



BETA RADIATION THERAPY IN OPHTHALMOLOGY



From early explorations to modern investigations.

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Beta therapy has long been used for scar prophylaxis following pterygium surgery. Several investigators have explored the use of this therapy for scar prophylaxis in trabeculectomy and have reported good outcomes. The recent advent of transscleral drainage MIGS devices, for which Ike Ahmed, MD, FRCSC, has proposed the nomenclature *minimally invasive bleb-involving surgery* (MIBS), has intensified the need for effective scar prophylaxis. Clinical data indicate that beta therapy may improve the long-term outcomes of these procedures.

This article reviews the history of beta therapy in ophthalmology, advances in its use over time, and the evidence supporting its application to glaucoma drainage surgery today, in both traditional trabeculectomy and with new MIBS devices.

A BRIEF HISTORY

Beta radiation applied as an antime-tabolite therapy utilizes beta electrons for therapeutic energy, measured in grays (Gy). The radiation occurs from the natural decay of radioisotopes, in modern times supplied by strontium-90 (^{90}Sr).

Beta radiation has been in continuous use in ophthalmology for scar prophylaxis for approximately 110 years. In 1911, Albert Terson, MD, the director of the Eye Clinic at the Hôtel-Dieu Hospital in Paris, was gifted some of the first radium by Marie Curie. Dr. Terson used

that radium source as an adjunctive therapy following pterygium excision. His approach was successful, and ophthalmic brachytherapy has been utilized for scar prophylaxis ever since.

By the 1930s, radon gas-filled ophthalmic applicators were widely used. In the United States, William F. Hughes, MD, introduced the Hughes radon applicator, which became a standard of care for delivering beta therapy to the eye. In the early 1950s, ^{90}Sr beta ophthalmic applicators became available. Despite beta therapy's widespread use, not all practitioners were convinced. In 1958, Fred Wilson, MD, wrote, "Few types of therapy in ophthalmology have enjoyed more undeserved praise or received more unjust condemnation than beta radiation. Since its first ophthalmic use over 40 years ago, confusion and fickle opinion has strongly influenced the estimates of its good and evil."¹ The purpose of this article is to review, explicate, and elaborate on the utility of the therapy.

A CENTURY OF SAFETY DATA

Beta radiation is quickly attenuated over short distances. As demonstrated by Bahrassa and Datta,² the lens receives only 4% of a dose of ^{90}Sr , suggesting that beta radiation stays where it is delivered. This characteristic makes beta radiation ideal for use within the eye.

An extensive history of published studies supports the safety of beta therapy. Investigators have shown that, at a low

dose and with its inherent low penetration in the eye, episcleral beta therapy for scar prophylaxis does not adversely affect the lens or the retina. Additionally, several long-term follow-up studies have reported that radiogenic side effects were low^{3,4} and no complications or notable adverse events developed with its use.⁵

Rather than dive deeply into those studies, it may be more instructive to focus on one cautionary publication, with additional analysis of its data. In 1980, Tarr and Constable reported on a series of 51 patients with scleral necrosis who received beta therapy concomitant with pterygium excision.⁶ A closer look at the study, however, shows that these patients were part of a long-term follow-up—3 to 20 years postoperatively—and that the denominator, the number of treated patients these reports were drawn from, was not explicitly stated. The study authors reported that their hospital performed 1,600 beta therapy procedures per year. Thus, these case reports could represent 51 adverse events in approximately 20,000 patients, for a complication rate of 0.25%. Any patient harmed is one too many, but it is important to consider how these findings compare to the risk-to-benefit ratios of other therapies.

Tarr and Constable also noted that the pterygium excision they performed left bare sclera, a technique that has since fallen out of favor. Furthermore, they used high doses of radiation (average of 36 Gy and maximum of 88 Gy), and

one-third of the reported 51 patients with adverse events had recurrent pterygium and underwent repeated radiation therapy. Tarr and Constable did not conclude that beta therapy was to be avoided; instead, they suggested that a dose reduction was warranted. The same argument was made by Barron et al,⁷ who noted that the doses of radiation used in the early stages of the treatment's development were unnecessarily high, as is often the case during the initial use of many therapies.

ADVANCES IN BETA RADIATION

Several advances have occurred in beta therapy related not only to the dosing and devices but also to the understanding of both mechanism of action and toxicity.

Dosing. It is axiomatic in radiation oncology that an optimized dosing technique (ie, generally a lower dose and more uniform distribution) drives improved outcomes. This has been demonstrated across a number of disease states and indications. In ophthalmology specifically, a notable improvement in survival has occurred for orbital rhabdomyosarcoma, with an increase in survival rate from 30% to 90% over the past 15 years or so.⁸ Similar improvements have occurred in early-stage lung cancer and prostate cancer survival.^{9,10} The improved response rate is primarily attributable to new technologies in radiation oncology that enable better dosing of the lesion while sparing non-targeted tissue rather than to new chemotherapeutic agents.

Devices. Advances in devices for ophthalmic applications are also helping to improve outcomes. ⁹⁰Sr is a pure beta emitter with high activity, enabling a short application time as well as a long half-life (30 years), which makes it especially well suited for incorporation into medical devices. ⁹⁰Sr beta ophthalmic applicators were introduced in the 1950s and were widely used for decades. Unfortunately, a discontinued supply chain poses a challenge for reinvigorating the use of this therapy.

Understanding the mechanism of action of scar prophylaxis. The understanding of beta radiation's mechanism of action in scar prophylaxis has improved over time. It is now known that low-dose (sublethal) beta radiation can reprogram the p53 expression on a highly localized level to downregulate fibroblast metabolism, thus reducing the postoperative scarring response.

The understanding of dose response in scar prophylaxis has also improved over time. Peng Tee Khaw, PhD, FRCP, FRCS(Glasgow), FRCS(Eng), FRCOphth, of Moorfields Eye Hospital exposed fibroblast cell cultures to radiation and found that a dose of radiation between 5 and 10 Gy inhibited cell proliferation by more than 50% but did not cause a decrease in the cell population of fibroblasts.^{11,12} This modern dose is significantly lower than doses administered in the past.

Understanding of toxicity. Insight into ocular radiation toxicity has also improved significantly, thanks in large part to the Collaborative Ocular Melanoma Study (COMS).¹³ Twelve-year follow-up data from this study, which enrolled more than 1,300 patients, demonstrated the safety of high-dose retrobulbar episcleral brachytherapy. A review article published decades later by Brady and Hernandez¹⁴ concluded that ocular toxicity data have been well established for various ocular tissues.

DEFINITIVE MODERN STUDIES

Several definitive modern studies of ophthalmic applications of beta therapy—from pterygium excision to trabeculectomy—have been published.

Wilder et al conducted a retrospective study of patients with pterygia in the US Desert Southwest.¹⁵ A total of 338 patients were observed for 16 years. These patients underwent pterygium excision and application of beta therapy in three weekly 8-Gy fractions. The investigators found a crude local control rate of 88%. Importantly, no severe complications and no complications

related to beta therapy developed in 16 years in this patient population.

In 1991, Miller and Rice published retrospective 3-year follow-up data for 66 eyes with congenital glaucoma.¹⁶ Thirty-one eyes were treated with beta irradiation with a ⁹⁰Sr applicator at the time of trabeculectomy, and 35 eyes underwent standard trabeculectomy. The investigators found that beta radiation was associated with a significantly lower IOP at 6 months, 1 year, and 3 years ($P < .05$) and called for more studies to be done.

The call for additional data was answered by a seminal 2006 article by Kirwan et al.¹⁷ This double-masked, randomized controlled trial enrolled 320 patients undergoing trabeculectomy with 10-Gy beta radiation or trabeculectomy without beta radiation. The investigators found that the probability of bleb survival at 3 years was approximately 50% in the placebo group but 90% in the bleb group. Although the occurrence of adverse events is unclear in the article, a follow-up article reported that there were no adverse events attributed to beta therapy in the study.¹⁸

In a noncomparative study of 43 Chinese patients with primary open-angle glaucoma, Lai et al found that trabeculectomy with a single beta radiation dose of 10 Gy used as an adjunctive measure achieved a qualified success rate of 88.4% at 7 years.¹⁹

Current efforts to preserve the bleb by preventing scarring rely on the Moorfields Safer Surgery System, which was developed to improve the consistency and outcomes of trabeculectomy. In addition to stipulating the surgical site and techniques, the system involves subconjunctival application of the anti-cancer drugs mitomycin C (MMC) or 5-fluorouracil.²⁰ This process can complicate and prolong surgical procedure time and may not provide an enduring benefit. Although the use of these anti-metabolites protects against surgical failures by improving bleb survival after trabeculectomy, it may also increase the incidence of complications, including

ischemic blebs, corneal epithelial damage, scleral toxicity, wound leakage, and a shallow anterior chamber.^{21,22}

Beta therapy as an adjunct to surgery has been shown to be as or more effective than antimetabolites at preventing surgical failure.²³ It reduces scarring by modulating fibroblast activity and causing cell cycle arrest. A single controlled dose of beta radiation applied using a ⁹⁰Sr applicator at the end of surgery can be delivered rapidly, easily, and precisely. Importantly, dosimetry and the area treated can be controlled with a high degree of accuracy.²⁴

A 2012 Cochrane review found four studies that randomly assigned 551 people to trabeculectomy with beta irradiation versus trabeculectomy alone.²⁵ The review concluded that patients who underwent trabeculectomy with beta irradiation had a lower risk of surgical failure compared to patients who underwent trabeculectomy alone. The study authors concluded that “a trial of beta irradiation versus antimetabolite is warranted.”

In 2018, Cook et al conducted a randomized controlled trial, powered for efficacy and superiority, that enrolled 117 patients undergoing trabeculectomy.²⁶ Patients were randomly assigned to receive MMC (n = 56) or beta therapy (n = 61). The investigators found that eyes treated with beta therapy were 3.2 times more likely to have a functioning bleb than eyes treated with MMC (P = .009). Eyes treated with beta therapy were 5.6 times more likely to have an IOP of less than 16 mm Hg on no medication than eyes treated with MMC (P = .008). On average, IOP was 4 mm Hg lower in beta therapy eyes than in MMC-treated eyes at 1 year postoperatively.

In 2019, El Mazar et al conducted a prospective, interventional, comparative masked clinical trial of 50 patients.⁵ Half of them underwent trabeculectomy plus MMC intraoperatively and beta radiation preoperatively at the bleb area (group 1), and half underwent trabeculectomy with MMC alone (group 2). A single dose (10 Gy) of beta

radiation was administered 5 to 7 days before surgery using a ⁹⁰Sr probe. MMC (0.2 mg/mL) was administered for 2 minutes. The investigators found that patients in group 1 had a mean IOP of 15.5 mm Hg compared with 18 mm Hg in group 2. Group 2 had a higher frequency of complications, including intraoperative hyphema and hypotony. The study authors also noted that the blebs were more diffuse and less vascular in eyes treated with beta therapy.

Ian Murdoch, MSc, MD, FRCOphth, and colleagues at Moorfields Eye Hospital recently completed a 20-year retrospective chart review, representing the longest follow-up reported to date.²⁷ The review identified 292 patients treated with trabeculectomy plus beta therapy between 1992 and 1996 with a mean follow-up of 20 years. The investigators reported no adverse events attributed to beta therapy. They found the bleb survival rates to be 96% at 5 years postoperatively and 83% at 20 years postoperatively.

Beta radiation is in use today electively for glaucoma drainage surgery. At the 2020 World Ophthalmology Congress, Polla Roux, MMed(Ophth), MB ChB, reviewed the beta therapy protocol used concomitantly with trabeculectomy in his clinic.²⁸ Dr. Khaw and his colleagues at Moorfields Eye Hospital are using beta therapy concomitantly with MIBS devices. Dr. Khaw told me that the hospital's case reports suggest that “additional use of beta radiation has an enhancing effect on the success rate of minimally invasive bleb surgery combined with cataract extraction, compared with MMC alone.”

SUMMARY

Beta therapy has been in continuous clinical use in ophthalmology for more than a century. Modern techniques generate excellent outcomes and little toxicity. There is growing interest in beta therapy for scar prophylaxis in glaucoma drainage procedures. Clinical trials have shown that beta therapy provides superior outcomes in trabeculectomy. Evidence shows that it may also enhance

clinical outcomes achieved with MIBS devices. A new supply chain is needed to provide beta ophthalmic applicators for the clinic, and an opportunity exists for concurrent improvements in dosimetry for glaucoma. ■

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