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Long-term safety and outcomes of β-radiation for trabeculectomy

Ian Murdoch* FRCOphth [1,2]

Renata Puertas MD MBBS [2]

Mehran Hamedani MBBS [1]

Peng Tee Khaw FRCOphth [1 2 3]

1 UCL Institute of Ophthalmology, London

2 Glaucoma Service, Moorfields Eye Hospital NHS Foundation Trust, London, UK

3 NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom

* Corresponding author email i.murdoch@ucl.ac.uk

UCL Institute of Ophthalmology, Bath Street, London EC1V 9EL

Telephone 02076086800

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Précis

Beta-radiation is a neglected anti-scaring therapy with past concerns for safety. This report found it safe and efficacious when used as an adjuvant to trabeculectomy surgery in 101 people (135 eyes) over 20 years

Abstract

Purpose

Beta-radiation has been used as an adjunct to prevent scarring in trabeculectomy surgery for many decades. Safety concerns were raised with the use of high doses on bare sclera. Moorfields Eye Hospital has a large cohort of patients who have received beta-radiation therapy. We report a review of the long-term safety and efficacy.

Methods

Cases undertaken between August 1992 and August 1996 were reviewed. Those with records available for postoperative review more than 5 years were included. Failure (reintervention/>21mmHg on 2 successive occasions) and any complication previously reported in association with β-radiation were the primary outcomes.

Results

In total, 292 operations using β-radiation were recorded and 101 people (135 eyes) with trabeculectomy surgery and post-operative follow-up for over 4.5 years were included. The median follow-up period was 22.5 years. At final follow-up 50 (48%) eyes had failed and 20/51 (51%) eyes with primary open angle glaucoma had had cataract surgery. Other complications were rare and associated with co-pathology.

Conclusion

In glaucoma patients at risk of scarring and failure after trabeculectomy, as an anti-scarring adjuvant, a 750cGY dose of beta radiation was found to be safe and efficacious in the long-term.

Keywords

Beta-radiation, trabeculectomy, glaucoma, anti-scarring

Introduction

Various agents have been used to reduce the excessive healing that leads to failure of trabeculectomy. The most widely used agents are Mitomycin C (MMC) and 5- fluorouracil (5FU). Mitomycin C on a sponge was introduced in 1983[1] although widespread use did not occur until the mid-1990s. Another antimetabolite, 5-Fluorouracil given as post-operative injections, was popularised in the 1980s, after positive reports from a NIH randomised controlled trial (RCT) and was used widely until use of Mitomycin C in a sponge became the standard of care[2-4].

Although these antimetabolites have proven effective clinically, they are associated with complications. Both MMC and 5-Fluorouracil are used in liquid form, delivered either by placing microsurgical sponges soaked in the drug directly onto the operative site or by injection. Because the antimetabolites are liquids, they carry the risk of leakage away from the treatment site. This leakage can lead to extraocular or, more seriously, intraocular toxicity[5]. Furthermore, the variability of the delivery of the drug between the impregnated sponge and the sub-conjunctival tissues means that accurate dosimetry has proven difficult. Both treatments have been associated with the development of thin, avascular filtration blebs, and these are in turn associated with an increased risk of sight threatening complications including hypotony (a very soft eye) and endophthalmitis (intraocular infection)[6-8].

One alternative to the use of antimetabolites is β-radiation. This applied using a Strontium-90 applicator at the completion of surgery (Picture 1, Supplemental Digital Content 2, http://links.lww.com/IJG/A667). Precise control of dose and area of treatment may be easily achieved using a 12mm plaque.

Picture 1

Radiation has been used in medicine for both diagnostic and therapeutic purposes since the early 1900s. β-radiation is an ionising radiation made of high-energy, high-speed electrons. In medicine Strontium 90 is the isotope most used to produce β particles. Whilst β particles may travel a few meters in air they are readily stopped by skin, Perspex, and other materials. As for all radiation the depth of penetration depends on the dose and length of application. At doses of 750-1000cGy typically used in glaucoma surgery, penetration into soft tissues is about 1mm.

In ophthalmology from the 1950s onwards saw several uses of β-radiation. The most common being application post-pterygium excision to prevent recurrence. Concerns were raised where high doses from 2,100cGy to 5,300cGy were applied to bare sclera. These and other complications reported with the use of β-radiation in the eye have been summarised in table 1.

Table 1

β-radiation was first used for glaucoma surgery in the 1940s [18] and has been used at Moorfields Eye Hospital for many years in the management of paediatric glaucoma. Good results were reported with a non-randomised retrospective study in a cohort of these patients [19]. The use in trabeculectomy has been subsequently shown effective in several studies. This is now being advocated as a treatment for ensuring survival of the new generation glaucoma treatment devices such as Preserflo (formerly InnFocus, Santen, Osaka, Japan), Xen (Allergan, Dublin, Ireland) and others; though questions have been raised concerning safety. We report an audit of cases at Moorfields in which 750cGy of β-radiation was applied to the conjunctival surface after completion of trabeculectomy surgery. This audit was designed to review the clinical records for signs that have been previously reported in association with radiation exposure.

Methods

This audit was approved by the Moorfields Eye Hospital audit process. Using a written log of cases receiving radiation therapy, a note was made of all cases undertaken between August 1992 and August 1996. Using what data was available we then searched for hospital identification numbers. The notes were requested and a proforma completed including demographic, ocular and therapeutic details. Criteria for inclusion were trabeculectomy surgery using β-radiation as anti-scaring therapy at the time of surgery. Exclusion criterion were additional surgical manoeuvres at the time of surgery (most commonly cataract extraction) and less than 5 years post-operative review.

Trabeculectomy failure was defined as:

- Two successive intra-ocular pressure (IOP) readings >21mmHg (a second definition of two successive readings >18mmHg was also recorded to allow comparison with existing literature)
- Reintervention in the form of drainage surgery (including needling if undertaken more than 3 or more months post-operatively) or cyclodestructive laser.
- Partial failure was the use of topical medications in order to achieve sufficiently low-pressure outcomes.

Outcomes specifically recorded were:

- Any mention of scleromalacia or ulcer formation, telangiectasia, corneal scarring, granuloma formation, symblepharon formation, conjunctival or other scarring
- 5 yearly outcomes (5, 10, 15, 20, 25 and final follow-up) using time +/- 6 months as the definition of the time interval (thus for 5 years the appointment review date nearest to 5 years post-surgery was used within the bracket 4.5 to 5.5 years)
- The date of failure was recorded to allow survival analysis.
- Cataract: any mention of cataract was recorded at each time period and the date of cataract surgery if undertaken was recorded. The type of cataract was also recorded if mentioned in the notes
- Best corrected acuity was recorded at each time period.

Analysis

Where collinearity could be a problem one eye per person was used for the analysis. In those with two eyes included in the dataset the right eye was taken for inclusion in the analysis. All analysis was done using Stata/SE v 14.2 for Windows, survival analysis was undertaken using the ‘st’ commands.

Results

Trabeculectomy

In total 292 operations using β-radiation were recorded between August 1992 and August 1996. Of these, we identified 101 people (135 eyes) with records available for data collection in whom the operation was trabeculectomy surgery and there was post-operative follow-up for over 4.5 years. There were 56 (55%) male and there was a mean follow-up period of 19.5

years, median 22.5 years, range 4.7 to 27.2 years. The mean age at surgery was 26.3 years median 12.7 years range 0.05 to 79.5 years. The diagnosis is shown in table 2.

Table 2

Per-operative complications were few with four cases of hyphaema and no other major events.

At final follow-up 50 (48%) eyes had failed at 21mmHg or repeat intervention. If the stricter failure criterion of 18mmHg or repeat intervention is used this increases to 56 (54%). Finally this increases to 63 (61%) if a criterion of medications or 18mmHg or repeat intervention is used.

Of the 135 eyes that had surgery the frequency of side effects possibly related to β-radiation is shown in (table 3):

Table 3

Figure 1

There was a trend towards cataract surgery being performed at a shorter interval following trabeculectomy in older individuals ($r^2 = 0.1$ p=0.04) but the spread was large (figure 1). Our reviewer suggested comparing those having cataract surgery aged 0-40 years and those >40 years at the time of their original surgery. The time to cataract surgery was 13 years in the first group and 8.5 years in the older group (ttest p=0.039). Trabeculectomy failure was defined by IOP 21+mmHg or further intervention which happened in 20 of 41 (49%) eyes. Of those 20 eyes, 16 (80%) had already failed at the time of surgery. The time to failure post cataract surgery for the remaining 4 eyes was 4 months for one and 3years for the other three.

Of the 28 eyes with cataract recorded, who had not had surgery, the cataract was noted as being uniquely nuclear sclerosis in 14 (50%) cases and this was noted significant in only 4 for of those. Mixed early nuclear sclerosis and early posterior subcapsular was recorded in one

case and a mature cataract in one other. The remainder cases did not have the type of cataract specified

In terms of survival of trabeculectomy figure 2 shows the survival curves for one eye per person. Where there were two eyes with the same surgery the right eye was taken for the purposes of this analysis. Failure is given by three definitions further intervention laser or surgery for pressure lowering and

1 a pressure of 21mmHg on two successive clinics despite topical therapy
2 a pressure of 18mmHg on two successive clinics despite topical therapy
3 reintroduction of topical therapy

Figure 2

In order to compare our findings with prior literature we also collected data at each time point 5-, 10-, 15- and 20-years post-surgery (+/- 6 months). The time point survival for both eyes and individuals at each these intervals is shown in table 4.

Table 4

Of the 135 eyes that had trabeculectomy with β-radiation, 57 (42%) had procedures prior to the trabeculectomy. 40 had goniotomy, one goniotomy and trabeculectomy and another goniotomy and retinal detachment surgery. Six had laser trabeculoplasty and a further 6 trabeculotomy, the final eye had cataract surgery. The contingency table for failure by prior procedure showed little difference between the groups. Since the numbers were small and percent failures comparable all procedures were combined for table 5.

Table 5

Cataract combined with trabeculectomy

A total of 13 people (8 male, 17 eyes) underwent combined cataract and trabeculectomy surgery with β-radiation. They were not included in the principal data set. They were followed for a mean of 12.4 years, median 12.4 years, range 0.6 to 26.4 years. The mean age at surgery was 73.1 years median 73.9 years range 42.2-86.4 years. If the right eye is taken of the person with two eyes operated, 7/13 (54%) were still functional by both 21mmHg and 18mmHg criteria, one of whom was on pressure lowering drop therapy. Two were noted to have conjunctival scaring and one a band keratopathy. No radiation linked complications were noted.

Discussion

The principal aim of this retrospective study was to determine the frequency of adverse effects from β-radiation therapy application in the form of 750cGy to the conjunctival operative site immediately after trabeculectomy surgery. The long-term follow-up has been facilitated by a large proportion of the patients being children at the time of surgery providing very valuable data. In short, no major complications were found in this cohort that could be directly linked to the radiation augmentation of the surgery. No cases of granuloma or symblepharon formation were found and the two cases of telangiectasia had sound alternative aetiologies. Out of the four with scleral thinning, three were probably a consequence of multiple procedures in eyes that have thinner tissues. The final case in which a hole was detected at the time of repeat surgery is, in our experience, an accepted potential finding when re-exploring trabeculectomies found in eyes with sclerostomies without beta radiation or MMC application. The more frequent complications merit more detailed discussion.

Corneal opacity and endothelium

Unsurprisingly the layer of the cornea with the highest metabolic and reproductive activity, the epithelium, is the layer that has most frequently been associated with radiation damage in both animals[20] and humans. Shah reported 32 patients receiving γ-emitting iodine-125 plaque

radiotherapy for iris melanoma.[21] They reported epithelial complications in 6 of the 32 (3 erosion and 3 superficial punctate keratopathy) no case had corneal stromal oedema. In the discussion they state: 'It is remarkable that the cornea generally tolerates the irradiation and remains clear despite a median radiation dose of 22 350 cGy directly delivered to the corneal surface.'

Razzaq et al reported the corneal endothelial density after β-emitting Ruthenium plaque application for iris melanoma[22]. They found no change in endothelial density in 45 eyes however there was a significant reduction in density in 18 eyes that had phacoemulsification in addition to the plaque therapy. Using a formula from prior studies they found a greater cell loss than predicted in their cohort. This led to a hypothesis of prior incapacity from the radiation only evident with the trauma of subsequent surgery. All four of our cases with corneal surgery had cataract surgery several years prior to the graft.

de Silva et al[23] reported 1/30 eyes and Kim et al 12/320 eyes with congenital glaucoma requiring graft surgery.[24] The 2/61 eyes in our series is comparable (Chi^2=0.03 p=0.87) especially considering our cohort with congenital glaucoma were the ones in whom goniotomy and other procedures had failed.

Cataract

Cataract formation following trabeculectomy surgery is common; up to one-third requiring cataract surgery by 2 years[25,26] and up to two-thirds by 8 years [27]. The incidence we report is lower than this prior literature. However, our population included a large number of young patients. If those eyes with congenital glaucoma are taken, we found a record of the lens status in 60 of the eyes and no cataract was recorded in 50. This means a large proportion of the other eyes developed cataract, indeed only 5 of 39 eyes with a diagnosis of POAG had no cataract at all at final review. At final review 20/51 (51%) eyes with POAG had had cataract surgery, directly comparable with the prior reports.

Nature of cataract

It is established that doses of 1 Gy or more may induce posterior sub-capsular cataract with increasing evidence that low to medium radiation doses (0.05-5.0Gy) may induce cortical cataract however there is little evidence that nuclear cataracts are radiogenic.[28,29] Whilst the type of cataract was only recorded in just over a quarter (17/64 (27%) eyes) of those identified with cataract (either surgery or noted in records); it is noteworthy that all had

nuclear sclerosis and only one had a mention of posterior subcapsular and none of cortical lens opacity.

Trabeculectomy survival

Long-term follow-up of trabeculectomy beyond 5 years is less commonly reported in the literature and differing outcomes are reported. The most frequently reported outcome is an IOP≤21mmHg with or without medication. At 5 years reports of survival range from 44% to 100%[30-36] at 10 years this outcome is in two papers as 82-85% success[33,35], an outcome of reoperation or IOP ≤21mmHg without medication is in three papers and ranges from 42-67%[32,38,39] at 15 years two papers report an IOP≤21mmHg with or without medication of 70-74% success[33,35] and at 20 years two papers report the same outcome as 71-88% success[35,37]. The findings of these papers is summarised in supplementary table 1, Supplemental Digital Content 1, http://links.lww.com/IJG/A666. As can be seen, our own findings exceed most of the reported literature when calculated the same way. This is not the case if the survival is read directly from the survival plot. The only explanation we can think for this observation is that the cumulative failure of the survival curve includes all and there must be fewer failures who were observed at the specific time points. This observation has major potential implications for the interpretation of literature concerning operative survival and we are making this the subject of a separate discussion paper.

β-therapy

β-therapy has been shown to significantly improve glaucoma filtration surgery outcomes in three randomized controlled clinical studies[40-42]. The most recent of these studies reported odds ratios indicating that β-irradiation therapy patients were five and a half times more likely to have an intraocular pressure less than 16 mmHg (lower IOP) at the end of one year than patients treated with antimetabolite mitomycin-C.[42] β-therapy fits well into the surgical workflow and reduces scarring by using β-irradiation to down-regulate the fibroblasts at the heart of the scarring process – thus helping to maintain reduced IOP whilst minimizing stray dosing to non-target tissues. β-therapy also avoids exposing medical staff to hazardous chemotherapy drugs, such as mitomycin-C – the current standard of care. This study has found no evidence of major adverse effects over 20 years from the use of this anti-scarring therapy. This is important as long-term side-effects of antimetabolites may not be detected for 5 or more years. This would match the physical predictions of dose received by non-target tissues which strongly indicate non-toxic levels of radiation as a result of the rapid attenuation by the target tissues.

Conclusion

From this long follow up series the use of a 750cGY dose of beta-radiation appears to have a good safety profile without the side effects seen with much larger doses used on bare sclera for other conditions such as pterygium. Furthermore, the success rate matches existing results of trabeculectomy with anti-scarring therapy, particularly as this is a group with a higher than normal risk of failure after surgery. The safety and likely further enhancement of the success proportion offered by a slightly higher dose (1000cGY) has been suggested by three studies to date[39-41] and will be the subject of future studies.

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Picture 1

Beta-radiation probe sized against ruler. A similar probe was placed over the conjunctiva after surgical closure. The dose rate delivery is measured by the amount of time the probe is in contact with the area to be treated. The time depends on individual characteristics of each probe and can vary from a few seconds to several minutes depending on the source.

Figure 1

Plot of time interval between trabeculectomy surgery with β-radiation and subsequent cataract surgery for the 41 eyes that underwent this. The regression line of best fit is shown.

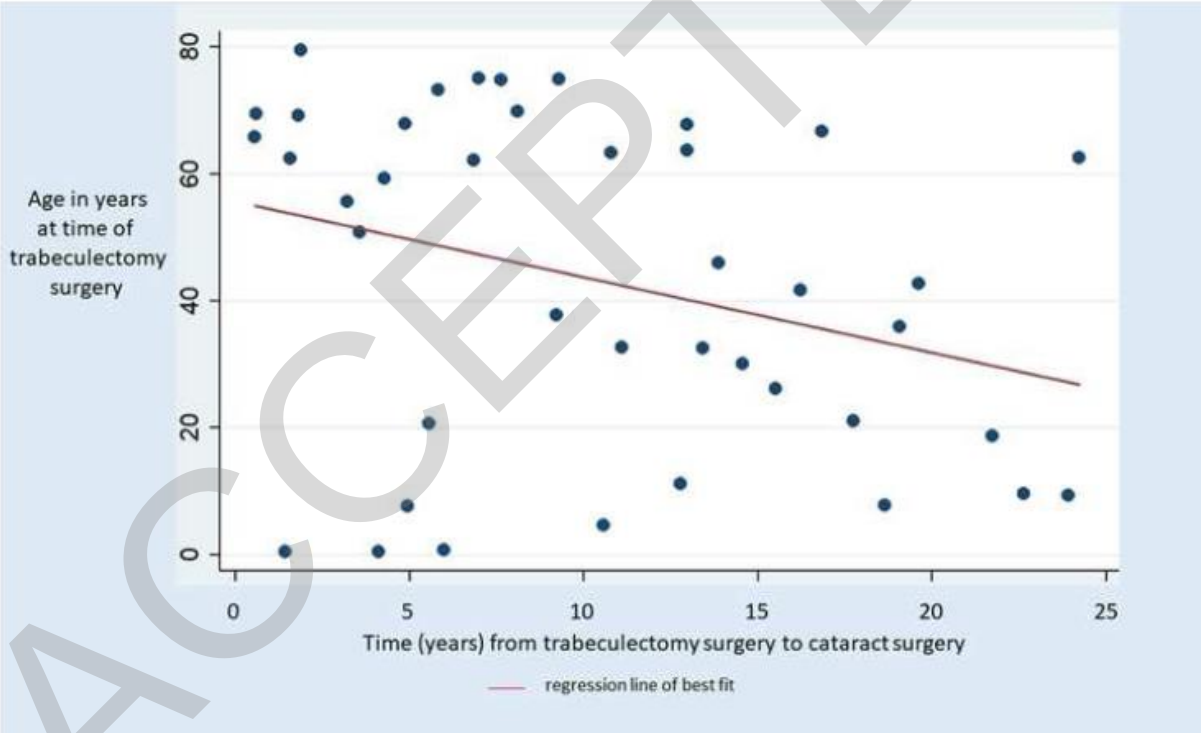

Figure 2

Survival curve for trabeculectomy with β-radiation using three different failure criteria. Further laser/surgical intervention or an IOP of >21mmHg on two successive visits, one of >18mmHg on two successive visits and any use of topical medication. The upper curve shows the censored individuals for the graphs. One eye was used per person for this analysis.

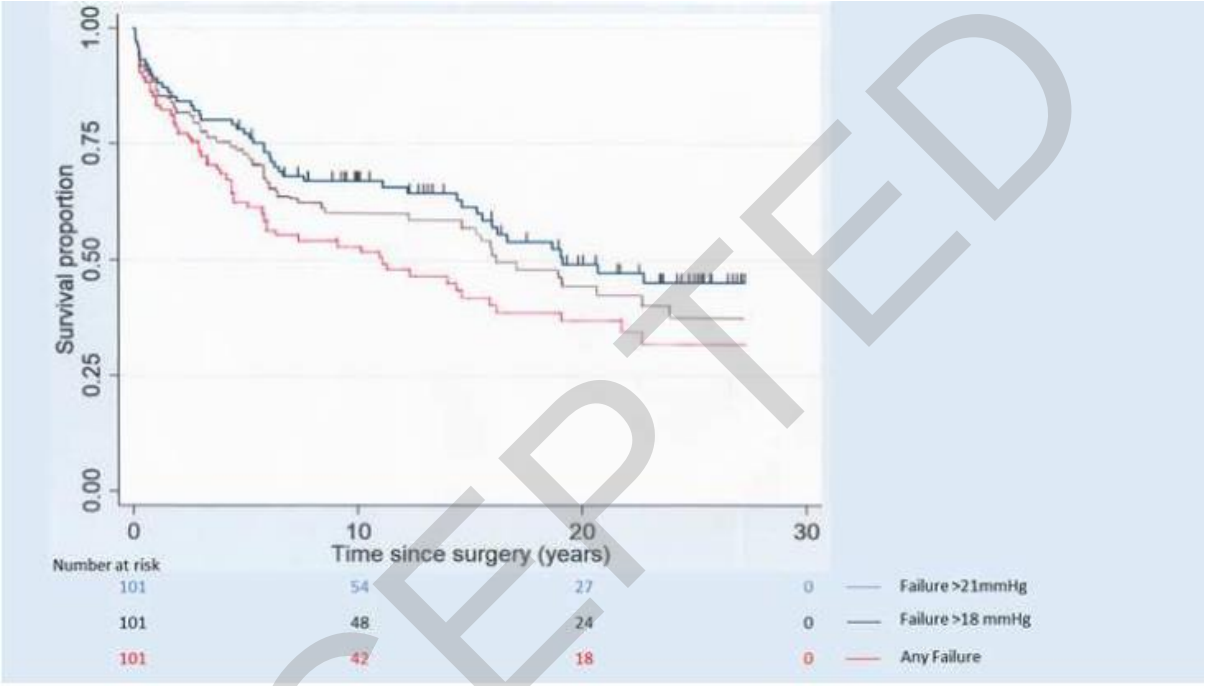

Table 1

Susceptibility of ocular structures to radiation damage. Corneal thinning[11] and symblepharon have been reported[15] however the literature is unclear of likely association with other pathology or extensive surgery.

Ocular tissue	*Radiation dose*	*Follow-up*	*Effects*
Conjunctiva	5,000 cGy 3,000-60,000 cGy	4-6 weeks 5-20 years	Conjunctivitis Late onset mild telangectatic vessels about 25% cases at 5-20 years.[9,10]
	4,650-9,300 cGy	5 years	Epithelial keratinisation [11]
	3,600-5,500cGy	Mean 46.5months	79 cases pterygium therapy to conjunctiva, 'no scleral thinning, necrosis or scleral calcification as well as iatrogenic (radiogenic) cataract was induced during or after the treatment[12]
Cornea	23,400-49,700cGy	13 months	Epithelial ulceration and stromal oedema[10]
	9,300cGy	12 years	No effect on endothelial count compared with fellow eye[13]
	3,600-5,000cGy	10-12 years	Two cases reported indolent corneal ulcer [14]
Sclera (Bare)	2,200-2,400cGy	10-20 years (mean 14.5 years)	11 cases described of late infected scleral necrosis [15]
	2,100-5,300 cGy	Mean 12 years	Scleral thinning reported in 51 eyes of 46 patients gathered by asking for cases from ophthalmologists in area. More than 2/3 of scleral depth in 31 eyes. 4 of these cases had history of pseudomonas infection. It should be noted that conjunctival covering was not present is several cases. One case of thinning with 750cGy to bare sclera developed after 10 years steep sides 1.5mm diameter with conjunctival covering. [14]
Lens	6,460-90,000cGy	5-21 years (72% 16-21 years)	25/69 eyes had small focal non-progressive lens changes (equatorial vacuoles) at site of application [10] Uncertain but ?applied at limbus with conjunctiva intact.

Conjunctival application	5,580 and 9,300-23,250cGy	Inference is 15+ months	5/7 cases lens change.Application to conjunctiva for pterygium all non-progressive peripheral focal opacity - single case lower dose 4 cases with the higher doses[16]
Bare scleral application	1,209-13,392cGy	Inference is 15+ months	13/83 cases. Lowest doses were 1,209 and 1,814cGy. The remainder 3,348-13,392cGy. All focal peripheral non-progressive changes save 4 who received 9,300 – 13,020 cGy and had opacity extending more centrally.[16]
Retina	71,800-92,800 cGy	Mean 5 years	Dose to bare sclera for melanoma. 70/166 radiation retinopathy, 41 grade 1-2 and 29 grade 3-4.[17]

Table 2 Diagnosis by person and by eye in 101 people (135 eyes) with trabeculectomy surgery using β radiation.

Diagnosis	*N (eyes)*	*%*
POAG	30 (39)	30
Congenital glaucoma	44 (61)	44
Aniridia	3 (4)	3
Axenfeld/Reigers	8 (12)	8
Sturge Weber	4 (4)	4
PXF	2 (2)	2
PDS	3 (3)	3
Secondary glaucoma	5 (7)	5
Peter's anomaly	1 (2)	1
ACG	1 (1)	1

Table 3 The frequency of mention of complications mentioned in prior literature as possibly associated with β radiation, in 135 eyes with trabeculectomy surgery and β radiation.

Complication	Final frequency N(%)	Comments
Scleromalacea	4/130 (3%)	Had some mention of thinning. One had a hole on redo, (which was not thought to be associated with the beta radiation) and 3 had thinning of the sclera although some of these eyes had extremely thin sclera to start with. All were young aged 0.1-19.4 years; 2 Axenfeld / Reigers and 2 buphthalmos. All had multiple surgery with at least one redo-trabeculectomy some with tubes others goniotomies etc. 1 became phthisical and the others, whilst failures in our study were eventual successes as a result of the repeat surgery.
Cataract	67/135 (50%)	63 none 41 surgery 5 unknown 26 noted cataract (6 probably operable because graded +++ or more). Mean time to cataract surgery in the 41 was 10.4 years post trabeculectomy, median 9.3 years range 0.5 to 24.2 years. Type of cataract noted in 17 (16 of whom had uclear sclerosis and one Nuclear Sclerosis +Posterior Subcapsular Cataract+)
Telangiectasia	Mentioned in two cases 2/130 (2%)	Both cases were Axenfeld/Reigers. One was a blind rubeotic eye with telangiectasia. The other had failure of the β trabeculectomy at review one year postoperatively so had a redo trabeculectomy with 0.4 mg/ml MMC this resulted in a thin cystic bleb with surrounding scarring ++ and mild injection
Final scar	Noted in 11/130 (8%)	In 9 scarring was specifically noted and in a further 2 inferred but not specifically stated. 3 cases only had the β surgery one had extensive post-operative needling, 2 were aniridic eyes with ocular surface surgery after the trabeculectomy and 5 had further drainage operations after the β irradiation surgery.
Corneal opacity	20/131 (15%)	Those with Haab striae and a clear cornea were not included. 6 had notably hazy cornea prior to surgery which then cleared. A further 5 had an opaque cornea prior to surgery that never cleared 2 eyes in the same patient had aniridia with surgery for surface disease. 1 had band keratopathy, 1 had exposure keratopathy requiring botulinum toxin to the lid, 1 simply had a hazy cornea noted 4 (one with POAG, one with secondary glaucoma and 2 with congenital glaucoma) had corneal graft surgery (2 DSAEK and 2 PK)
Granuloma	0	None had mention of a granuloma formation
Symblepharon	0	None had mention of symblepharon formation

Table 4 The time point survival for eyes and individuals at 5, 10, 15 and 20 years following trabeculectomy surgery with beta-radiation.

	Number eyes (people) reviewed	Number eyes (people) failed	% eyes (% people) fail	% eyes (% people) success
5 years	135 (99)	5 (2)	4% (2%)	96% (98%)
10 years	122 (85)	10 (8)	8% (9%)	92% (91%)
15 years	96 (64)	12 (10)	13% (14%)	87% (86%)
20 years	89 (57)	15 (13)	17% (19%)	83% (81%)

Table 5 Failure of trabeculectomy surgery with beta-radiation at final review according to whether eyes had procedures prior to the trabeculectomy surgery. (Chi^2= 0.5 p=0.46)

Operation prior to trabeculectomy with β-radiation	Success at final review	Failure before final review (repeat surgery or IOP>21mmHg on two consecutive occasions)	Total
No prior surgery	46	32 (41%)	78
Prior laser/surgery	30	27 (47%)	57