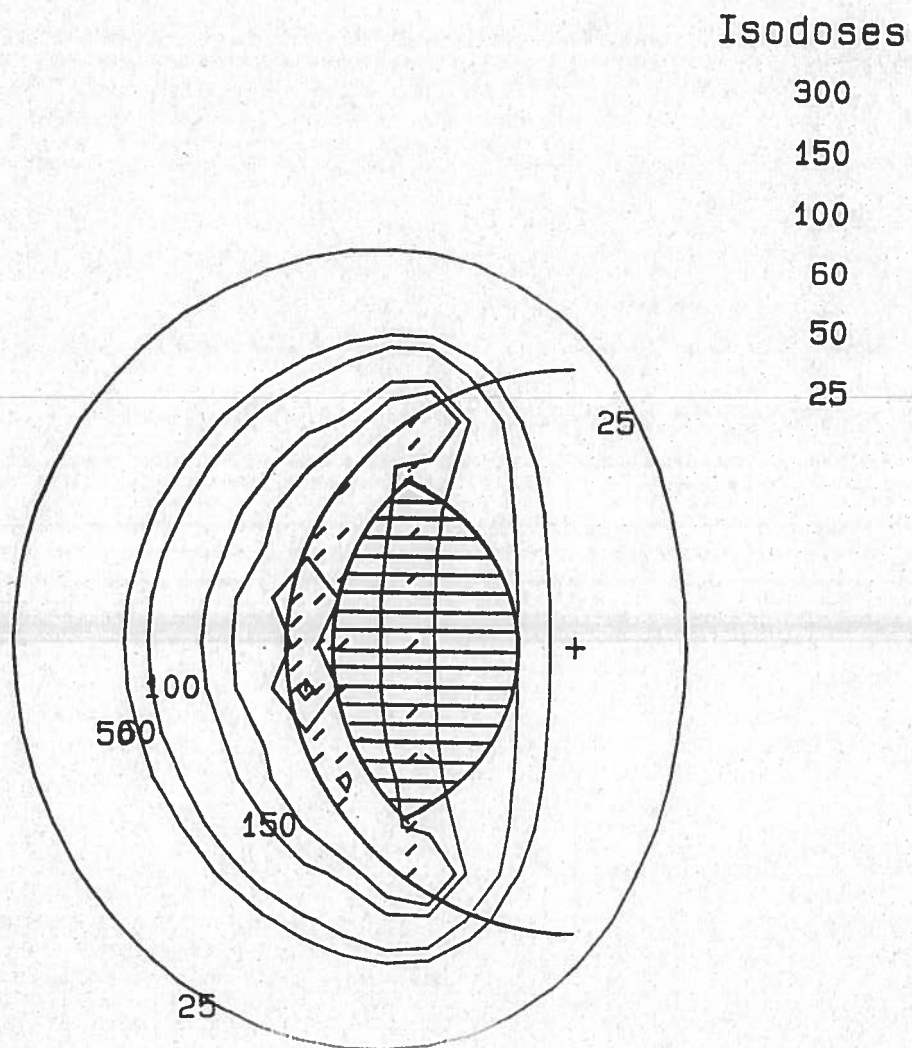


Figure 14.0 Computer generated dose distribution

4 RINGS ALL LINEAR 0.8 MCI/CM.

2.0, 1.5, 1.0, 0.5 CM DIA

cGy/hr. In this plan, there is a high dose covering the plaque surface due to the linear activity that covers the surface of the plaque. The 60 cGy/hr dose rate line covers the tumor but note the 60% dose rate gradient down the axis of the tumor.

In figure 15, there are also 4 rings, 2.0 cm, 1.85 cm, 1.65 cm and 1.5 cm, all linear activities. In this plan the axial dose gradient is more uniform with the 75 cGy/hr dose rate line covering the tumor. The "hot spots" are larger than the previous plan but are confined to the base of the tumor.

In figure 16, the rings are the same as in the previous plan except the 1.65 cm and the 1.5 cm diameter rings have different activities of 0.56 mCi each seed instead of 0.8 mCi each seed. The dose rate at the plaque surface is now reduced and the 65 cGy/hr isodose rate line covers the tumor.

The usual linear activities used can vary from 0.2 to 0.5 mg radium equivalent per centimeter with 0.1 mm platinum filtration to filter all beta radiation.

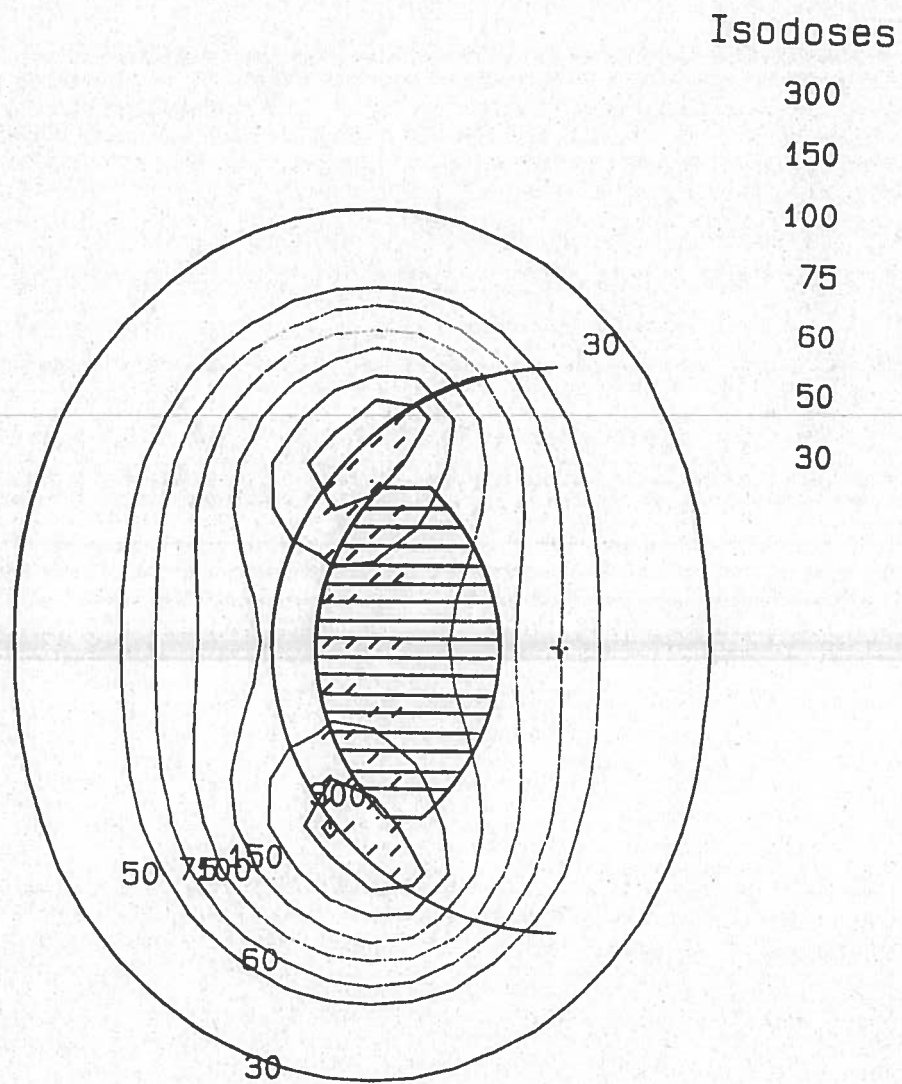


Figure 15.0 Computer generated dose distribution

4 RINGS ALL LINEAR 0.8 MCI/CM.

2.0, 1.85, 1.65, 1.5 CM DIA

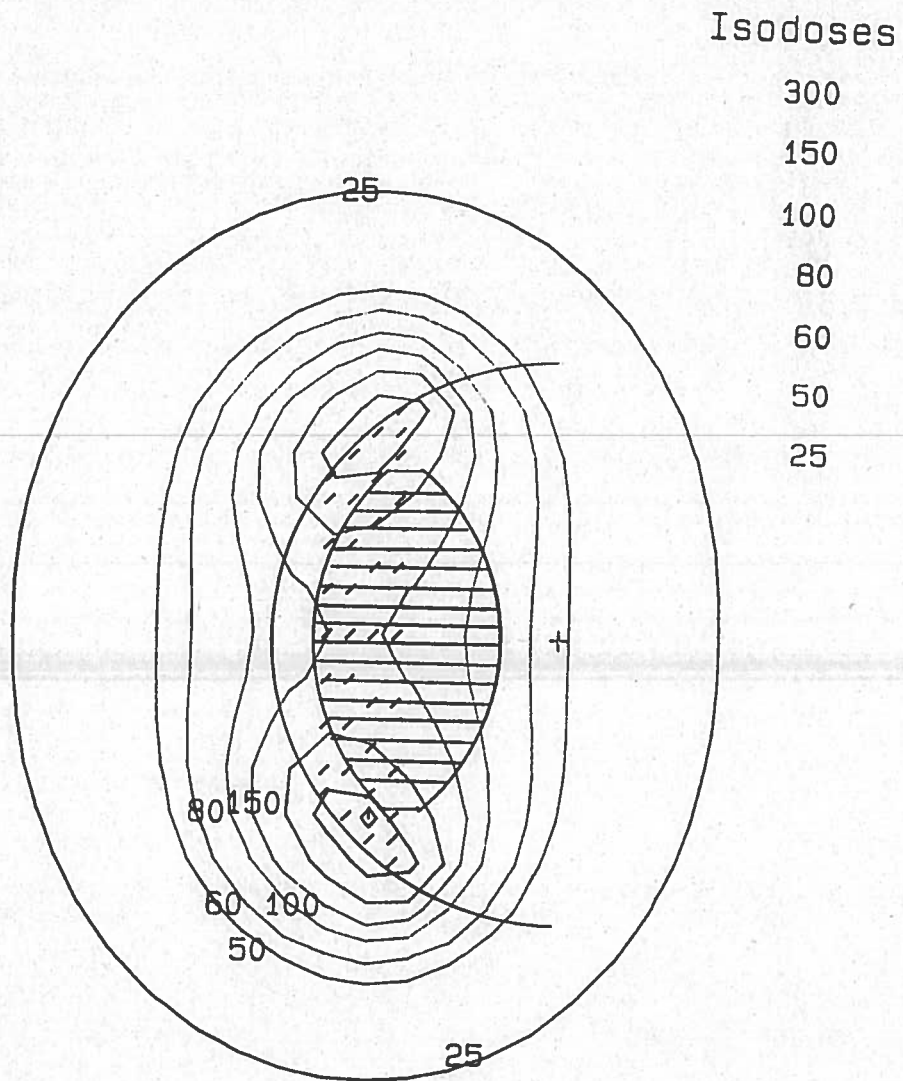


Figure 16.0 Computer generated dose distribution

4 RINGS SAME SIZE AS 3RD PLAN

BUT LAST TWO ARE 0.56 MCI/CM

DISCUSSION

The treatment of choroidal melanoma is a very controversial subject which ranges from observation alone, to bombarding the tumor with proton beam irradiation; all of which have their advantages and disadvantages. The sources of radiation that have been used with eye plaques include cobalt-60, ruthenium-106, radon gas, iodine-125, and iridium-192.

Shields, et al, reported a 40% complication rate in 100 cases treated with cobalt-60 plaques during a 1-5 year follow-up period. The problem with using cobalt plaques is one of shielding. The vital structures adjacent to the tumor, i.e., lens, optic nerve and orbit receive a substantial amount of radiation due to the high energy of cobalt-60 (1.25 MeV average).

Ruthenium-106 decays to rhodium-106 and produces a maximum beta-ray of 3.5 MeV with an average beta energy of 1.5 MeV. The use of ruthenium-106 in beta applicators is encouraging with a cure rate of 64.4% in 205 patients. However, of the 64.4% cured, 96.9% were small tumors (29). Tumors less than 5 mm in height above the scleral surface and 15 mm in diameter at the tumor base are the maximum tumor dimensions that can be treated using this radionuclide because of the limiting penetration depth of beta-rays. Small choroidal melanomas have a better prognosis and less complication rate than medium or large tumors. Ruthenium applicators are also limited in other

ways.

One group has used radon gas in the treatment of choroidal melanoma (maximum beta energy 1.2 MeV and an average photon energy of 780 KeV) and they reported an 86% complication rate in 14 cases followed for 32 months. Radon gas has some disadvantages. 1) the high energy and short half-life (3.8 days) means the total dose is given at a very high dose rate. The tissues near the radon get an excessive amount of radiation. 2) the radon gas is supplied in the form of metal seeds which does present some radiation safety problems if the seeds were to leak or become damaged.

Iodine-125 is a popular radionuclide in the treatment of choroidal melanoma for many reasons. The dose distribution is good and the normal surrounding tissues receive a lower dose. There is less exposure to operating room personnel and the patient does not have to be isolated. However, iodine-125 is not without its disadvantages. The seed array in the plaque containing iodine-125 is critical in order for the tumor to receive a uniform dose distribution. Also, the rapid fall off doses at the edge of the plaque could result in tumor failures (13).

In one study using iodine-125, 29 patients were treated with a complication rate of 34% after an average of 38 months follow-up. Sixty-nine percent of these patients had large melanomas. The other 31% were medium-size tumors - no small tumors were treated.

This study had the lowest complication rate, with longer follow-up, including larger tumors than were reported with cobalt-60, ruthenium-106, and radon gas.

At the time this report was written, there were no reports about the use of iridium-192 wire or seeds for treating choroidal melanoma. At the Ontario Cancer Institute, they did treat approximately 7 patients with iridium-192 wire. They used an average dose rate of about 61 cGy/hr with an average total dose of 72 Gy to the apex of the tumor (3). In one study by the same hospital, an average dose of 77.5 Gy to the apex of the tumor was achieved at an average dose rate of 50 cGy/hr. Two to four concentric differentially loaded iridium-192 rings of 0.5 to 2.2 cm in diameter were used. Of the seven patients that had been followed for 14 months or more, 71% had dramatic shrinkage in their tumor as evidenced by ultrasound while the other 29% had less of a dramatic response.

CONCLUSION

For the use of iridium-192 wires to be effective in the management of choroidal melanomas, the question lies mainly on the ability to shield this relatively powerful source to prevent over exposure of normal tissues and thus prevent severe complications. The half-value-layer for iridium-192 using gold was calculated to be about 1.7 mm. If a solid gold plaque is made two half-value-layers, then this may provide adequate shielding to protect normal surrounding tissues. Iridium-192 is considered a relatively high-energy radioisotope with an average gamma energy of 380 KeV, and a tissue penetration half-value-layer of 5.0 cm. Therefore, the opposite retina and lens could get a substantial dose unless measures are taken to shield the unaffected eye.

In summary, the successful treatment of choroidal melanoma depends on many factors, but the size of the tumor, in particular the tumor diameter, is the single most important prognostic factor. Small (T1) tumors (not more than 2.0 mm high and up to 10 mm in basal diameter) have the best prognosis and lowest complication rate as opposed to medium or large tumors.

For this reason, small tumors have more treatment options, i.e., observation, photocoagulation, radiation and local resection are all possible forms of useful alternatives to enucleation.

For medium to large size tumors, local resection is the only alternative to enucleation with the exception of some forms of brachytherapy using eye plaques. In cases where there is only one eye remaining then enucleation would be the last resort.

Radioactive eye plaques can be individualized to treat specific tumor volumes within the eye. Radioactive wires deliver a uniform dose along the tumor axis with a complete distribution throughout the entire tumor mass. The most homogeneous radiation isodose distributions can be determined with the aid of computer calculations for concentric, multiple, and differentially loaded rings of iridium-192 wire.

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