Full-thickness eye wall resection: An experimental approach for treatment of choroidal melanoma

II. Homo- and heterograft

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To further evaluate the feasibility of the full-thickness eye wall resection of the posterior segment, this operation was performed on a series of experimental animals. The resected eye wall was replaced with live and dead homo- and heterografts. The technique of the operation and clinico-histological examination of these eyes in the postoperative period is reported. The encouraging preliminary results obtained may open future avenues in ophthalmic surgery.

Key words: malignant melanoma, full-thickness eye wall resection, homo- and heterograft.

Since the first description of melanomata of the eye in 1806, the treatment of uveal melanoma has remained a challenge to ophthalmologists. The malignant nature of this tumor, its unpredictable growth, and the manifestation of metastases (even as long as 36 years after enucleation or exenteration) have made it one of the most feared tumors in the field of ophthalmology. While tumors of the iris and ciliary body have been treated surgically with good results, their counterparts in the posterior segment remain more intractable. The more conservative treatment of these tumors, by photocoagulation, radiotherapy, diathermy, and cryocoagulation, has not yielded completely satisfactory results, especially in the larger tumors with more than 7.5 mm. base diameter.

In a previous study, we presented a new surgical approach for treatment of tumors of the posterior segment. The aim of that experiment was to remove tumors of the eye wall en bloc (including sclera, choroid, and retina). Dacron patches, fixed in place with cyanoacrylate glue, were used to replace the resected area. The numerous complications encountered in using these materials indicated the need for further modification in the procedure. Full-thickness eye wall resection in the current experiment is performed with a modified technique employing tissue graft materials of various species.
Materials and methods

Thirty pigmented rabbits were used in this experiment. Full-thickness eye wall resection was performed, and the resected area was replaced utilizing: (a) fresh rabbit sclera, as a live homograft (3 rabbits), (b) preserved rabbit sclera (preserved in liquid nitrogen) as a dead homograft (12 rabbits), (c) fresh cat sclera, as a live heterograft (3 rabbits), and (d) preserved human sclera (preserved in liquid nitrogen) as a dead heterograft (12 rabbits). After dilation of the pupils with 1 per cent Cyclogyl and clipping of the hairs around the eye, the animals were anesthetized by intravenous injection of sodium pentobarbital. A large lateral canthotomy was performed on the right eye of each rabbit. The conjunctiva was separated from the sclera. A previously described instrument (eye basket) was placed over the resection area and around the eye, and was sutured to the sclera using 8-0 silk (Figs. 1 and 2). After tapping the anterior chamber to decrease the intraocular pressure, the eye wall (including sclera, choroid, and retina) was resected with a sharp cutting tip of the cutting Bovie Electrosurgical Unit. An area of approximately 7.5 by 7.5 mm. was resected in all cases. A previously prepared tissue graft, measuring approximately 8 by 8 mm. (Fig. 3), was then sutured to the wound edge, using 7-0 chromic gut. This graft completely covered the area of resection (Fig. 4). In order to effect sufficient adhesions of the conjunctiva to the graft, 0.2 c.c. of fibrinogen was applied to the external surface of the graft site after removal of the eye basket. Thrombin was then added to produce a fibrinous clot. Sufficient amounts of saline and air were injected into the anterior chamber to reestablish the intraocular pressure and reform the anterior chamber. After the canthotomy was repaired, topical antibiotic ointment (Garamycin ophthalmic ointment) was applied. The animals received daily antibiotics, locally and systemically, for 7 days following the operation. Fundus photographs were taken at two week intervals for seven months. In addition, intraocular pressures were measured using an applanometric tonometer (Bausch & Lomb, Rochester, N. Y.). Retinal function was tested by ERG (electroretinogram) recording. The wound strength was measured three to four months following the operation in some of the eyes by insertion of two sharp cannulas into the anterior chamber. One of the cannulas was connected to a pressure bulb for inflation, and the other was connected to a manometer. The intraocular pressure was increased to 180 mm. Hg, and the results were noted. The animals were killed and the eyes enucleated at various intervals up to eight months postoperatively. The eyes were fixed in a 1:1 formaldehyde glutaraldehyde solution in a phosphate buffer of pH 7.4. The anterior segments were removed and the eye cups were dehydrated with alcohol and embedded in paraffin. Sections were cut with an
American Optical microtome, stained with hematoxylin and eosin, and Masson trichrome, and examined under a light microscope.

**Results**

During the first two weeks postoperatively, the eyes were inflamed. The conjunctivae were red and edematous. The air in the anterior chamber was visible for five to six days. In most eyes there was a fibrinous reaction in the anterior chamber which eventually subsided. In some eyes, however, some of this fibrinous material became condensed, adhering to the anterior surface of the lens. This latter change, if it occurred, was rather permanent; although the fibrinous condensation did not progress, it caused a localized lens irregularity and appeared as an opacity overlying the anterior surface of the lens. The vitreous reaction was relatively minimal. It consisted of slight whitish changes where a small amount of bleeding had occurred. No severe vitreous reactions were encountered. The edges of the resected area, postoperatively, showed changes similar to those seen after diathermy or photoagulation (Fig. 5). One could observe a whitish discoloration of the retina in this area. As a result of induced hypotony during the operation, the retinal surfaces of the fundus elsewhere were somewhat irregular and edematous in the immediate postoperative periods. In addition, there were areas showing slight choroidal detachment.

Six to eight weeks postoperatively, the eyes had a practically normal appearance and the above-mentioned retinal and choroidal changes had disappeared. The healing process was slightly faster in the homografts as compared to the heterografts. However, with the exception of one eye lost to endophthalmitis, all the eyes operated upon showed an uneventful recovery. Surprisingly, ophthalmoscopically, the retinas were attached in all of these cases (Figs. 6 to 8). The resected area appeared whitish (Fig. 8), surrounded by varying amounts of chorioretinal scarring. In all
Fig. 9. External photo. Arrow shows the graft edge; graft is covered by conjunctiva.

Fig. 10. External photo: An experimentally inflated eye intraocular pressure measured 180 mm. Hg. Arrows show graft still intact.

Fig. 11. Experimental setup for measurement of the wound strength (see text).

Cases, the conjunctiva covered the graft well (Fig. 9). In those eyes which were examined for wound strength (see Methods), there was sufficient strength to tolerate an increase of intraocular pressure to 180 mm. Hg, without wound separation (Figs. 10 and 11).

The above-mentioned findings did not change during the course of the experiment. In addition, the eyes remained motensive and the ERG readings showed a decrease in the voltage for the photopic response in the resected eye (Figs. 12 and 13). These changes could be attributed to the decreased number of electrically active cells due to resection of a large portion of the retina (4 to 5 disc diameters).

Histologically, at the site of resection, one could see chorioretinal scar formation (Figs. 14 through 21) in both homo- and heterografts. At the area of the transition between the graft and the normal sclera, we saw at the beginning a moderate inflammatory cell response. The latter subsided completely in homografts (live or dead) and dead heterografts (Figs. 18 to 20). However, the above-mentioned reaction was more permanent for the live heterograft (Fig. 21). Strikingly, these inflammations did not cause a sudden scleral sloughing with the result of wound...
Figs. 14-17. Histologic section of the eyes after holoresection. Arrows show the edge of the graft. 14 live homograft, 15 dead homograft, 16 dead heterograft, and 17 live heterograft.

leakage and hypotony; specially we did not notice an inflammatory response from the vitreous because of this foreign body protein.

Complications encountered during the operation included, in some cases, slight choroidal bleeding from the wound edge (10 per cent). The bleeding, in all such cases, was controlled by further cautery of bleeding areas. Vitreous loss occurred in all cases. The amount of vitreous loss differed, but was never complicated by severe vitreous retraction, postoperatively. In two cases, however, one could see slight tractional changes from the resected area to the adjacent retina. However, these changes did not progress to retinal detachment.

Discussion

The results of this experimental study are encouraging. The previous experiment was complicated by frequent failure of the conjunctiva to cover the dacron graft completely, resulting in continuous conjunctival irritation. However, in this experiment the conjunctiva healed well over the graft. This improvement in conjunctival healing may in part be attributed to the fibrinous clot, which was produced using fibrinogen and thrombin prior to the wound closure, or to effect of tissue rather than dacron. The external inflammatory reactions, postoperatively, were less pronounced than in the previous experiment. The fibrinous exudative reactions in the anterior chamber from the iris and ciliary body were the same in both studies. In our experience, rabbit eyes appear to react strongly to any situation which is accompanied by hypotony, even for a short time period. Although the collapse of the eyeball was prevented by the use of the eyebasket, vitreous loss was inevitable in this operation. However, we did not encounter, clinically or histologically, a cellular reaction in the vitreous as a result of vitreous loss; nor was any cellular reaction observed in response to homo- or heterograft materials. Resection of the eye-wall utiliz-
Fig. 18-21 Magnified view of a transitional zone between graft and host sclera. 18, live homograft; 19, dead homograft; 20, dead heterograft; 21, live heterograft. Single arrow shows chorioretinal scar formation at the edge of the resection. Double arrows show inflammatory cell response at the edge of live heterograft (Fig. 21).

Electrocautery prevented, in most cases, immediate bleeding from the choroidal vessels. A small amount of bleeding was encountered, however, in 10 per cent of the cases during the operation. Although this complication in rabbits was arrested by further cauterization of the bleeding areas, it could, theoretically, present a major problem in other species or in humans.

The healing process of the graft to the surrounding normal sclera was very rapid and complete, more so in homografts than in live heterografts. The tolerance of the graft to an induced increase of intraocular pressure without wound separation is significant with regard to the stability of the eye-wall postoperatively. In addition, the observation that this procedure was in no case complicated by retinal detachment is of great significance; theoretically, retinal detachment could be completely prevented by a photocoagulation barrage around the area of excision three weeks prior to the operation. The ERG response recorded in the operated eyes supports a favorable prognosis for the operated eye. Finally, it is interesting to know that the eyes were normotensive postoperatively. Hypotony or glaucoma did not occur in the postoperative period.

The almost uneventful results achieved in this experiment should not, however, obscure its danger. As previously mentioned, massive hemorrhages from the wound, choroidal and retinal detachment, intraocular infection, and cataract formation are complications which can be found after any intraocular surgery.

In conclusion, we have presented a further improvement in our approach to a holoresection of the eye wall. Although this method could theoretically be used in humans, we believe that we are still in an early stage of investigation of a clinically acceptable surgical method for the resection of choroidal tumors. The results of future experiments in this direction should be awaited.

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