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CASE STUDY

A clinical study of intensity-modulated radiotherapy-induced dry eye disease in head and neck malignancies

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Context-Dry Eye Disease is a multifaceted disorder caused by a variety of factors ranging from age to demographic profile. Radiation-induced dry eye disease is a relatively unexplored domain of this disease.
Aim: To explore the various factors contributing to dry eye disease in patients receiving radiation therapy for head and neck malignancies with a fixed dose and duration of radiotherapy.
Settings and design: A cross-sectional study conducted at a tertiary healthcare centre during a period of 1 year.
Materials and methods: The study included 101 patients with head and neck malignancies who received a 60-Gray (Gy) dose of radiotherapy over a duration of 30 weeks. Patients were evaluated for signs and symptoms of dry eye on day 30 after completing their radiotherapy cycles using slit lamp biomicroscopy and various other tests for dry eye and compared with age, gender, location of malignancy, and adjunctive chemotherapy.
Results: Out of a total of 101 patients, 45% had mild dry eye disease. 44–45% of mild dry eye disease was seen in the age groups of 20–50 and 51–80 years. The incidence of mild-to-moderate dry eye disease was almost similar (47% and 50%) in both genders. The incidence of severe dry eye was seen in only 1% of patients. Dry eye disease was more severe in malignancies located closer to the orbit. The use of cisplatin as an adjunctive chemotherapy agent proved to be a risk factor for dry eye disease.
Conclusion: Intensity-modulated radiotherapy is not enough to prevent the development of dry eye disease. A close and strict follow-up with an opthalmologist is essential for its prevention and early management.

Keywords: dry eye disease, fixed dose, location of malignancy, radiotherapy

1. Introduction

Dry disease (DED) is a disorder that results from deficiencies or defects in the components of the tear film, leading to abnormalities in the structure and function of the ocular surface.

Radiation-induced ocular morbidity encompasses a spectrum from transient eyelid erythema to complete loss of vision. (1) Despite significant improvements in mechanisms of delivery and protective shielding, complications of radiation can affect the ocular surface when radiotherapy is given for malignancies near the eye. (2) Radiation exposure greater than 30 Gray (Gy) to the orbit causes ocular surface and/or lacrimal gland damage, resulting in dry eye disease (DED), which is a known complication of radiotherapy (RT). (3).

Adverse effects on normal tissue have significantly reduced with advanced planning techniques in RT, such as intensity-modulated radiotherapy (IMRT) compared to conventional techniques. By selective delineation of target tissue, it employs computerized specialized dose distribution methods, enabling optimum delivery of radiation specific to the target. This reduces damage to the surrounding tissues and increases the probability of adequate disease control in the target tissue. But even with better conformal dose distribution, preventing exposure to adjacent organs like the ocular surface is difficult in the head and neck region (3).

However, there are limited studies evaluating RT to head and neck malignancies other than involving the orbit. In the

FIGURE 1 | Patient of oral cavity malignancy.

present study, we analyzed the ocular surface effects of IMRT in specifically head and neck malignancy patients to check for the development of DED and to improve care and follow-up of these patients.

2. Research elaboration

2.1. Methodology

The present cross-sectional study examined 101 patients having specifically head and neck malignancies admitted at a tertiary healthcare centre between April 2021 and April 2022 (**Figure 1**).

The inclusion criteria for the study were that all the patients were receiving concomitant chemotherapy with Cisplatin (100 mg/m^2) and adjunctive radiation therapy. Stage 2 and above head and neck malignancies involving the oral cavity/pharynx that were planned for an average radiation dose of 60 Gy and completed in 30 fractions of radiation therapy were included in the study. Patients presenting informed written consent were included only after clearance from the ethical review committee.

Patients with intraocular malignancy, malignancy with intracranial extension, head and neck malignancy with distant metastasis as excluded by PET-CT, and pre-existing ocular symptoms were excluded from the study.

Patients were examined by a set of subjective questionnaire and objective tests to study ocular surface disease after 30 days of completion of radiotherapy cycle.

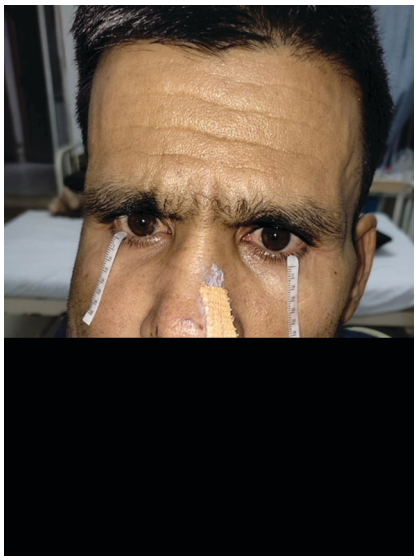

FIGURE 2 | Schirmer test of patient post radiotherapy.

TABLE 1 | Grades of dry eye disease.

	Normal	Mild DED	Moderate DED	Severe DED
OSDI score	0–12	13–22	23–32	33–100
Schirmer test	> 15	10–15	5–10	< 5
TBUT	> 15	10–15	5–10	< 5

The Ocular Surface Disease Index (OSDI) is a validated and reliable questionnaire. The OSDI is a 12-item questionnaire assessing both dry eye symptoms and their effects on vision-related functioning over the past week. It contains 3 subsections including vision-related function, ocular symptoms, and environmental triggers. Patients are asked about the frequency of occurrence of symptoms and difficulty with vision-related activities, and their responses are noted on a 0–4 scale that ranges from "none of the time" to "all of the time." The final score is calculated by multiplying the sum of all the scores by 25 and then dividing the total by the number of questions answered. The range of scoring is from 0 to 100, with 0–12 being normal, 13–22 mild DED, 23–32 moderate DED, and 33–100 severe DED (4–6).

DED can be diagnosed from symptoms alone, but all patients in our study underwent a battery of objective tests. These tests included the use of slit-lamp biomicroscopy to check the changes in the tear film and corneal surface; Schirmer's test I (**Figure 2**) to evaluate aqueous layer of tear film; tear breakup time and tear meniscus height test evaluating lipid and mucin layers of tear film to gauge the tear film instability.

We divided the patients into four grades of DED, namely, normal, mild DED, moderate DED, and severe DED (**Table 1**).

3. Results

A total of 101 patients diagnosed with head and neck malignancy and receiving IMRT at a tertiary level hospital were selected for our study. The mean age of the patients was 46 $\pm$11.57 years with 68 patients (67.3%) in the age group of 20–50 years and 33 (32.6%) patients in the age group of 51–80 years. In the age group of 20–50 years, most patients had mild-to-moderate DED, which accounted for 30 and 26% of the total, respectively. Only 5% patients had severe DED. Similarly, in patients with an age range of 51–80 years, mild and moderate DED are more prevalent accounting for 15 and 12% of the cases, respectively. Only 1 patient had DED in this age group, as depicted in **Table 2**. This relationship was not statistically significant with a p value of <0.01.

The male to female ratio was 3:1 with males making up 75 out of the total 101 patients. As illustrated in **Table 3**, male patients had a higher incidence of mild dry eye being 35% of the total, followed by 25% of patients having moderate DED. Female patients also had a similar picture, with 13% having moderate DED and 10% having mild DED. Severe DED was seen only in 5% of male patients and 1% of female patients. This relationship was not statistically significant with a p value of > 0.01.

With regards to diagnosis, 84 (83.1%) of the participants had malignancy inside the oral cavity, namely, malignancy of buccal mucosa, alveolus, tongue, and base of tongue. A total of 8 (7.9%) malignancies were located outside the oral cavity in the maxillary bone and maxillary sinus, 8 (7.9%) patients had glioblastoma, and 1 (0.9%) patient had orbital rhabdomyosarcoma. Patients with malignancy of oral cavity had mostly mild and moderate DED, forming 35% each of the total patients with malignancy outside the oral cavity had mostly mild DED being 5% of the total patients. Similarly, patients with GBS also had mostly mild DED, i.e., 5% of the total patients. The patient with orbital rhabdomyosarcoma had severe DED. This is elaborated in **Table 4**. This relationship between location of malignancy and DED is statistically significant with a p value < 0.01.

In radiotherapy regime, the mean dose of IMRT was 60.35 Gy for a mean duration (fractions) of 30 weeks. We had 45% of patients with mild DED and 38% of patients with moderate DED. Severe DED was noted in only 6% of the cases. Twelve patients were those who had no DED. **Table 5** elaborates on the same.

In total, 97 (96.0%) of the participants had chemotherapy. The most used chemotherapy agent was cisplatin in 89 patients. The patients were divided as receiving a single agent or a combination therapy or none. Of the total 91 patients who were receiving a single chemo agent, 40 patients had mild DED and 37 had moderate DED. Among patients on combination therapy, 2 were normal, 2 had mild DED, and 2 had severe DED. Patients not on any chemotherapy mostly had mild DED (3 patients) and moderate DED (1 patient). **Table 6** gives the details of this data. This co-relation of chemotherapy and DED is statistically significant with a p value of < 0.01.

Our data analysis shows that symptomatic patients had mostly moderate DED (32%), and mild DED was mostly present in asymptomatic patients (29%) (**Table 8**). As shown in **Table 7**, out of a total 101 patients, 59 (58.4%) presented with a history of ocular symptoms. Rest 42 patients all were

TABLE 2 | Comparison of age groups of patients with grades of dry eye disease (DED).

Age	Normal (total %)	Mild DED (total %)	Moderate DED (total %)	Severe DED (total %)
20-50 years (68)	7(7%)	30(30%)	26(26%)	5(5%)
51-80 years (33)	5(5%)	15(15%)	12(12%)	1(1%)

TABLE 3 | Comparison of gender of the patients with grades of dry eye disease (DED).

Gender	Normal (total %)	Mild DED (total %)	Moderate DED (total %)	Severe DED (total %)
Male (75)	10(10%)	35(35%)	25(25%)	5 (5%)
Female (26)	2(2%)	10(10%)	13 (13%)	1 (1%)

TABLE 4 | Comparison of location of malignancy with grades of dry eye disease (DED).

Location	Normal (total%)	Mild DED	Moderate DED	Severe DED
GBS (8)	1(1%)	5(5%)	2(2%)	0 (0%)
Outside oral cavity (8)	1(1%)	5(5%)	1(1%)	1 (1%)
Orbit (1)	0(0%)	0(0%)	0(0%)	1 (1%)
Oral cavity(84)	10(10%)	35(35%)	35(35%)	4 (4%)

TABLE 5 | Comparison of dose and duration of radiation therapy with dry eye disease.

	Normal	Mild	Moderate	Severe
Dose(60.34 Gy Gy)	12	45	38	6
Duration30weeks	12	45	38	6

TABLE 6 | Comparison of chemotherapeutic agent with grades of dry eye disease (DED).

Chemo agent	Normal(total)	Mild DED	Moderate DED	Severe
Single (91)	10(11%)	40(44%)	37(41%)	4(4%)
Combined (6)	2(33%)	2(33%)	0(0%)	2(33%)
None (4)	0(0%)	3(75%)	1(25%)	0(0%)

asymptomatic. Out of 59 patients OSDI score was almost equally distributed in all the categories of mild (17,29%), moderate (18,31%), and severe (19,32%). Majority, 36 (86%) out of 42 asymptomatic patients had normal OSDI score, and 30 (51%) out of 59 had Schirmer score of > 10. Only 6 (10%) patients had Schirmer score of < 5.36; 86% of patients who were asymptomatic had Schirmer score of > 10. None of these patients had Schirmer score of > 5. Out of 59 patients who were symptomatically positive, 49 (83%) had TBUT of 5–10 seconds, 33 patients (79%) with no ocular symptom had TBUT of > 10 seconds, and 41 (69%) patients who had ocular symptoms had TMH of > 1 mm and all 42 (100%) patients without any ocular symptoms had TMH > 1 mm.

4. Discussion

Among the malignancies of anatomical site of head and neck, oral and oropharyngeal malignancies are most common, and squamous cell carcinoma is responsible for more than 90% of the total number. The use of radiotherapy (IMRT), whether primary or adjuvant, is a mainstay of treatment, and it can either be used alone, in combination with chemotherapy, or following surgical resection. Radiotherapy is successful in reducing the malignancy burden, so much so that for early stages of head and neck malignancies, it is the standard treatment modality. But the key limiting factor is the associated damage to the adjacent normal tissues, which is dependent on the malignancy location and size, RT total dose, and fractionation. With the advent of IMRT, some factors are expected to be of lesser concern in the patient management plan. But even IMRT is not totally foolproof in avoiding these side effects.

Radiation used in radiotherapy damages the mebomian glands, thus causing a reduction or deficiency of the lipid layer of the tear film and damage to acinar cells, leading to dry eye. Dry eye affects the entire ocular surface, including the conjunctiva and cornea.

Radiation therapy might cause either an immediate or a delayed corneal response. Conjunctivitis, ocular edoema, and vascularization make up an acute reaction that appears between 1 and 3 weeks. An immediate severe damage by the use of high radiation can be manifested as keratitis, which can be reversible or result in necrosis and ulceration of the cornea. Permanent central corneal opacification is one of the late reactions that develops between the ages of 3 months and 2 years. The most serious side effect is extensive and late corneal necrosis. The limbal vessel obliteration, which is the underlying mechanism, is most likely vascular (7).

Dry eye disease presents mostly as burning sensations and grittiness in the eyes. Blurring of vision due to tear film instability is also a presenting feature. Decreased ear film height, punctate epithelial keratopathy, and irregular corneal surfaces are seen mostly. The lack of uniform criteria for the diagnosis of DED necessitates the use of patient history and one or two tests for determining both the quality and quantity of tears.

We noted a prevalence of 45% mild DED in the age group of 20–50 years and 38% moderate DED in the age group of 51–80 years. This shows that incidence of DED post radiotherapy is not dependent on the age of the patient. This was comparable to earlier studies that concluded that although populations over 40 years of age have a higher frequency of DES, post-RT DES is not age-predisposed (8, 9). Additionally, Parsons et al. (8) showed that patient age had no bearing on the incidence of damage when they examined the incidence of severe DES according to patient age.

Incidence of dry eye in north India as studied by J. Titiyal et al. in 2018 (10) was 32%, and it mostly prevalent in the age group of 20–40 years. We in our study noted a prevalence of 45% mild DED in the age group of 20–50 years. This being higher than the above said study (10) points to the fact that dry eye is caused by radiation therapy as well.

A male predilection was noted in our study sample, with the male to female ratio being 3:1. Mild-to-moderate DED was seen in both genders, with 47% of men having mild and 50% of women having moderate DED. But any gender dependence cannot be established by this data. This was in contrast to a study conducted by Shubha Tiwari et al. at the LV Prasad Eye Institute Hyderabad, (11) where male gender was found to be a protective factor for DED after orbital radiotherapy, but the result was attributed to the small sample size (47 patients, 51 eyes) of that study as compared to our sample size of 101 patients.

Various locations for malignancies were recorded in our study. The patient having orbital rhabdomyosarcoma had severe DED (1%). Majority of the patients (84 out of 100) with malignancy inside the oral cavity had moderate DED (35%), and patients with malignancy outside the oral cavity and glioblastoma had mostly mild DED (5%).

As we selected patients receiving a fixed dose and fraction of radiotherapy, we were able to establish a more clear relationship between location of malignancy and dry eye

TABLE 7 | Comparison of ocular symptom with various tests for dry eye disease.

Ocular symptoms	OSDI score				Schirmer 1			TBUT		TMUH	
	Normal	Mild	Mod	Severe	< 5	5-10	> 10	5-10	> 10	< 1	> 1
Yes (59)	5(8%)	17(29%)	18(31%)	19(32%)	6(10%)	23(39%)	30(51%)	49(83%)	10(17%)	18(31%)	41(69%)
No (42)	36(86%)	6(14%)	0(0%)	0(0%)	0(0%)	6(14%)	36(86%)	9(21%)	33(79%)	0(0%)-	42(100%)

disease. We were able to establish that proximity of tissue receiving RT to ocular surface does have an incremental effect on the incidence of DED. Therefore, such patients should be closely monitored for ocular surface changes beginning on the first day of RT. They should be followed up regularly for a complete ophthalmic evaluation.

The mean dose of IMRT in our study was 60 Gy. A dose above 60 Gy was not received by any patient. The time period (fraction) for radiotherapy was 30 weeks. We observed incidences of mild (45%) and moderate (38%). This was in line with various other studies, which show an incremental trend in DED as the dose of RT increases.

Two studies (8, 9) revealed a substantial rise in the incidence of severe DED with a dose of > 30 Gy. According to the total radiation dosage, the incidence of DED has been recorded in a few studies (8, 9). The trustworthiness of these results is decreased by the limited sample size. However, for dosages below 30 Gy, the emergence of DED was not seen. For doses of 30–40 Gy, Parsons et al. (8) reported a 25% incidence of DED, 50% for doses of 40–45 Gy, and 100% for doses of > 57 Gy. DED increased from 4.5% for doses of 30–39 Gy to 23% for doses of 40–49 Gy, according to Bessell et al.

The purpose of keeping a fixed dose and fraction in our patients was to establish a clearer co-relation between other factors and RT-induced DED. Consequently, we were able to draw a co-dependence between location of malignancy with DED and adjunctive chemotherapy and DED.

Out of 101 patients, the bulk of the patients (97 patients) studied by us were receiving IMRT as well as chemotherapy, and the remaining 4 were treated with only radiotherapy. Chemotherapeutic agents are known to have several systemic side effects. Mild-to-moderate DED (77%) was seen in patients receiving cisplastin as chemoagent. Combined therapy patients had minimal incidence of DED (2% mild DED and 2% severe DED). This makes cisplastin a major risk factor for DED in malignancy patients.

TABLE 8 | Comparison of ocular symptoms with grades of dry eye disease (DED).

Ocular symptoms	Normal	Mild	Moderate	Severe
Yes (59)	5(5%)	16(16%)	32(32%)	6(6%)
No (42)	7(7%)	29(29%)	6(6%)	0(0%)

Data on the beneficial interactions between chemotherapy and EBRT in the development of DES are still scarce and ill-defined. 2 of the 3 individuals who got DED despite receiving relatively low radiation doses (32–45 Gy) were noted by Parsons et al. in their study. Jiang et al. (12) came to the conclusion that chemoradiotherapy, at doses of $56 Gy, significantly impacted the likelihood of corneal damage and connected the use of chemoradiotherapy to variations in latency times. However, study conducted by Niranjan Bhandare et al. (13) deemed adjunct chemotherapy not significant.

As per our results, in cases receiving adjunctive chemotherapy, we need to be extra cautious and should keep a close eye for signs of early DED so that we can prevent blinding corneal late sequelae of DED.

Patient symptomatology was compared with OSDI score, test results of Schirmer, TBUT, and TMH. It showed that patients presenting with dry eye symptoms had Schirmer score of mostly moderate-to-mild disease, TBUT of moderate category and TMH > 1 mm. So, our study secondarily was able to check the reliability of all these test for establishing DED. We inferred that the OSDI score being subjective to the patient and the TMH being subjective to the observer are less reliable criteria for the diagnosis of DED, and the Schirmer test and TBUT are better predictors of DED. Treatment options are very limited in dry eye disease. The use of topical tear film substitutes like carboxymethylcellulose and hyaluronic acid can be helpful in patients with mild-to-moderate dry eye disease. Radical steps like punctal plugs, temporary followed by permanent, can be beneficial in severe dry eye disease. Life-style changes like avoiding screen time and air conditioning are of very limited value to these patients.

Conclusion

So we can conclude from our analysis that RT-induced DED is not only dose- and duration-dependent but is also affected by the location of malignancy (proximity to the eye) and adjunctive chemotherapeutic agent. This necessitates an active involvement of the ophthalmologist in the follow-up of patients receiving any kind of radiotherapy or chemotherapy to prevent severe blinding complications or to improve the quality of life of such patients.

Author contributions

This is to declare that the following authors have taken part in the conduction of research work in the Department of Ophthalmology for concept, conduction, data collection analysis, writing manuscript, and its submission. They have done all of it jointly.

Conflict of interest

We declare that the research was conducted in the absence of any commercial or financial relationships.

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