

# Ocular Complications of Radiotherapy For Head and Neck Tumours

Sarita Maharia, Kalpna Jain, H.S. Kumar

Department of Ophthalmology, S.P. Medical College, Bikaner, Rajasthan, India

**Aim:** To study the various ocular complications associated with radiotherapy and correlate them with duration & dose of radiation.

**Design:** Hospital based prospective study

**Methods:** The present study comprises of 100 patients of head and neck tumors who received radiotherapy by linear accelerator from September 2015 to February 2017. Ocular examination was done prior to the start of therapy, 1st follow up at 15th day of therapy, 2nd at last day of therapy (23-35 fraction), 3rd at 3 month after completion of therapy for side effects, 4th at 6 month, 5th at 12 month and 6th at 18 months after completion of therapy for assessing chronic side effects.

## Abstract

**Results:** Astrocytoma was the most common tumour (35%). Maximum tumours of head and neck received 50-60 Gy of radiation. Nasopharyngeal carcinomas received maximum dose of radiation i.e. 60-70 Gy. Seventy one percent patients were male and 21% were female. Acute side effects were madarosis (19%), dermatitis (13%), conjunctivitis (3%), meibomitis (12%). Dry eye (33%) was seen in patients within hours to days after exposure to radiation or within 3 months of completion of therapy. Chronic side effects were dry eye (26%), punctal stenosis (1%), cataract (in 4 eyes), seen after 3 months or even a year after completion of therapy. Cataract occurred after > 20 Gy dose received by the lens. Radiation retinopathy and Optic neuropathy were not seen till our last follow up.

**Conclusion:** The current study suggests the importance of total dose as well as dose per fraction despite advancement of radiotherapy techniques and using protective mechanisms for eye complications developed.

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**Keywords:** Radiotherapy, Linear acceleration, Dry eye.

## Introduction

Head and neck cancers (HNC) are the sixth most common malignancy worldwide.<sup>1</sup> Modern radiation therapy (RT) for cancers of the head and neck is administered by linear accelerator machines which produce high-energy external radiation beams. The absorbed dose of radiation is relevant for both the therapeutic efficiency and the toxicity of the radiation. In order to reduce the negative effects of irradiation, the cumulative dose of radiation therapy is divided into multiple smaller doses.

Despite significant improvements in mechanisms of delivery and protective shielding, acute and chronic complications of radiation can affect different segments of the eye when radiotherapy is given for tumors near the eye.

## Materials and Methods

**Study design:** This prospective hospital based study was done on 100 patients of head and neck tumours receiving radiation by linear accelerator machine from September 2015 to February 2017. The inclusion criteria were patients receiving radiotherapy for head and neck tumours by linear accelerator and patients with informed consent. The exclusion criteria was patients receiving radiotherapy other than by linear accelerator, radiation not reaching up to ocular structures, systemic illness like diabetes mellitus, hypertension and AIDS, pre existing ocular diseases like dry eye, retinal and neuro-ophthalmic diseases.

## Radiation Protocol

Radiation dose comprised of 30-70 Gray (Gy) delivered in 20-35 fractions (usually 1.8-2 Gy), delivered over a period of 3-6 weeks by Linear acceleration, five days per week. The eye was shielded by protective shields.

## Methods of Evaluation

After permission of Institutional ethics committee and obtaining informed consent from the patients, ophthalmic examination was done prior to the start of radiation therapy. First follow-up was done at 15th day of radiation therapy, second at last day of radiation therapy (23-35 fraction), third follow up was done 3 months after completion of therapy for monitoring the acute effect. The fourth follow-up was at 6 months, fifth and six follow ups were done at one and one and a half year respectively after completion of therapy for assessing chronic complications of radiation therapy.

## Results

This study comprised of 100 patients of head and neck tumours, out of which 71 were males and 29 were females. The head and neck tumours were astrocytoma (35%), ganglioma (1%), glioblastoma multiforme (GBM) (21%), glioma (1%), medulloblastoma (1%), oligodendrioglioma (10%) and nasopharyngeal carcinoma (31%). Total dose of radiation given was 45-70 Gy. Most of the head tumors received 50-60 Gy. Nasopharyngeal carcinomas received maximum dose of radiation 60-70 Gy.

Prior to radiation therapy (RT), watering was present in 6 patients and foreign body sensation was present in 2 patients. In these patients watering and foreign body sensation increased further after RT. Post radiotherapy, watering was the most common symptom (32%). It occurred within days of treatment (generally after doses of at least 20–30 Gy) with conventionally fractionated (1.8-2 Gy per fraction) radiation therapy and persisted for a few days to months (Table 1). Other symptoms were foreign body sensation (6%), irritation (5%), photophobia (3%) and pain (2%). These symptoms also subsided after few days to months of completion of radiotherapy.

**Table 1: Frequency of symptoms in study population**

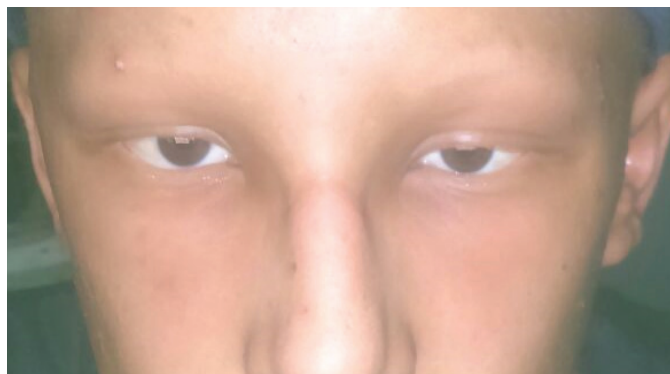
Symptoms	Follow-up (In months)						
	Pre RT	½	1	3	6	12	18
Watering	6	27	30	32	19	19	8
Foreign body Sensation	2	6	4	1	0	0	0
Irritation	0	5	5	1	0	0	0
Photophobia	0	3	3	1	0	0	0
Pain	0	2	1	0	0	0	0

**Acute Side Effects**

Acute side effect of radiation therapy were seen within hours to days after exposure to radiation or within 3 months of completion of radiation treatment.

Madarosis or loss of eyelashes (Figure 1a) and erythema were the first side effects with conventionally fractionated (1.5-2 Gy per fraction) radiation therapy with cumulative doses over 20 Gy. Madarosis was reported in 18 patients. In 2 patients, the eye lashes had not grown till last follow up. Erythema was noted within days of treatment (generally after doses of at least 20–30 Gy) and persisted for a few days. Erythema resolved after a few days of completion of RT. Dermatitis is also common as an acute side effect of RT. It occurs after the initial doses of radiation and in our study, dermatitis was found in 13 patients. Conjunctival inflammation (conjunctivitis), which manifest itself as vascular injection with clear or mucoid discharge was found in 3 patient within 1–3 weeks after the start of radiation treatment and lasted for a few days. Meibomian gland exhibits an acute inflammatory response to radiation therapy, it occurs within days of radiation and meibomitis was noted in 12 patients in our study (Table 2).

Dry eye occurred due to the effects of radiation on the conjunctival epithelium, goblet cells, corneal surface and lacrimal glands. Symptoms of dry eye developed within days to months of radiation. In our study, dry eye was seen in 33% patients as acute side effect of radiation (Table 3). In 7 patients, it subsided and in 26%, it was seen till our last follow-up.



**Figure 1a: Madarosis**

**Table 2: Acute Side Effects of Radiation in Study Population**

Acute Side Effects	Follow-up (Months)					
	½	1	3	6	12	18
Dermatitis*	8	13	4	0	0	0
Erythma	3	5	0	0	0	0
Pigmentation	3	4	1	0	0	0
Madarosis	10	15	18	12	6	2
Meibomitis	8	12	7	0	0	0
Conjunctivitis	1	2	0	0	0	0

\*Dry eye occurred as both acute and chronic side effect

**Chronic Side Effects**

Chronic side effects of radiation therapy were seen after 3 months or even years after completion of radiation therapy. Chronic side effects that were seen in our study till last follow-up were dry eye, cataract and punctal stenosis.

Dry eye was seen in 59% (acute 33% and chronic 26%) patients in our study (Table 3), the incidence increased as dose of radiation increased.

- 44 patients received a dose of 45–55 Gy and of these, 13 patients (29.5%) developed dry eye. p value was 0.93 (not significant).

**Table 3: Dry eye in patients in accordance with Total dose of Radiation**

Total Dose of Radiation (Gy)	Total no of Patients	No of Dry Eye Patients	Follow up (months)	Mild (Schirmer score 10-15) mm	Moderate (Schirmer score 5-10) mm	Severe (Schirmer score <5) mm
45-55	44	13	Acute	3	2	2
			Chronic	2	2	2
56-65	40	33	Acute	8	6	6
			Chronic	4	6	3
66-70	16	13	Acute	2	2	2
			Chronic	2	2	3

2. 40 patients received a dose of 56-65 Gy and of these, 33 patients (78%) developed dry eye. p value was 0.64 (not significant).
3. 16 patients received a dose of 66-70 Gy and of these, 13 patients (95%) developed dry eye. P value was 0.39 (not significant).

Therefore, the incidence of dry eye was related to the total radiation dose. A steep increase in the incidence of dry eye at dose >66Gy was noted.

In the left eye, in 98 eyes, the lens received up to 30 Gy radiation dose and it was well tolerated by the lens and no cataract formation occurred. Only in 2 eyes, the lens received >30 Gy. These two eyes developed cataract and it was highly significant (p value 0.0001). In the right eye, in 97 eyes, the lens received up to 20 Gy radiation dose and no cataract formation occurred and only in 3 eyes, the lens received >20 Gy, 2 eyes developed cataract and it was highly significant (p value 0.0001) (Table 4 & Figure 1b). Punctal stenosis occurred in 1 patient after one year of completion of radiotherapy.

**Table 4: Distribution of the Case according to Cataract Formation with Radiation Dose in the Lens**

Radiation dose (Gy)	Left eye	Cataract	Right eye	Cataract
0-10	91	0	94	0
11-20	5	0	3	0
21-30	2	0	1	1
31-40	1	1	2	1
41-50	1	1	0	0



**Figure 1b: Cataract (Right eye)**

Dermatitis and erythema were treated by dermatologist. Patients with dry eye were treated with lubricant eye drops and patients with radiation induced cataract were operated by cataract surgery after completion of radiotherapy. Patient with punctal stenosis was treated with punctal dilatation with perforated punctal plug.

### Discussion

Radiation exerts its greatest impact on rapidly proliferating cells, as found in hair follicles, sebaceous glands and the basal layer of the epidermis that causes acute radiation side effects.

The susceptibility of the skin to radiation is due to the rapid rate of proliferation and maturation of cells. So the basal keratinocytes, hair follicle stem cells and melanocytes are the most susceptible.<sup>3</sup> Radiotherapy interferes with normal

production and maturation of epithelial and hair matrix cell. With the first dose of radiation therapy, there is immediate tissue damage with generation of short-lived free radicals, irreversible breaks in cellular DNA and generation of an inflammatory response.<sup>4,7</sup>

The acute ocular side effects were present in 87% patients receiving radiation therapy for head and neck tumours in our study. Lana et al (2004) reported that 76.5% of patients receiving radiation therapy of tumors of the head and neck experienced acute ocular effects, varying from mild to severe.<sup>8</sup> These results are almost similar to our study.

The most common presenting symptom in our study was watering, which occurred in 32% patients at a dose of 20-30 Gy. Symptoms started appearing few days after first dose of radiation therapy and persisted for few days to months.

Madarosis was noted as the first side effect of radiation therapy in 19 patients, at conventionally fractionated dose of 1.5-2 Gy per fraction and cumulative doses of over 20 Gy. Eye lashes grew back in 17 patients but hair loss occurred permanently in 2 patients, these results were similar to a study done by Haik et al (1983).<sup>9</sup>

Erythema was noted in 5 patients within few days of treatment at dose 20-30 Gy and it persisted for a few days, it occurred because the radiation damaged the deeper cells of the basal layer of the skin. These results were similar to a study done by Haik et al (1983).<sup>9</sup>

Dermatitis was the first acute side effect of radiation therapy seen in 13 patients at dose of 10-20 Gy. It occurred after the initial dose of radiation, tissue damage occurred immediately, and every subsequent fraction of radiation generated inflammatory cell recruitment. Acute radiation dermatitis is the combined result of decrease in functional stem cells, changes in the skin's endothelial cells, inflammation, skin-cell necrosis and death. It was similar to a study done by Brady et al (1989).<sup>10</sup>

Parsons et al observed 100% incidence of dry eye for doses >57 Gy.<sup>11</sup> In our study, we found 71% incidence of dry eye above the dose of 57 Gy. Jiang et al (1994) reported 30% incidence of dry eye for dose > 40Gy.<sup>12</sup> In the present study, 28% incidence at dose 45 -55 Gy was found. Bessell et al noted that the incidence of dry eye increases as the dose of radiation is increased.<sup>13</sup> We also found in our study that the incidence of dry eye was increased as radiation dose was increased.

Dry eye occurred due to effects of radiation on the conjunctival epithelium, goblet cells, corneal surface and lacrimal glands. Changes in quality and quantity of tear production lead to the impairment of the dynamic stability of the tear film resulting in chronic dry eye.<sup>14</sup> For doses >45 Gy, symptoms of dry eye developed within 1 month after radiation.<sup>14</sup> In our study, we also found that the symptoms of dry eye occurred at first follow-up. Karp et al demonstrated, on histological analysis, meibomian gland atrophy due to radiation therapy.<sup>15</sup> It exhibits an acute inflammatory response to radiation therapy and causes complete loss of meibomian glands and ducts. The dilated duct filled with keratin and squamous metaplasia predisposes to dry eye.

Bhandare et al (2012) described radiation-induced cataracts as posterior sub capsular cataract (PSC). Irradiation of mitotically active cells in the germinative zone leads to

cell death, compensatory mitosis, and differentiation into fiber cells resulting in defective lens-fiber formation, and migration to the posterior pole. They also reported that the severity of cataract formation is related to total dose and fractionation.<sup>16</sup> According to that study, cataract formation occurred within 2 to 3 years (range 6-64 months) of radiation therapy.<sup>9</sup> In the present study, we also found that cataract formation occurred approximately after one year of completion of radiation therapy and that the severity depends on total dose and fractionation.

According to a study in Philadelphia, the threshold for detectable opacity in the lens is 2 Gy in a single exposure.<sup>17</sup> However, in our study, none of the patients received 2 Gy dose in the lens in a single exposure because the cumulative dose of radiation therapy was divided into multiple smaller doses so in one exposure very minimum dose was received by the lens.

An incidence of 62-100% for cataract in humans has been described in literature at a dose of 40 Gy or more.<sup>18</sup> In our study, the lens of one patient receive 40 Gy and he also developed cataract.

Henk et al (1993) observed that the lens tolerated a total dose of 5 Gy after fractionated RT.<sup>19</sup> In our study, we found that none of the patients who received up to 10 Gy of radiation to the lens developed cataract.

Takeda et al (1999) reported that the irradiation doses to the retina that developed late complications ranged between 54-75 Gy and they found that no patients who received less than 50 Gy developed retinal complications.<sup>18</sup> In our study, most of the tumors received 50-60 Gy of radiation and no retinal complication were found till our last follow-up.

There was limited availability of literature on ocular complications of radiotherapy.

### Limitation of The Study

Taken into account the length of the period between exposure to radiation and the clinical occurrence of late complications such as retinopathy and optic neuropathy, these complications were not found during the research period. Further research with more patients and longer follow-up is necessary to determine other late complications of radiation therapy.

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### Address for correspondence

**Kalpna Jain MS**

Professor, Department of Ophthalmology  
S.P. Medical College, Bikaner-334003,  
Rajasthan, India  
Email id: kalpnadaga@gmail.com



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