Proton irradiation of simulated ocular tumors

Ian J. Constable, Andreas M. Koehler, and Robert A. Schmidt

Silicone sponges were sutured to the sclera of owl monkeys to create an indentation which would simulate a tumor of the posterior segment of the eye. A tantalum clip inserted in the silicone sponge served as a marker for radiographic localization of the simulated tumors. The acute lesions obtained on the retina and choroid after moderately high doses of proton irradiation suggest that this method of aiming the proton beam will be adequate for human clinical trials.

Key words: protons, irradiation, ocular tumors, stereotactic radiography, ultrasonography.

It is possible to apply large doses of ionizing radiation to localized areas of the eye by means of external beams of protons. When these heavy particles are accelerated to appropriate energy levels, they will penetrate tissues and deposit more irradiation as they stop than along their entrance path. If this peak dose, termed the Bragg peak, falls on a localized area of retina and choroid, much smaller doses are delivered to the tissues in front and behind this target. Furthermore, the minimal scatter of protons in tissues makes it possible to collimate small beams and to protect the tissues adjacent to the path of the beam.

To utilize proton beams for the treatment of human ocular tumors, aiming procedures must be developed which are convenient, safe, and completely reliable. Reported here are aiming experiments on simulated ocular tumors, utilizing stereotactic radiography.

Materials and methods

Preparation of animals. Under pentobarbital anesthesia (15 mg. per kilogram intramuscular injection) and sterile operating conditions, an episcleral silicone sponge was sutured to a total of 22 owl monkey eyes. The sponges were either 5 mm. long and 3 mm. in diameter or 7 mm. long and 5 mm. in diameter. In each case a piece of a thin tantalum clip 2 mm. long and 0.5 mm. wide, was inserted into the center of the sponge in a thin slit made at one end along its long axis. After extensive lateral or superior orbitotomy and disinsertion of a rectus muscle, the sponge was fixed radially to the sclera with a 5-0 Dacron mattress suture at a variable site from the equator back to the posterior pole in one of the lateral or the superonasal quadrants.
Fig. 1. Operative view of a 3 mm. silicone sponge sutured to the sclera in the upper temporal quadrant after lateral orbitotomy.

(Fig. 1). A large internal bulge of approximately 7 by 5 mm. or 9 by 7 mm. was obtained in each case without draining ocular fluid. The rectus muscle was reattached, and Tenon's capsule, conjunctiva, and skin closed after irrigation with penicillin solution. A temporary tarsorrhaphy was also done to prevent postoperative exposure keratitis.

Three to five weeks after surgery, stereoscopic photographs were taken of the simulated ocular tumor with a Zeiss fundus camera. In many cases, combined A and B-scan ultrasonography3 was also done in order to assess the dimensions of the target. For this procedure the animal was anesthetized with pentobarbital, the head was partially shaved, and a plastic drape was both glued and sutured to the skin to provide a seal for the water bath.

Proton irradiation of the eyes. About six weeks after surgery, the animals were again anesthetized with pentobarbital, and then immobilized in the stereotactic head-holding apparatus previously described. A postero-anterior radiograph was taken along the path of the proton beam, and a beam spot of protons superimposed. The head was then adjusted and the radiographs repeated until the tantalum marker within the episcleral sponge was precisely aligned in the center of the proton test beam spot (Fig. 2). The animal was then rotated exactly 90° and the alignment process repeated using lateral radiographs and a superimposed beam spot of protons (Fig. 3). The alignment of the x-ray focal spot with the central axis of the proton beam was verified on each occasion.

A single peak dose of 5,000 to 10,000 rads was then delivered to the eye at a dose rate of 800 to 1,000 rads per minute using a 7 or 10 mm. diameter circular beam, depending on the dimensions of the intraocular bulge. Dosimetry was carried out using a small silicon diode and a water-filled phantom as previously described.1 The Bragg peak was aligned with the center of rotation of the stereotactic system and hence with the ocular target in phantom experiments prior to the treatment.1 When the 7 mm. beam was employed, it was delivered through the center of the lens. General anesthesia alone was found to be sufficient to immobilize the owl monkey eye. When the 10 mm. diameter beam was used, it was directed posterior to the lens across the vitreous cavity. In this case the eye was fixed in maximal duction by two limbal traction sutures before the radiographic alignment was started. This was necessary because the axes of rotation of the eye do not correspond with the axes of rotation of the stereotactic apparatus. In these cases it was usually also necessary to disinsert one rectus muscle, since the owl monkey eye does not rotate easily.
Fig. 2. Postero-anterior radiograph of an owl monkey showing a tantalum marker exactly aligned in the center of the superimposed circular proton-beam test spot. The tantalum marker is contained within a silicone sponge which is sutured to the sclera in the supero-temporal quadrant.

Fig. 3. Lateral radiograph showing the tantalum target aligned in the center of a proton-beam test spot.
Histopathology. Representative animals were prepared for histopathologic examination by retrograde aortic perfusion with 10 per cent formalin. Whole eyes and tissue samples of the orbital structures and the forebrain lying immediately posterior in the path of the beam were examined by light microscopy.

Results

The initial internal bulge tended to decrease gradually in height over the six weeks prior to proton irradiation, but a target of suitable size and elevation was obtained in 20 eyes (Fig. 4). Two eyes on which silicone sponges were placed were excluded from the experiments. One developed chronic orbital infection with extrusion of the sponge, while the other lost its internal bulge completely due to loosening of the scleral suture.

The dose delivered to the ocular target and adjacent tissues by the 7 mm. beam, when the Bragg peak was positioned on the tantalum clip within the scleral sponge is shown by the isodose lines superimposed on a scale drawing of the owl monkey eye and orbit (Fig. 5). The depth-dose characteristics of the 10 mm. beam were similar to those of the 7 mm. beam. About 55 per cent of the peak dose was delivered to the sclera at the entry point opposite the target area.

A circumscribed opaque area of edematous retina and choroid developed within 24 hours in all 20 eyes irradiated. The diameter of the visible acute lesion depended on the diameter of the beam used and on the peak dose delivered. In 18 of the treated eyes, the acute radiation burn was well placed, overlapping the oblong bulge of indented retina and choroid on all sides. An example of the chorioretinal reaction seen two days after application of 10,000 rads to a small superotemporal indentation with a 7 mm. diameter beam through the center of the lens is shown in Fig. 6. In each case this edematous white lesion settled within ten days, leaving the clinical appearance of a thin atrophic retina and proliferated pigment, both over the dome of the indentation and immediately around its edges (Fig. 7).

The acute lesions were characterized histologically by shallow retinal detachment, and intraretinal swelling which resulted in multiple small folds (Fig. 8). The inner and outer segments of the photoreceptors were almost completely destroyed two days after irradiation but the other retinal cell layers were essentially intact. The small retinal vessels were markedly dilated and there was swelling of the choroid. Immediately outside the visible circular lesion, the retina and choroid appeared entirely normal.

Histologically the permanent retinal thinning in the bombarded area was found
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Fig. 5. Isodose lines, expressed as a percentage of the Bragg peak dose of the 7 mm. proton beam, superimposed on a scale drawing of the owl monkey eye and orbit. It is apparent that diameter of the visible lesion depends partly on the total peak dose delivered.

to be due mainly to destruction of receptor cell layers and collapse of the outer plexiform layer (Fig. 9). As a result, the reduced numbers of surviving cells of the outer and inner nuclear layers were compacted into one layer. The ganglion cells, inner plexiform layer, and nerve fiber layer appeared relatively intact six months after irradiation. The retinal pigment epithelium showed mild proliferation and clumping of its pigment. Within the dose ranges used in this experiment the choriocapillaris in the bombarded area was partly obliterated, but the larger choroidal vessels were relatively spared. The retina and choroid immediately outside the treated area appeared entirely normal after six months (Fig. 9).

Similar changes in the retina were also seen after irradiation of large sponges with the 10 mm. beam directed across the vitreous cavity posterior to the lens (Fig. 10). No ocular side-effects such as corneal ulceration or edema, lens changes, or optic nerve damage have been seen so far in periods of observation of up to nine months in any of the 20 eyes, treated either through or around the anterior segment. There were no histopathologic changes found in these tissues at six months. In addition, the orbital muscle, bone, and brain samples, which were taken immediately posterior to the irradiated ocular tissues were also normal.

In two eyes the visible radiation response failed to overlap the target area adequately. One was a superotemporal target in which the internal bulge was not surrounded by the zone of treatment inferiorly (Fig. 11). Although held in sursumduction by limbal traction sutures, it was noted at the end of the treatment period that the eye had been rotated further upward by pressure from the extension nozzle. The second inadequate result was with a very high nasal bulge, the B-scan of which is shown in Fig. 12. Treatment of this target with 5,000 rads from a 7 mm. diameter beam resulted in a visible
Fig. 6. Circular area of chorioretinal edema photographed 48 hours after 10,000 rads were delivered by the 7 mm. proton beam, the Bragg peak being aligned with the episcleral tantalum clip. The indentation (outlined by the black arrows) is well overlapped by the area of visible reaction (S, scleral suture site).

Fig. 7. The same eye as shown in Fig. 6 five months later. The indentation caused by the episcleral silicone sponge is less prominent. The treated retinal area is sharply outlined due to atrophic thinning and diffuse pigmentation (S, scleral suture site).

Fig. 8. A. The irradiated retina and choroid are markedly swollen after two days. The photoreceptors are destroyed and being removed by macrophages in the subretinal space. The outer nuclear layer is folded, while cystic spaces are evident in the inner nuclear and ganglion cell layers (×200). B. There is an abrupt juncture (↔) between normal and irradiated retina and choroid. The retinal and choroidal detachments are artifacts (×80).
Fig. 9. The irradiated retina after six months (A) is very thin compared to the normal retina outside the treated area (B). The photoreceptors are absent, the inner and outer nuclear layer cells are reduced in number and collapsed into a single layer. The retinal pigment epithelium shows irregular clumping of the pigment granules and an increased number of cells. The choroid appears relatively intact. The abrupt transition at the junction (↓) of irradiated and unaffected tissues is shown in (C). A and B, x200. C, ×60.

reaction on the summit of the bulge only. The surrounding retina showed no visible lesion at all.

Discussion

Proton irradiation provides an attractive dose distribution for the treatment of small targets such as discrete ocular tumors. However, its adoption for clinical use requires accurate and reliable aiming techniques. Indirect stereotactic radiography, using the orbital bones as landmarks, has proved inadequate in monkeys because of marked individual variation. However, the present experiments provide evidence that direct stereotactic radiography of a metal marker placed over the center of the tumor on the scleral surface may be satisfactory. This procedure is clinically practical, since adults with melanomas are usually subjected to a $^{32}$P uptake test, while children with retinoblastomas are always subjected to diagnostic examinations under anesthesia. A small tantalum marker could be sutured in place over the tumor at the time of these procedures. Subclinical orbital extension of the tumor could also be ruled out at the same time.

The two inadequate results in these experiments illustrate two important problems. One is that besides adequate head fixation, reliable eye fixation is also required. We are currently evaluating the relative merits of mechanically fixing the eye after retrobulbar anesthesia, or voluntary fixation by the patient with an inbuilt mechanism to automatically stop the treatment if the eye moves. Mechanical fixation would be necessary for patients with imperfect ability to fixate, but voluntary fixation would be preferable for most patients. If a fractionated treatment regime
Fig. 10. Large nasal indentation overlapped by opaque white chorioretinal changes 48 hours after 6,000 rads, delivered by a 10 mm. proton beam. Arrows delineate the edge of the high indentation.

Fig. 11. Edge of a superotemporal indentation (arrows) incompletely covered by the visible chorioretinal reaction 48 hours after 6,000 rads. This eye was aligned correctly, but inadvertently rotated upward by the water-filled extension nozzle which was in direct contact with the eye during treatment.

Fig. 12. Compound B-scan of a large nasal indentation obtained with an episcleral silicone sponge (arrow), which measured approximately 7 mm. in height in front of the normal ocular contour.

was employed and the doses were delivered at 1,000 rads per minute, the time necessary for fixation would not be excessive. If an electronic fail-safe mechanism was added, the patient could rest between periods of fixation, as the proton beam would automatically switch off.

The second inadequate result may have been due to the excessive height of the indentation caused by the scleral sponge (Fig. 12). The Bragg peak of the proton beam was focused on the tantalum marker, which in turn was pushed anterior to the line of the undisturbed retina surrounding the bulge in this particular eye. Because an unmodulated beam with a narrow Bragg peak was used (Fig. 5), it follows that the surrounding retina, in fact, received much lower doses of irradiation than the summit of the bulge. Since ocular tumors also vary greatly in height, precise evaluation by B-scan ultrasonography and selection of a Bragg peak of sufficient width to overlap this dimension of the tumor would be just as important as selecting a beam of sufficient diameter. We are now preparing to use proton beams whose Bragg peaks are smeared out to a greater extent in depth. This may be conveniently accomplished by means of a rotating lucite absorber wheel of varying thickness.4
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REFERENCES