

# Review of Radiation Therapy in Benign Ocular Diseases

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## ABSTRACT

Radiotherapy is a modality used for the treatment of malignant diseases. However it is also used as an effective modality in the treatment of many benign disorders. It is generally not the first choice of therapy in non malignant conditions but usually used when other modalities have failed or may induce more side effects.

Benign disorders of the eye can cause severe morbidity in terms of inflammatory symptoms, loss of vision, pain and diplopia.

Radiotherapy in such conditions is given in very low doses and the goals are controlling the condition and at the same time minimizing late tissue sequelae, if any.

Here we highlight the use of radiotherapy in most common benign conditions of the eye; mainly Pterygium, Haemangioma, Graves' Orbitopathy and Pseudotumour Orbitae.

**Keywords:** benign ocular conditions; Graves' Orbitopathy and haemangioma; pterygium; pseudotumour; radiotherapy.

## INTRODUCTION

Radiotherapy for benign diseases was first proposed by Sokoloff in 1898 mainly for the analgesic effect for the treatment of painful arthritis. Prior to taking up the patient for radiotherapy for benign conditions; risk-benefit analysis should be performed with multi disciplinary consultations and potential risks<sup>1</sup> should be informed to the patients and a written consent obtained. Long term meticulous follow up is necessary keeping in mind the late effects of radiotherapy.

Benign disorders of the eye can cause severe morbidity in terms of inflammatory symptoms, loss of vision, pain and diplopia.

Radiotherapy should be given after careful patient selection and good modern radiotherapy 3 D planning systems incorporating Computed tomography (CT) and Magnetic resonance imaging (MRI) scans should be used.

Here the use of radiotherapy in most common benign conditions of the eye; mainly Pterygium, Haemangioma, Graves' Orbitopathy and Pseudotumour Orbitae are highlighted.

### Pterygium

It is a benign fleshy wing shaped (in Greek-pteron means wing) or triangular shaped fibro vascular tissue. It is more commonly seen in dusty, warm and dry conditions mainly due to increase in Ultra Violet (UV) exposure.<sup>2</sup> They occur more commonly in the age group of 20 to 50 years and develop in the nasal aspect of the conjunctiva. Pterygium causes damage to the corneal stem cells leading to overgrowth of fibroblasts. These fibroblasts use the Bowman's layer as a guiding structure and encroach towards the centre of the cornea slowly over months to years.<sup>3,4</sup>

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Once a pterygium encroaches onto the cornea, it can lead to visual loss due to loss of corneal transparency within the visual axis. The patient complains of foreign body sensation due to inflammation.

Primary treatment is usually surgery with the removal of the fibrous tissue down to the level of Tenon's capsule and replacement of the lost stem cells by autograft. The common indications for surgery are loss of visual acuity, unacceptable cosmetic findings, symptoms of irritation unrelieved by conservative methods, restriction and limitation of ocular motility and progressive growth. The recurrences after surgery are usually frequent and in the range of 20-68%.<sup>5-7</sup> These recurrences may probably result from incomplete excision, post surgical stimulation of the fibroblasts or neovascularisation.

Other adjuvant treatment modalities to decrease the rate of recurrence include topical application of chemotherapeutic agents such as Mitomycin C or thiotepa and the use of radiotherapy.

The use of radiotherapy for the treatment of pterygium goes back to 1912, when it was first used by Kiel, an ophthalmologist from Germany.<sup>8</sup> Since 1950 Strontium-90 (<sup>90</sup>Sr) as the radio-active material has been used in the form of an applicator for irradiation of pterygium.<sup>9</sup> <sup>90</sup>Sr emits  $\beta$  rays; the energy of which falls rapidly as it penetrates in the tissues. The percentage depth dose in the tissue drops off to 41% at 1mm, 19% at 2mm, 9% at 3mm and 1% at 5mm<sup>10</sup> and hence no damage to the underlying structures. The strontium is bound in a silver foil and mounted to one end of a metal rod. The active source diameter may vary from 0.6 to 1.2mm and it has 0.002mm stainless steel and 0.01mm aluminum filtration.

In spite of radiotherapy being in use for so many years for the treatment of pterygium; there exists a wide variety of dose fractionation schemes, ranging from 20 Grays (Gy) in single fraction immediate post operative period to 60 Gy in 6 weekly fractions with a few authors even using 24-30Gy in 3 weekly fractions.<sup>2,11,12</sup>

The Utrecht group<sup>2</sup> has proven the advantage of immediate post operative radiotherapy of 25 Gy in single fraction. They operated 96 eyes of 91 patients using the bare sclera technique and then post operatively randomized the patients to 25 Gy in single fraction 24 hours later versus sham radiotherapy. Ten patients were lost to follow up and in 18 months of mean follow up they observed no complications. They observed that in 44 eyes that received radiotherapy, only three relapses versus 28 recurrences in the 42 eyes that received sham radiotherapy (93% versus 33%;  $P < 0.01$ ).

Brenner and Merriam<sup>13</sup> used the Linear Quadratic model and implied that fractionation rather than single dose gives an increased therapeutic ratio between non recurrence and late side effects.

There is strong consensus that radiotherapy gives best results when started within 24 hours of complete excision. This evidence is supported by Paryari et al<sup>12</sup> of the North Florida Pterygium study group and various other authors.<sup>2,12,14-16</sup>

Acute reactions following radiotherapy; which may last for few months include ocular burning, foreign body sensation, photophobia, conjunctival scar, corneal opacity leading to further decrease in visual acuity,<sup>17,18</sup> radiation cataracts, granuloma formation and atrophy of the sclera.<sup>12,19-22</sup>

Bacterial corneo-scleritis as a severe complication can occur years after treatment.<sup>23,24</sup> Tarr and Constable studied 10,000 patients over an eight year period and observed complications such as sclera ulceration, symblepharon and pseudomonal corneoscleritis.<sup>18</sup>

In conclusion; because of the high rate of recurrence after primary pterygium excision alone, post operative radiotherapy is generally indicated; which decreases the risk of recurrence.  $\beta$  irradiation with <sup>90</sup>Sr is the most commonly applied; however there is generally no defined and acceptable technique for either single dose versus total dose and treatment time.

### Haemangioma

Haemangiomas can be further classified as choroidal and capillary.

### Choroidal haemangiomas

Choroidal haemangiomas are rare, congenital, benign vascular tumours of the choroid which enlarge over time and can cause serous retinal detachment leading to decrease in visual acuity. These haemangiomas are of two types: circumscribed and diffuse.

They do not transform into malignant tumours and therefore the usual indications for treatment is loss of visual acuity, extensive retinal detachment and associated glaucoma.

Treatment options include laser photocoagulation, transpupillary thermotherapy, photodynamic therapy (PDT) and radiotherapy. Laser photocoagulation usually leads to poor visual acuity,<sup>25</sup> high rate of recurrent subretinal exudates requiring more photocoagulation and high rate of retinal detachment.<sup>26</sup> Its use can also lead to irreversible formation of scotoma when treating haemangiomas close to the optic disc or macula.

PDT is a new modality used for the treatment of haemangiomas. Various small studies on the outcomes of PDT for circumscribed choroidal haemangiomas have been published which show excellent results with rapid resorption of the subretinal fluid and complete flattening of haemangiomas with follow-up periods of three to 50 months. However since it is a new modality; issues such as the criteria for selection, parameters of treatment, number of sessions, treatment intervals, long-term recurrence rate and complications are yet to be properly understood.<sup>27</sup>

Radiotherapy when compared to photocoagulation in retrospective studies has shown improved resolution of subretinal fluid, improved visual acuity (if used shortly after development of visual impairment). It is specially used when haemangiomas are close to the macula, are extensive and when present with bullous subretinal fluid that precludes PDT or photocoagulation.

Radiotherapy can be administered via fractionated lens sparing technique on a Linear Accelerator, episcleral plaque therapy, proton beam or by Stereotactic Radiotherapy (SRT).

External beam radiotherapy (EBRT) is usually indicated when there is lack of response to laser photocoagulation, proximity of the tumour to the macula, infiltration of the macula and bullous subretinal fluid overlying the haemangioma. The usual dose of EBRT is 18-30 Gy in 10-18 fractions<sup>28,29</sup> and it is usually delivered using a single direct beam with the beam tilted posteriorly in order to spare the contra lateral lens and optic chiasm. In case of bilateral diffuse haemangiomas, bilateral parallel opposing portals can be used. The side effects of EBRT include retinopathy, papillopathy and sometimes lens cloudiness years later (mainly due to back scatter of radiation).

Episcleral plaque therapy is usually limited to circumscribed choroidal haemangiomas. Various radioactive isotopes can be used such as Iodine- 125 (<sup>125</sup> I), Ruthenium-106 (<sup>106</sup>Ru) and Cobalt-60 (<sup>60</sup> Co); which show excellent response in terms of complete and permanent resolution of subretinal fluid and reattachment of the retina and preservation of the pre-treatment visual acuity.<sup>28,29</sup> The dose of radiotherapy when using <sup>60</sup> Co is 40-60 Gy to the apex and 90-240Gy to the base and 26-50 Gy to the apex and 85-237 Gy to the base when using <sup>106</sup>Ru or <sup>125</sup>I. As compared to EBRT there is no late complication such as retinopathy or papillopathy, however the disadvantages include two surgical procedures, one for the brachytherapy and the other for removal of the plaques under anesthesia. Another disadvantage from radiotherapy point of view is the large dose inhomogeneity between the apex and

base.

Proton beam radiotherapy has been used for a decade. It allows homogenous irradiation. A 200 MeV beam is used for a dose of 20-30 cobalt Gy unit in four doses of 15 s each over four to eight days.<sup>30</sup> The patients head is fixed using a stereotactic head holding device and the patient is asked to voluntarily fix the eye movement. The drawbacks of this therapy are that it is expensive, not easily available and the late side effects on the anterior segment of the eye.<sup>28,29,31</sup>

A recent study on the use of Stereotactic Radiotherapy (SRT) by Kivela<sup>32</sup> to treat posteriorly located circumscribed choroidal haemangiomas has shown results consistent with lens sparing EBRT using linear accelerators.

### Capillary haemangiomas

They can be either found on the eyelid or on the retina.

Eyelid haemangiomas may be seen as a part of VHL or Sturge Weber syndrome. They spontaneously regress over three to four years. However when they are large they may lead to obstruction in the vision thereby leading to amblyopia. They may also ulcerate due to vascular compression. The usual initial treatment for these haemangiomas is steroids, laser photocoagulation, cryotherapy and photodynamic therapy. Radiotherapy is employed in select cases which have failed to respond to the above modalities. A dose of 5-7.5 Grays in 2-3 fractions to a total dose of 16-20 Grays is used.<sup>33,34</sup>

Retinal haemangiomas are usually seen as multifocal lesions. They develop in the superior portion of optic disc and cause exudative retinal detachment, secondary tractional retinal detachment with subretinal fibrosis and degeneration of the macular retina leading to vision loss. These are usually treated with laser photocoagulation, cryotherapy, transpupillary thermotherapy and photodynamic therapy. Fractionated radiotherapy has been tried in cases of epipapillary, juxtapapillary and relatively large tumors with a dose of 20 Gy in 2 Gy fractions; but it has not shown to be that effective. Higher doses have been tried with proton beam (dose 42-48 Gy), episcleral plaques (dose 45-50 Gy) and fractionated photon beam (40-50 Gy) with some benefits.<sup>29</sup>

The early side effects include skin erythema, blepharitis, conjunctival hyperemia, keratitis, epilation, iritis and retinal edema. These side effects are usually temporary and recover within several weeks with good supportive care.<sup>35,36</sup>

The late side effects include hyper pigmentation, of the eyelid, scarring of the eyelid, eyelid lymph edema,

lacrimal gland atrophy leading to decreased tearing, corneal ulceration, cataracts, second tumours and growth failure of orbital bones in children.<sup>35</sup>

### Graves' Orbitopathy

First described by Robert Grave, it is a part of the auto immune disorder of Graves' disease associated with hyperthyroidism, goiter, dermopathy and exophthalmus.<sup>37</sup> The activated T lymphocytes invade the orbit and lead to fibroblasts production which in turn causes tissue edema leading to periorbital swelling, proptosis causing corneal exposure and thereby causing ulceration. The process also causes enlargement of the extraocular muscles and optic nerve compression.<sup>38</sup>

Grave's Orbitopathy (GO) is clinically seen in 20-50 % of patients suffering from Grave's disease<sup>39</sup> and more in females (male: female ratio-1:5).<sup>40</sup> It is most commonly seen as bilateral presentation; unilateral being only in 5-15 % of cases.<sup>41</sup>

The patients complain of tearing, photophobia, gritty sensation over cornea and retro orbital pain and the signs are usually chemosis, periorbital edema, lid lag, lid retraction, visual loss and ophthalmoparesis.<sup>42</sup>

The first classification for the severity of the GO was proposed by Werner<sup>43</sup> which was later adopted by the American thyroid association and modified to NOSPECS classification. The NOSPECS classification takes into account the signs and symptoms (from class 1 to class 6) and even the grades (from absent to marked) The major drawback of this system of classification was that it depends upon subjective criteria and cannot predict the activity of the disease. There are various other classifications proposed.<sup>44,45</sup>

In 1999; EUGOGO (European Group on Graves' Orbitopathy) was founded.<sup>46</sup> They developed a standardized documentation of the clinical activity of Graves' Orbitopathy; the Clinical Activity Score (CAS) which incorporates the various degrees of clinical involvement.

Once a diagnosis has been made after good clinical examination, measurement of thyroid functions and an ophthalmic evaluation; a T2 weighted MRI is helpful not only for radiotherapy treatment planning but also for monitoring the treatment outcome since it can help differentiated edema from fibrosis.<sup>47</sup>

Surgery, corticosteroids and radiotherapy are the treatment options for GO. However the 1<sup>st</sup> thought would be the treatment of systemic hyperthyroidism. A study by Aranow and Day in 1965 has suggested that rapid decrease in thyroid hormone levels may aggravate

ocular manifestation of Grave's disease.<sup>48</sup> Other authors however have not seen this effect as long as the state of hypothyroid was avoided.<sup>48, 50</sup> Another study reported significant increase in risk of worsening Orbitopathy in patients undergoing radio-iodine therapy (as compared to patients undergoing surgery or receiving anti-thyroid drugs). This was mainly due to the fact that radio-iodine patients were allowed to go in to hypothyroid state.<sup>51</sup> Thus there is evidence that Orbitopathy worsens more in patients who develop hypothyroidism due to treatment.

Steroids have been used as the first line of management of GO since 1950.<sup>52</sup> They are used due to their anti-inflammatory and immune-modulatory properties. They give relief to the pain, retrobulbar pressure and edema and thereby relief of proptosis; but there is high relapse rate of the proptosis if they are withdrawn. The usual dosage is 60-100 mg prednisolone per day for at least two weeks and then tapered by 10mg every one to two weeks. The best results are seen in patients with shortened duration of symptomatic disease.<sup>53,54</sup> However the activity of steroids may be decreased in hyperthyroid patients due to altered drug metabolism.<sup>55</sup>

Radiotherapy has been in use since 1936 for the treatment of GO. It is a proven modality which controls the acute inflammatory process, reduces the proptosis and impairment from optic neuropathy and also decreases the use of systemic steroid requirement.

The first clinical series of megavoltage radiotherapy in Graves' orbitopathy was published by the Stanford group.<sup>56</sup> They radiated 311 patients to both orbits to a dose of 20 Gy in 2 G fractions and observed excellent response rates in 60-70 %. They observed poor outcome in patients who were male, of advanced age and had persistent hyperthyroidism and good response in patients who received treatment within 12 months of the onset of the disease.

Studies have shown that clinical signs that best respond to radiotherapy are soft tissue infiltration and corneal involvement.<sup>57</sup> Radiotherapy has the same effect when used as initial treatment or used after the failure of steroids.

The German Cooperative Group on Radiotherapy for Benign Disease (GCGBD) conducted national patterns of care study (PCS) to assess the consensus on the indications of radiotherapy. Eighty eight percent justified clinical use of radiotherapy in GO staged II-IV; 76 % used 15-20 Gy and 67 % used CT based planning to deliver radiotherapy.<sup>58</sup>

A study by Prummel et al<sup>59</sup> was a double blind randomized trial comparing prednisolone versus radiotherapy in

GO. They randomized patients to two arms, one arm receiving 60mg prednisolone with sham radiotherapy while the other arm receiving retrobulbar radiotherapy 20 Gy and placebo capsules. They had 28 patients in each arm; 14 patients (50%) responded to prednisolone and 13 patients (46%) responded to radiotherapy. Side effects were more common in the prednisolone group with a significant increase in body weight. Thirteen of the 28 patients had no side effects; four had transient hair loss at the temples and another four had transient increase in NOSPECS class 2. They recommend the replacement of standard steroid treatment with radiotherapy as the initial treatment because of better tolerance and similar results.

Patients being considered for radiotherapy should be in stable euthyroid state and should undergo an ophthalmic evaluation and a CT or MRI for radiotherapy planning. An immobilization mask should be used and preferably should be treated on a Linear Accelerator using CT based treatment planning system in order to decrease the dose to lens, pituitary, hypothalamus and skin. The standard dose is 10-20 Gy in 5-10 fractions of 1.8 to 2 Gy per fraction as per the ICRU 50 to control the disease with minimal side effects.<sup>60</sup> A standard technique of two opposed isocentric lateral fields with the beam tilted posteriorly to spare the contralateral lens and anterior chamber should be employed.<sup>61-64</sup> The relative contraindications to radiotherapy reported in some series are pre-existing retinopathy, diabetes and age younger than 40 years.

Approximately 30% of the patients with GO require surgery (corrective or cosmetic) after orbital radiotherapy. The surgical intervention is not due to radiotherapy failure but usually due to remaining disease process that needs further corrective surgery. The various procedures include orbital decompression surgery in case of danger to the optic nerve,<sup>65</sup> eye muscle surgery for avoidance of diplopia and lid correction for full closure of the eye (avoidance of exposure keratitis).

### Pseudotumour

First described by Birch-Hirschfield<sup>66</sup> as an inflammatory orbital pseudotumour; it is a rare and uncommon disorder which can mimic a neoplastic process. It comprises 4-7% of all orbital tumours<sup>67</sup> and equally found in males and females. Three main causes attributed to it are: A) infectious process,<sup>68-70</sup> B) auto-immune process proposed by Easton and Smith<sup>71</sup> and C) fibro-proliferative disorder.<sup>72-74</sup> Presence of lymphoid hyperplasia makes it difficult to differentiate it from malignant Non Hodgkin Lymphoma (NHL). It is necessary to exclude all possible orbital diseases as the diagnosis is mainly of exclusion. It has been described by Wagner et al<sup>75</sup> as “chameleon”

considering the diagnostic and therapeutic aspects.

It may have a wide range of presentation depending upon the anatomic location :retrobulbar location giving rise to proptosis and vision loss, anterior location causing chemosis, erythema and lid swelling and muscles location causing decreased eye mobility/ motility and diplopia. Lanciano et al described presence of systemic disease in 25% of cases and hence suggested intensive follow up even after successful treatment with radiotherapy.<sup>76</sup>

For diagnosis, CT guided biopsy should be performed as far as possible, especially to rule out sarcoma, lymphoma or metastatic carcinoma. Auto-immune disorders, endocrinopathies, granulomatous process and local infection (sinusitis/ abscess) should be considered as differential diagnosis. Radiological features for pseudotumour are infiltration of retrobulbar fat (71%), enlargement of extraocular muscles (57%), thickening of optic nerve/ optic sheath (38%), proptosis (71%) and contrast enhancement seen in 95% as described by Flanders et al.<sup>5</sup> Intracranial extension is not usual; seen only in about 8.8%.<sup>77</sup>

Therefore clinically and radiologically pseudotumour can be isolated as lacrimal, anterior, posterior, diffuse and myositic.<sup>73</sup>

Treatment options include steroids, surgery, radiotherapy and immunosuppressive medications.

Steroids are usually the 1<sup>st</sup> line of management. Momberts et al reviewed 27 patients treated with steroids as initial treatment. Seventy eight percent responded well but only 37% sustained it. Steroids have a poor response when there are mass lesions, fibrotic process and long interval between initial diagnosis and the treatment.<sup>78</sup> It is usually recommended to start with high dose of prednisolone 50-100mg for two to three weeks and if there is minimal response then to consider for radiotherapy.

Surgery should be considered only for extensive diffuse process, refractory disease with obvious compression of the optic nerve. Surgical procedures include orbitotomy, resection, enucleation and exenteration in advanced conditions. Henderson reported long term control in 80% patients undergoing surgery.<sup>79</sup>

Radiotherapy is usually considered when medical treatment fails, surgery is unacceptable and steroids are contra-indicated. Radiotherapy has been in use since 1964 with a local control of 67-100%. The contra-indications for radiotherapy include long standing visual loss and excessive fibrosis due to long delay before starting radiotherapy. Austin-Seymour et al<sup>80</sup> have reported young age, ophthalmoplegia, severe diplopia,

type I pseudotumour [lesion with fibrinoid vascular changes and fibrosis] as significant poor prognostic factors. Various authors have used radiotherapy and obtained response rates from 66-90%.<sup>76,80-82</sup> Electrons as well photon beams can be used for treatment depending upon location on the process. Immobilization masks should be made and CT based treatment must be employed in order to accurately delineate the target volume and spare the normal critical structures (lens sparing). The technique depends upon the location and the extent of the disease. Anterior lesions are usually treated with electrons or orthovoltage with central lens shielding and for conjunctival lesions plesiotherapy using <sup>90</sup>Sr can be used. Retrobulbar lesions are best treated with single lateral field with the beam tilted posteriorly to spare the contra lateral eye lens. Bilateral retrobulbar are treated with opposing lateral fields with half beam blocks.

The usual dose of radiotherapy is 20-36 Gy in 2 Gy fractions with no dose response relationship. It has been proposed for a step wise increment of radiotherapy dose i.e. to start with 0.5 Gy per fraction for 4 fractions @ 2 fractions per week and then if minimal response to reconfirm the disease and then increase the dose in the second step to 0.5 Gy/fraction for 6-10 fractions (@2 fractions/week) and then finally elevate to a total dose of 24Gy in 10-12 fractions.<sup>83</sup> The general principle is to give the lowest effective dose with the least side effects.

The early side effects include conjunctival irritation and mild skin erythema which usually resolve soon. The late side effects include risk of cataract formation due to lens irradiation and 1.2 % of theoretical risk of cancer development.<sup>84</sup>

Immunosuppressive therapy with cyclophosphamide, azathioprine and methotrexate are usually employed for aggressive or refractory lesions.

## CONCLUSION

Radiotherapy is an effective modality for the treatment of benign ocular diseases such as Pterygium, Haemangioma, Graves' Orbitopathy and Pseudotumour Orbitae with minimal side effects and good control rates. However a proper diagnosis and multidisciplinary consultation should be established prior to the use of radiotherapy. Radiotherapy must incorporate the use of CT and MR scans and modern 3 D treatment planning systems for accurate target and normal critical structure delineation. Proper documentation and long term follow up should be encouraged keeping in mind the late sequelae of radiation therapy.

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