EXTERNAL BEAM RADIATION FOR RETINOBLASTOMA*

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Retinoblastoma, a malignant retinal tumor of childhood, involves both eyes in one third of cases. Untreated, it is universally fatal, but with present techniques the survival rate is 90%.[1] The goals of treatment are preservation of both life and sight. Among the modalities presently used to treat the tumor, radiation therapy is most commonly employed, but such other techniques as diathermy, light coagulation, cryopexy, chemotherapy, surgical enucleation, and exenteration are important resources for an ophthalmic onocolgist.[2]

The first case of retinoblastoma was described in 1765 by a London surgeon.[3] In 1864 Virchow identified the tumor and called it a "glioma of the retina". Perhaps it was because the tumor was thought to be of glial origin (and it is known that glial tumors responded poorly to radiation) that it was not until 75 years ago that the first retinoblastoma was successfully treated with radiation.[4] In fact, it was not until 1926 that the term retinoblastoma was universally adopted. Since then it has been repeatedly emphasized that this tumor originates from the nuclear layers of the retina and not from glial cells. As the indications, contraindications, and complexities of radiation have been learned through trial and error, the usefulness of radiation therapy for retinoblastoma has become better established.

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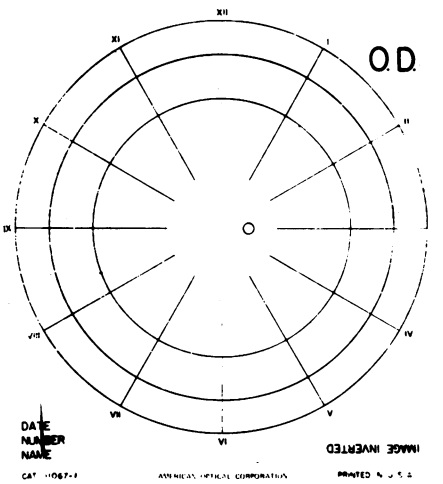

Fig. 1. Standard retinal drawing used to localize intraocular tumors

ANATOMY

Some basic points about ophthalmic anatomy are important to radiation therapists.

The distance between the front surface of the cornea and the retina is 18 to 19 mm. in children 6 to 12 months old. At this age the distance between the front surface of the cornea and the posterior pole of the lens is 7 mm. Although the lateral canthus or lateral bony wall of the orbit is frequently used as a landmark to establish portals, it is best to do this with careful localization of the eye because the degree of ocular protrusion from the orbit can vary considerably from patient to patient.

The standard retinal drawing used to describe retinal tumors is based on the following scheme (Figure 1). The central area of the drawing represents the macula, which is 1 mm. medial to and 1 mm. above the posterior border of the inferior oblique insertion. The circle to one side of the macula (Figure 1) represents the optic nerve head (or optic disc), which is 1.5 mm. in size. Tumor size is usually expressed in "disc diameters".

The retinal drawing represents, in two dimensions, the inner curved three dimensional aspect of the eye. Thus, as in any flat map, there are in-

herent distortions in the relationship between more anterior structures on the map. The more anterior ("peripheral") structures appear further from each other than they actually are. The space between the outermost circle and the middle circle on the retinal drawing represents the pars plana, which is 3 to 4 mm. wide and extends 8 mm. from the limbus in adults. The middle circular line represents the ora serrata, the anterior termination of the retina. Its edges are scalloped and extend 7 mm. from the limbus on the nasal side and 8 mm. from the limbus on the temporal side. The most posterior line is the equator, which represents the geometric equator of the eye and is 12 to 4 mm. from the limbus. The medians on the clock denote positions in the retina as they appear to the observer. Each meridan represents 30° of the anatomy with the overlapping central area of the meridans converging on the macula, not the optic nerve.

The insertion of the recti muscles as measured from the limbus are: medial rectus 5. 5 mm., inferior rectus 6. 5 mm., lateral rectus 6.9 mm., and superior rectus 7. 7 mm. Although the indirect ophthalmoscope projects an inverted image to the viewer, this is completely corrected in the retinal drawing. In vitreous seeding it is helpful to draw a side view of the eye to show the location of the seeds "in space".

TECHNIQUES

Radiation therapy was first introduced as an alternative to enucleation when both eyes were involved and the first eye had been removed[5] as a desperate attempt to salvage any vision and to prevent total blindness. While this technique did cure the tumor, the doses and techniques did ultimately destroy the vision and usually lead to enucleation because of radiation complications. These complications were sometimes extreme, and unfortunately tainted the earlier clinicians' appreciation of its ultimate value. There have been many modifications in dose, source, and technique since then. At the present time, several modalities are available for external radiation of retinoblastoma.

A *high energy* (4-6 MeV linear acclerator) *photon beam* is delivered through a 4 x 3 cm. lateral portal. The beam is angled 5° posteriorly to avoid irradiation of the lens of the diseased eye and to minimize radiation to the opposite eye (Figure 2). The set-up is easy, the position of the beam can be readily checked visually and by palpation of the bony canthus. No sedation is necessary if the child is immobilized. Two lateral opposing fields each angled in this way may be used to treat bilateral tumors (Figure 3). One

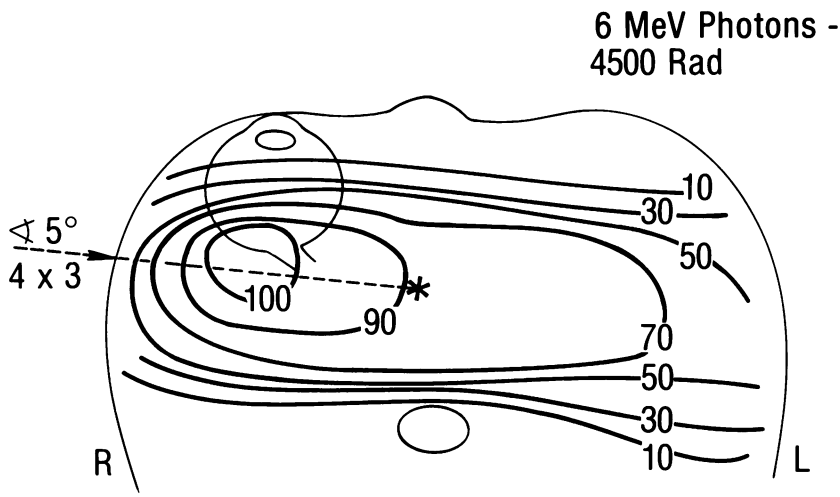

Fig. 2. Dose distribution of a photon beam from a 6Mev Linear accelerator placed laterally are angled 5° posteriorly

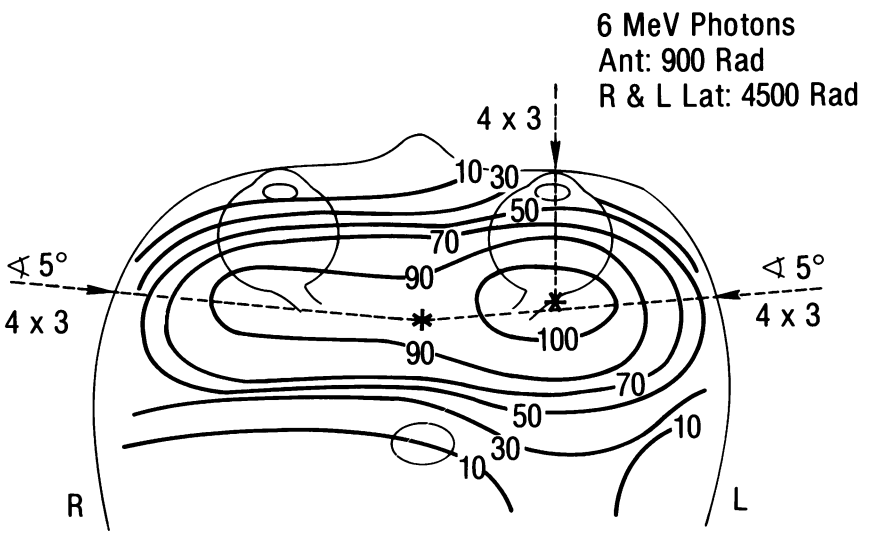

Fig. 3. Treatment plan for a child with bilateral retinoblastoma using two lateral opposing 6 MeV photon beams and one anterior 6MeV photon beam for the more advanced tumor in the left eye

point of caution in using either of these techniques is that full knowledge of the penumbra of the beam is essential. Because the light beam is used to position the field, one must be aware which radiation dose level corresponds

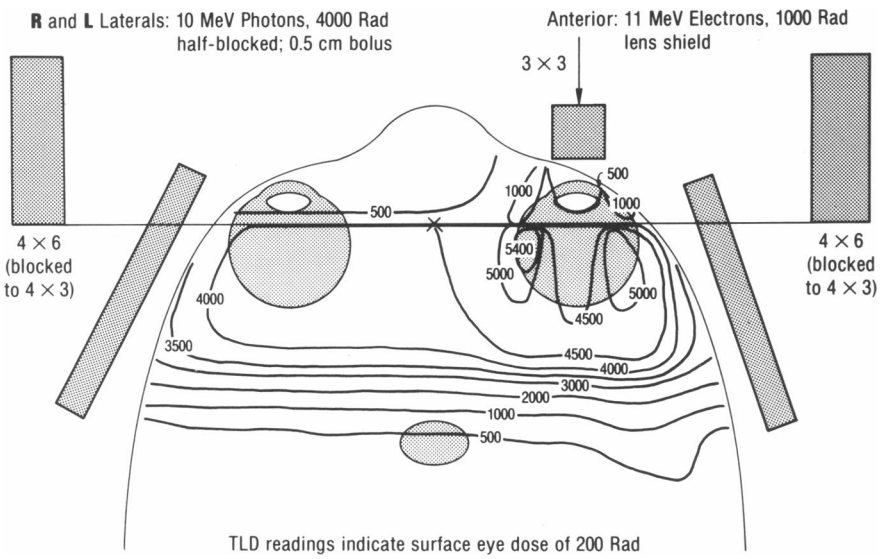

Fig. 4. Treatment plan for a child with bilateral retinbolastoma, using two lateral opposing 10MeV photon "split" beams and one anterior 13 MeV electron beam for the more advanced tumor in the left eye with shielding of the lens

to the edge of this light beam and how the dose falls off outside the light beam edge. In particular, some cobalt 60 units with large penumbra may not be suitable for use here because considerable doses to the lens and inhomogenous dose distributions to the retina can occur. Inhomogenous dose distribution may explain the poor response in large tumors, when the whole tumor does not receive the homogenous dose of radiation necessary for permanent control. It may also explain the appearance of new tumors if these already existed at the time of radiation therapy but were too small to observe. This method is chiefly indicated for small tumors located posteriorly.

A further disadvantage of a single energy photon beam for treatment of unilateral disease is high exit dose with undesirable effects in a relatively large volume of normal tissue (Figure 2). Although the large penumbra of some cobalt 60 units make them unsuitable for this treatment, the energy of ^{60}Co is actually preferable to that of some of the higher energy (15 MeV and up) linear accelerators because the lower energy gives a small build-up region with the maximum dose in the tumor tissue and a relatively low exit dose compared to a high energy accelerator, with its maximum dose occurring at depths corresponding to the energy (2.7 cm. for 10 MeV, 3.6 cm. for

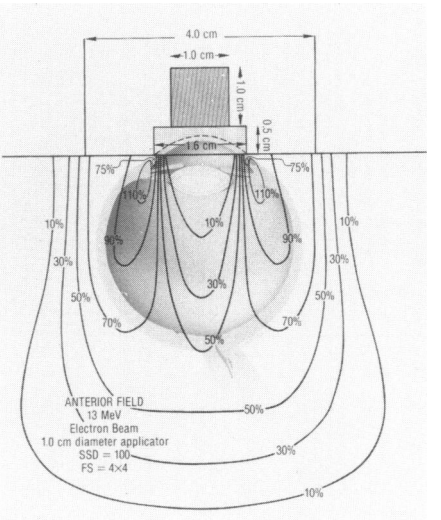

Fig. 5. Dose distribution in the eye of a 13 MeV. electron beam with a 1 cm. diameter and 1 cm. thick lead shielding of the lens

18 MeV) and a large exit dose. To reduce the depth for the maximum dose in tissue for this high energy photon beams a bolus has to be positioned on the skin (Figure 4).

Optimum treatment with this technique can be with a 4-6 Mev. linear accelerator with sharp penumbral characteristics or using a split beam technique on a cobalt 60 unit.

Electron beam can be used as a lateral beam in the same manner as the high energy photon beam. The exit dose and the dose to the opposite eye is considerably lower. The characteristic rapid fall off of dose with depth for the electron beam and the difference between electron absorption in bone and soft tissue, however, mean that large changes in dose distribution can result with this technique because of the large amount of bone through which the beam must pass when entering laterally. The dose distribution and gradient of the dose within the eye is comparable to that of the high energy photon beam.

Anterior electron beam, with insertion of a lens shield consisting of a 1 cm. thick lead block mounted on a low vac contact lens. The disadvantage of this modality is its inhomogenous radiation dose to the retina (Figure 5).

The "cold spot" behind the shield can be corrected by using the electron beam together with the shielding under four different angles. Theoretically, a very satisfactory distribution can be achieved, but a minimal displacement of the shield or change in the angle will result in considerable changes in the dose distribution. Another disadvantage of using electrons with lens shield is that the child must be sedated for each treatment. It is desirable to apply radiation individually and to choose the method most suitable for the particular patient. In order to decrease the disadvantage, two methods may be combined. Doses of radiation broadly used in the past, with good results, are between 3,000 and 3,500 rad in three weeks up to 4,500 rad in four weeks.

The following policy for treatment of children with retinoblastoma has currently been adapted at Memorial Hospital. First, a plaster of Paris cast is made to immobilize the head. It is imperative that the cast fit perfectly and be comfortable, and smaller, uncooperative children are sedated for its making. The next day the radiation beam control is performed on a simulator device, and no sedation is necessary if the cast fits perfectly. The aim is mainly to check that a lateral beam (average 3 x 4 cm.) tilted 5° posteriorly does not include the pituitary gland (Figure 6). A contour of the child is taken and an individual treatment plan is made for isodose distribution. Figure 7 shows a treatment plan for a child with unilateral retinoblastoma. Figure 8 shows a treatment plan for a child with bilateral retinoblastoma, postoperatively, for an advanced tumor in the remaining eye. The daily doses are 250 rad, delivered four times per week with a photon beam and 250 rad once per week with electrons with anterior eye shielding. For treatment with photon beam, the child is placed into the cast without sedation (Figure 9) while, for treatment with the electron beam, the child must be sedated to insert the lens shielding. For postoperative radiation of extraocular tumor invasion, a perpendicular electron beam is used for a dose of 4,000 rad in four weeks with 250 rad fraction four times a week.

For radiation of the central nervous axis in patients with tumor spread to the erebrospinal fluid, whole brain irradiation is used.

INDICATIONS

In unilateral retinoblastoma, four factors determine the use of radiation: age of diagnosis, location of tumor, multifocality of the tumor, and the size of the tumor(s).

Age at diagnosis. Retinoblastoma is diagnosed at a mean age of 2.4 months

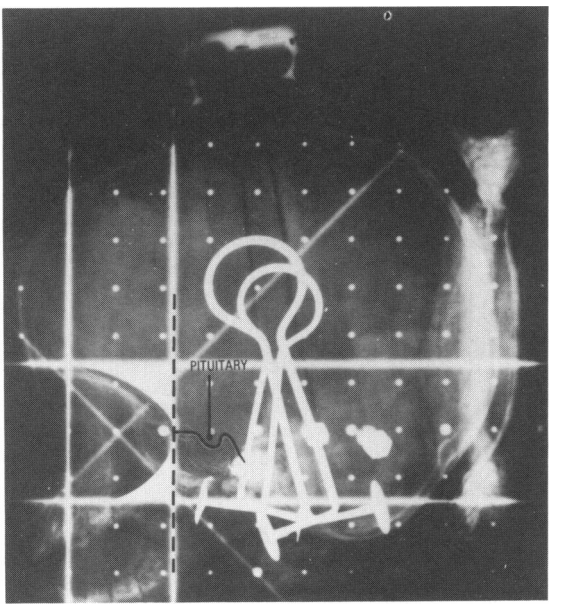

Fig. 6. Roentgenogram of the field of simulating treatment conditions

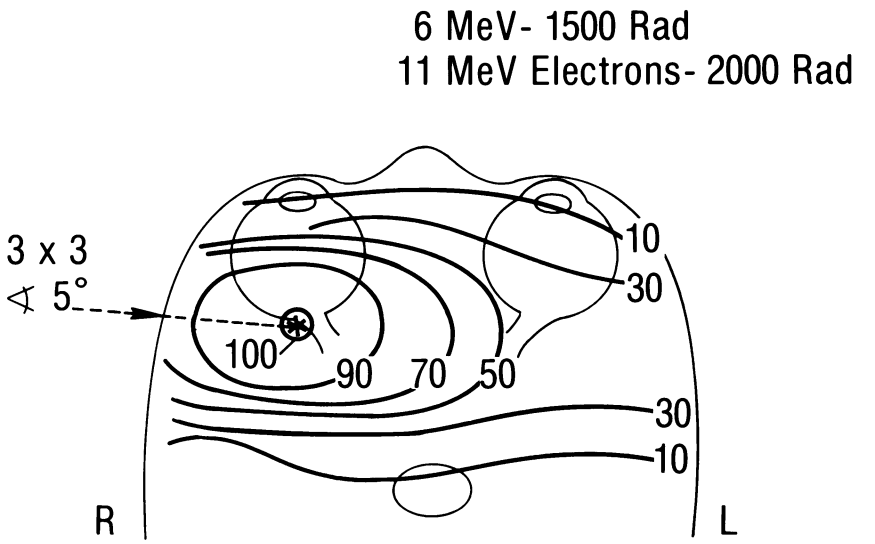

Fig. 7. Treatment plan for a child treated for a small (Group I) unilateral retinoblastoma using 6 MeV photon beam and 11 MeV electron beam through a single lateral portal 3x3cm. angled 5° posteriorly

when a patient harbors the germinal mutation and 24 months when there is no family history. Thus, early diagnosis (less than four months of age) strongly suggests a patient with the germinal mutation. Only 4% of such patients will have only a single solitary focus of intraocular tumor. Ultimately, they will have between four and five tumors. Thus, when diagnosis is made early, the chance that new tumors will appear during future months is high. The location of these additional tumors is largely unpredictable, but they tend to be in the periphery and below. Because of the possibility that the fellow "normal eye" may contain tumor in the future, all attempts are made to salvage the eye initially diagnosed as unilaterally involved. The new tumors which may develop in the "other eye" may ultimately do less well and require enucleation.

Location of tumor. When the tumor(s) present in the macular region, any modality other than radiation will cause significant permanent visual impairment. While the success of photocoagulation or cryopexy is high with such tumors, the central scotoma and peripheral visual field loss following these techniques may be significant. Radiation therapy of small posterior tumors may cause the tumor to disappear completely without impairment of sight or visual field loss.

On the other hand, tumors anterior to the equator are in a relatively poor location to treat by radiation. The lateral portal radiation of the unilateral tumor must be angled back 5° to avoid the sensitive lens in the other eye and, when this is done, the anterior retina (especially nasally) receives a smaller amount of radiation and recurrences are common. While anterior tumors can be successfully treated using an anterior field alone, the complications of such approaches are high and probably unacceptable in most unilateral cases.

Multifocality. All modalities except external irradiation will cause local destruction of surrounding normal retina and vessels. Thus, when the unilateral tumor is multifocal, extensive visual compromise will usually follow photocoagulation or cryopexy. Small, peripheral tumors are an exception to this. In addition, such modalities may have to be repeated under anesthesia 1 to 10 times. The greater the number of tumors in the eye, the greater the need for external beam irradiation.

In addition to the above, external beam irradiation may be the only way to treat retinoblastoma without enucleation when the vitreous is seeded. Vitreous seeding responds poorly to radiation and is best handled by enucleation.

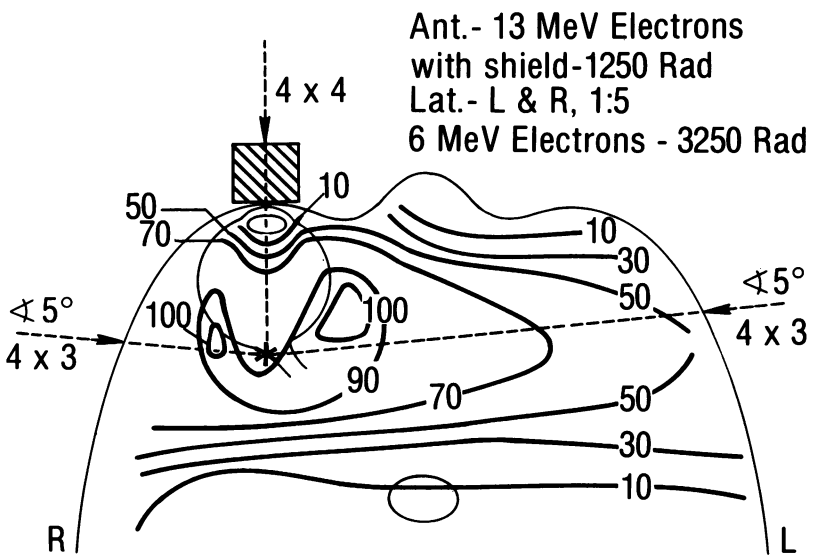

Fig. 8. Treatment plan for a child with bilateral retinoblastoma, treated postoperatively to the remaining eye with advanced (Group 5) tumor after enucleation. Two lateral opposing beams with weighting 1 to 5 and an anterior 13 MeV electron beam with lens shield are combined.

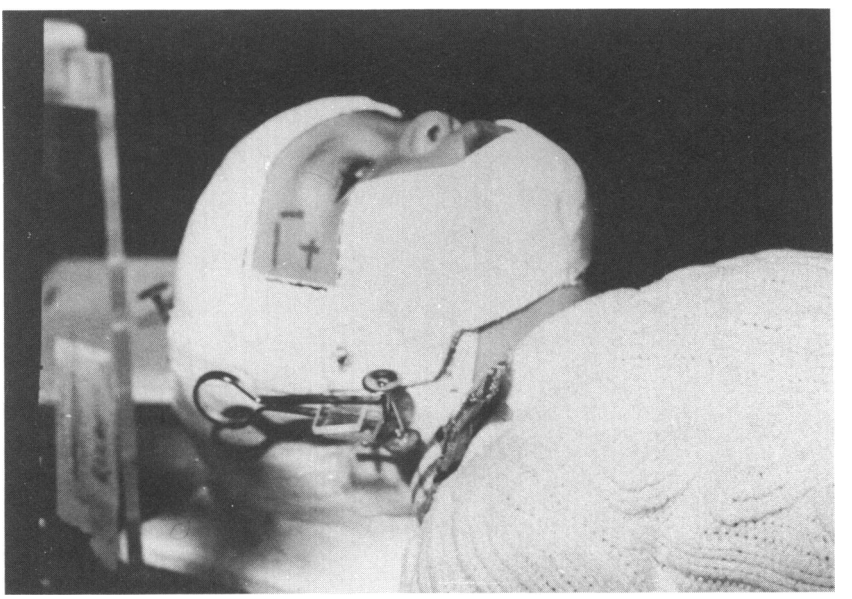

Fig. 9. The patient not sedated, in cast undergoing treatment

We have treated 50 cases of unilateral retinbolastoma using primary irradiation. Half of these required additional treatment. Half of these required additional treatment because of new tumors following radiation and half because the tumors did not respond to radiation. Ten percent of such eyes ultimately came to enucleation but there have been no deaths in this group to date.

Size of tumor. The limiting factor for the effective treatment of retinoblastoma by techniques not using radiation is the size of the ocular tumors. For example, cryopexy with nitreous oxide or carbon dioxide will successfully destroy tumors up to 4 dd. (6 mm.) in size but when the tumor is larger than 4 dd. repeated cryopexy will be necessary to destroy the tumor.[2] In large pedunculated tumors, it is impossible to freeze through the highly elevated tumors. Photocoagulation, on the other hand, is also limited by similar size restraints. In addition, photocoagulation cannot be employed when the media is clouded, the retina is detached, or the surrounding retinal pigment epithelium is disrupted or absent. Thus, most tumors larger than 4 dd. in size are best managed by external beam irradiation, cobalt plaques, or enucleation.

BILATERAL RETINOBLASTOMA

In the past, the standard philosophy for the management of bilateral retinoblastoma was to enucleate the more involved eye and to irradiate the less involved eye. In such cases the four guidelines used for irradiation of the remaining eye are the same as those used in unilateral retinoblastoma: the age of the patient, location, multifocality, and the size of the tumor(s).

In two situations, however, those guidelines can not be followed. In advanced bilateral retinoblastoma it is often difficult to distinguish which eye is more involved. In such cases both eyes may be simultaneously enucleated with a survival rate of 92%.[9] We have treated 34 cases of bilateral advanced retinoblastoma with simultaneous bilateral radiation and have long-term survival rates of 90%. More than half of the eyes so treated ultimately came to enucleation but fortunately some eyes were salvaged, some with useful vision.[9] In such cases it is imperative that complete metastatic tumor evaluations be carried out.

In bilateral symmetrical retinoblastoma, when the diagnosis is made early, before the eye completely fills with tumor, both eyes can be treated simultaneously by radiation. In 37 cases so treated we had patient survival of 88%.[10] Fifty percent of eyes so treated required additional treatment, and

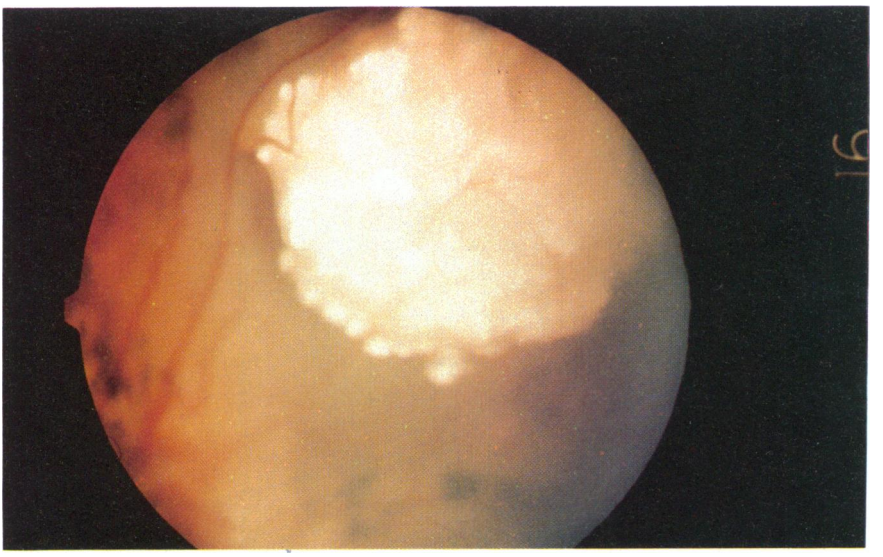

Fig. 10. Type I regression pattern of retinoblastoma

15% ultimately came to enucleation. It should be emphasized that in these cases of symmetrical advanced or minimal disease enucleations were not done because of radiation complications but because of radiation failures.

ORBITAL RETINOBLASTOMA

When retinoblastoma occurs in the orbit following enucleation or when it is present at the distal edge of the severed optic nerve, the patient's survival is dramatically affected. Only 60% of patients with tumor at the cut section of the nerve survive. When recurrent tumor arises in the orbit after enucleation, fewer than 10% survive. These cases are now managed by combinations of radiation and chemotherapy, not surgically, because the results with surgery are not as good as those with radiation.[2]

METASTATIC DISEASE

Local radiation to systemic metastases from retinoblastoma is of benefit for palliation but of no value for increasing survival.

RADIATION REGRESSION PATTERNS

Three typical radiation regression patterns for retinoblastoma have been described.[1] It is unusual for treated retinoblastoma completely to disappear, although occasionally tumors smaller than 3 mm. will do this. It must

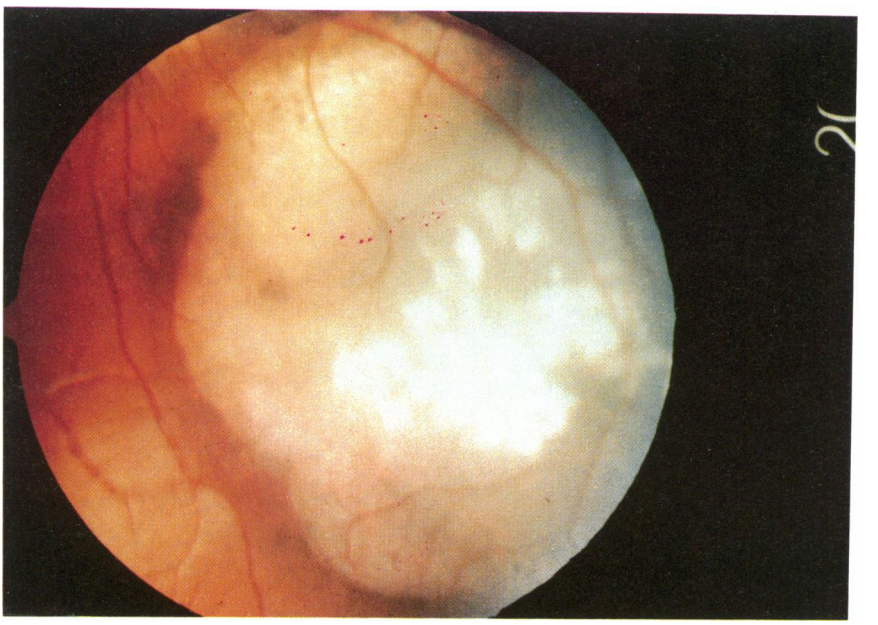

Fig. 11. Type III regression pattern of retinoblastoma

be emphasized that retinoblastoma treated by radiation will usually *not* disappear, and persistance of the tumor after radiation is *not* an indication for enucleation. Further, different tumors in the same eye may show different regression patterns.

Type I. The type I regression pattern is the most dramatic and satisfying pattern seen after treatment of retinoblastoma (Figure 10). By the end of the treatment (three weeks) and continuing for a few months, the tumor may show dramatic reduction in size and take on the appearance of "cottage cheese". The regressed tumors appear to be composed of DNA-calicum complexes and continue to change morphology for weeks and months. The tumor loses its blood supply and may have streaks of yellow "exudate" on its surface. With the dramatic shrinkage of the tumor there may be hyperplasia and hypoplasia of the surrounding retinal pigment epithelium. When tumors show this regression pattern, it is very unusual for them to reactivate following treatment. It has been suggested that the tumor foci that respond with such regression patterns consist of less differentiated, more malignant cell types of retinoblastoma. The true role of hypoxia in the generation of such regression patterns is unknown.

Type II. This response is quite different. The tumor shows a modest or no

appreciable diminution in volume at the end of radiation therapy. There is little if any change in the tumor months later. No calcified DNA-calcium complexes are seen ophthalmoscopically and the surrounding retina shows few changes. The tumor may lose some vascularity and appear more like "fish flesh". It has been suggested that while such a regression pattern is more disturbing to the clinician, it represents tumor cells that were more differentiated, less malignant, and therefore less responsive to radiation.

Type III. This type of regression pattern is the most commonly seen and has different aspects of both Type I and Type II patterns (Figure 11). This type of regression must be carefully followed because of a tendency for recurrences months later. Not all regression patterns will fall into the above classification. Occassionally, the tumor will develop ophthalmoscopic "holes" where underlying choroid can be seen through a clear mass of tumor. Massive retinal pigment hyperplasia can also be seen.

COMPLICATIONS

Complications of radiation therapy in the eye have interested investigators for many years.[11,12,13] As wider clinical experience has modified the type of radiation portal, radiation dose, and fractionation, it is now possible successfully treat to the eye and orbit without excessive complications.

The ocular tissue most sensitive to radiation is the lens. While it is known that the human lens can develop a localized cataract after only 200 r by delivering the radiation through a lateral portal and angling the beam 5 to 10° posteriorly, it is possible to avoid the lens of the eye being treated and its fellow respectively. Unfortunately, the use of orthovoltage, anterior portals, and excessive patient movement in addition to improper alignment of the patient and patients' normal bell curve response contribute to cataracts in 1% of retinoblastoma patients. It is of interest that of 23 retinoblastoma patients who received an average lens dose of 850 to 900 r in three months 10 patients did not develop a cataract and six developed a stationary cataract that did not impair vision.[12]

With the introduction of orthovoltage and superficial radiation to treat retinoblastoma, during earlier years the usual consequence of such high doses to the anterior segment were conjunctivitis, dry eye syndrome, corneal opacity and/or infection, cataract, rubeosis iridis, and intractable glaucoma requiring enucleation. With present techniques this is no longer seen.

The main complication of radiation therapy in its modern form is vascular damage and its sequella. In the eye this takes two forms. In one form there is dramatic localized or extensive occlusion of the retinal blood vessels or vascular supply to the optic nerve leading to ghost vessels and obliteration of blood supply. The other form has localized telangiectasia with exudation and new blood vessel formation (neovascularization) with hemorrhage, scarring, and retinal detachment. While those responses are clearly dose related, being rare at 3,500 r and occuring with a frequency of 80% in eyes receiving 8,000 r, some patients develop these devastating changes at 3,500 r while others show no effect after 8,000 r.

Many other complications of radiation are routinely seen but, because they have no affect on vision, are considered acceptable. These include local hyperemia, loss of lashes, fat atrophy with ptosis, impaired bone growth, permanent radiation dermatitis, and delayed wound healing following surgical operations or trauma. In addition, local bleeding tends to be greater when minor trauma occurs.

RADIATION INDUCED TUMORS

The association between retinoblastoma and subsequent nonocular malignancies has been a fascinating study in the understanding of cancer itself. With the first large series of cases successfully treated with enucleation of the more affected eye, it was noted that two of 55 patients developed sarcomas in the field of radiation following high dosages and after prolonged latent periods.[5] In 1961 Forrest reported on 17 patients with retinoblastoma who developed tumors after successful radiation treatment of the retinoblastoma.[14] Again, these cases represented mostly sarcomas with a mean latent period of 10 years and in the field of the radiation beam.

While the number of such cases is increasing, recent work has demonstrated that radiation may play a minor or no role at all in the development of such tumors.

We reviewed more than 2,000 cases of retinoblastoma from the Columbia Presbyterian Medical Center and Armed Forces Institute of Pathology and found that, although unilateral retinoblastoma represents 75% of all cases of retinoblastoma, 98% of patients who developed second nonocular tumors had been treated for the less common bilateral form of retinoblastoma.[15] Because patients with bilateral retinoblastoma harbor the germinal mutation, probably in the Q 1-4 band of chromosome 13, it

would appear that this germinal form of cancer predisposes such patients to a myriad of other tumors.

Osteogenic sarcoma of the skull occurs 2,000 times more frequently in survivors of bilateral retinoblastoma than in the rest of the population. Such tumors occur in the skull even when *no* irradiation is given.[14]

Osteogenic sarcoma of the bones of the extremities is 500 times more common in patients who survive bilateral retinoblastoma. Again, these tumors occur more commonly even if the patients are not irradiated.

Second nonocular tumors occur 10 or 11 years after the treatment for retinoblastoma, whether or not the tumor appears in the irradiated field and independently of the type of radiation used.[16] Radiation of unilateral nongerminal mutation retinoblastoma does not result in second tumors. The incidence of second tumors in survivors of retinoblastoma is 15 to 20% and, within time perhaps, 30% of survivors of treated bilateral retinoblastoma will develop second nonocular tumors. Because these second tumors are usually fatal, more patients die of their second malignancies than of bilateral retinoblastoma itself.

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