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ACUTE TOXIC EFFECTS OF OCULAR SURFACE AND ADNEXA INDUCED BY EXTERNAL BEAM RADIOTHERAPY IN HEAD AND NECK CANCER PATIENTS

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ABSTRACT

Head and neck cancers (HNC) are one of the commonest cancers in India. The primary treatment modality of these patients is either radiotherapy (RT) alone or combined surgical and radio/chemotherapy approach. RT of HNC leads to various acute and chronic ophthalmic complications. After approval from institutional ethics committee we conducted a prospective cohort study for a period of 3 months at a tertiary care center to find the incidence of various acute ophthalmic complications of radiotherapy in these patients specifically dry eye disease (DED) and also to correlate these findings with the total radiation dose (TRD). We recruited 40 patients "of HNC" undergoing. external beam radiotherapy by cobalt-60 machine. Patients were selected based on inclusion and exclusion criteria. Radiation records of all patients were noted. Patients were evaluated prior to start of RT and then at 1 week, 4 weeks and 12 weeks post RT. All underwent a thorough clinical history and complete ophthalmological examination including Ocular surface disease index (OSDI) questionnaire, visual acuity, anterior segment, angle and posterior segment examination, a complete dry eye work up including Schirmer test, tear meniscus height, tear break up time, corneal fluorescein staining & grading at each visit. Data was analysed using percentage and microsoft excel. Of the 40 patients; 24 (60%) were male and 16 (40%) were female (ratio1.5:1) and the median age of patients was 56 years with an age range of 35 to 63 years. Various acute complications found in our study were redness, madarosis, tylosis, limbal ischemia and dry eye disease (18 patients; 45%). We also found a strong positive correlation of DED with TRD. (r= 0.87)

Introduction

In general the tumour cells are considered more susceptible to radiation than normal cells as they are less able to reduce the amount of DNA damage inflicted by radiation and have less accuracy of DNA repair and proof check mechanism. [1] It is because of this property of radiation damage to tumour cells which is utilised in various radiotherapy (RT) treatment modalities for cancer especially squamous cell carcinomas. Most of the Head and neck cancers (HNC) are squamous cell carcinomas and RT is the current standard of treatment for these cancers. [2]

The main challenge of treatment by Radiotherapy is to control the tumour with minimum damage to the adjoining normal tissues. [3] RT used for the treatment HNC has the capability to cause adverse ophthalmic effects when the eye or peri-orbital area is included within the entrance or exit beam. [4]

Over the past decade use of advanced RT planning techniques and tissue shielding have been tried to reduce RT induced tissue toxicity. Nevertheless, despite all these measures there still occurs various acute and chronic side effects of RT in patients of HNC treated by external beam radiotherapy (EBRT). [3, 4]

Radiation-induced ocular toxicity ranges from acute (within 3 months of RT) conjunctival congestion, tylosis, madarosis, ocular surface disorder or keratitis to chronic (after 3 months to years post RT) permanent effects like cataract, retinopathy and optic neuropathy. [5]

Dry eye disease (DED) is one such radiation induced ocular toxicity, which can occur as an acute as well as a delayed complication. [6]

These complications depend on the total radiation dose (TRD) received, fractionation of the total dose, RT volume and tumour localization [3].

In this study we have found the frequency of various acute ocular toxicities of EBRT in HNC patients with emphasis on DED in particular. We have also tried to establish a correlation between DED and TRD.

Methodology

Study design-

It was a prospective cohort study conducted at a tertiary care centre in head and neck cancer patients undergoing EBRT by cobalt 60 machine done for a period of 3 months. Exclusion criteria were patients who had previously received EBRT or chemotherapy, those having a pre-existing disease of ocular surface or cataract or retina, those on topical anti-glaucoma medications and those not giving consent.

Treatment schedule-

A typical course of RT for HNC ranges from 3 to 6 weeks divided into 20 to 45 fractions, depending on tumour extent and differentiation, with daily treatment not exceeding 200 cGy per fraction; 5 days per week with 2 days off protocol.

Patient evaluation-

Radiation records of all patients were noted.

Patients were evaluated prior to start of RT and then at 1 week, 4 weeks and 12 weeks post RT for detection of the various acute complications. All underwent a thorough clinical history and complete ophthalmological examination including filling of Ocular surface disease index (OSDI) questionnaire, visual acuity assessment by Snellen's chart, intra-ocular pressure measurement by non-contact tonometry, anterior segment examination including lid margin abnormality assessment and evaluation of angle of anterior chamber by slit lamp and posterior segment examination by indirect ophthalmoscopy at each visit. Also a complete dry eye work up including Schirmer test I & II by standard whatmann filter paper no.42, assessment of tear meniscus height, tear break up time, corneal fluorescein staining and grading (by oxford grading scheme) of each patient was done at every visit. Diagnostic criteria for DED were decided based on the TFOS DEWS II diagnostic methodology report. [7] Data was analysed using appropriate statistical methods "viz a viz microsoft excel".

RESULTS

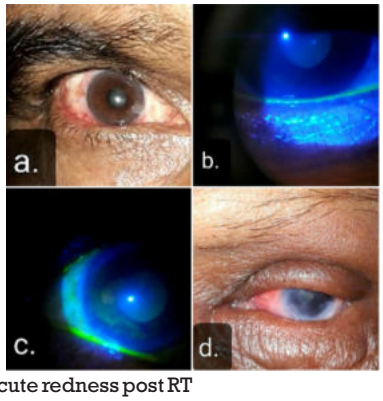
Of the 40 patients included in the study; 24 (60%) were male and 16 (40%) were female (with M: F ratio of 1.5:1) and the median age of patients was 56 years with an age range of 35 to 63 years. The commonest HNC in the study population were carcinoma oral cavity and lip (21 patients; 52.5%).

Most HNC received a TRD of 56-65 Gy (16; 40%) followed by 46-55 Gy (13; 32.5%), 66-75 Gy (9; 22.5%) and 36-45 Gy (2; 5%).

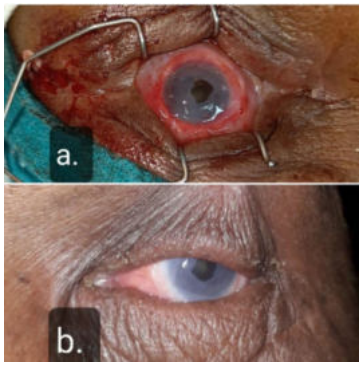
Various acute complications found in our study were redness (5; 12.5%), madarosis (2; 5%), tylosis (2; 5%), limbal ischemia (1; 2.5%) and dry eye disease (18; 45%). These complications occurred immediately after RT (as in acute conjunctival congestion) to up-to 11 weeks post RT (as in madarosis and tylosis).

The commonest symptom of DED in our study population was watering followed by burning, itching and foreign body sensation. The most common sign of DED in our study was filaments and erosions followed by plugged meibomian gland orifices. The various signs and symptoms appeared from as early as 5 days after EBRT to 12 weeks after routine RT doses. These patients were well managed on medical therapy. One patient developed limbal ischemia not responding to medical therapy and had to undergo simple limbal epithelial transplantation.

Figure 1



a) Shows acute redness post RT
b) Shows reduced tear meniscus height
c) Shows filaments and erosions
d) Shows madarosis, tylosis, limbal ischemia and resulting keratopathy.



a) Shows intra-operative Simple limbal epithelial transplant (SLET) procedure.
b) Shows post-operative day 7 photograph after SLET

Table 1- Incidence of Dry eye Disease in comparison to Total Radiation Dose

Total Radiation Dose	Total no. of patients	No. of Dry eye patients			
		Mild	Moderate	Severe	Total (%)
36-45 Gy	2	0	0	0	0
46-55 Gy	13	1	2	1	4 (30.7%)
56-65 Gy	16	3	3	2	8 (50.0%)
66-75 Gy	9	2	3	1	6 (66.6%)
Total	40	6	8	4	18 (45%)

Above table shows increasing incidence of DED with increase in TRD; none of the patients who received TRD of 36-45 Gy developed DED in contrast to that 30.7% patients who received TRD of 46-55 Gy developed DED and it increased to 50% and 66.6% in patients who received a TRD of 56-65 Gy and 66-75 Gy respectively. Pearson coefficient of correlation of DED with TRD came out to be r= 0.87 which signifies a strong positive correlation between DED and TRD.

Discussion

Radiation exerts its greatest impact on rapidly proliferating cells. The current study was done to find the frequency of various acute ocular complications of EBRT in HNC patients especially DED. We also established a correlation between DED and TRD. (r= 0.87)

DED is a widely known complication of RT when lacrimal gland or eyeball is exposed to a total radiation dose above 30 Gy. [4] Gazda MJ et al (1992) in their study found that RT damages lacrimal gland cells, causing cellular degeneration, necrosis and apoptosis which they termed as Radiotherapy-induced lacrimal gland injury (RILGI). [8]

Various acute radiation induced toxicities found in our study were redness (12.5%), madarosis (5%), tylosis (5%), limbal ischemia (2.5%) and DED (45%). Hence, the commonest acute RT induced toxicity was DED.

Similar results were found by Maharia S et al (2018) in their study. The acute side effects post irradiation were madarosis (19%), dermatitis (13%), conjunctivitis (3%), and meibomitis (12%) and Dry eye (33%). These complications occurred within hours to days after radiation exposure or within 3 months of completing RT. [9]

Parsons JT et al (1983) also found similar results in their study and concluded that DED is one of the commonest adverse effects after RT. Also that the concerned symptoms of ocular dryness can occur during the course of RT acutely and/or a progression of dry eye can occur as commonly experienced by patients. [10]

In our study there was an increase in the incidence of DED seen with increase in the TRD; none of the patients who received TRD of 36-45 Gy developed DED in contrast to that 30.7% patients who received TRD of 46-55 Gy developed DED and it increases to 50% and 66.6% in patients who received a TRD of 56-65 Gy and 66-75 Gy respectively. We also established a strong positive correlation between DED and TRD (r=0.87).

Parsons JT et al (1994) in their study also found a steady increase in the incidence of DED with increase in radiation dose and a steep increase in DED was seen in patients receiving TRD above 57 Gy. [6]

In a similar study by Bhandare et al (2012) out of the 78 patients studied; who were treated by EBRT for primary extracranial HNC and whose lacrimal apparatus/ entire globe was exposed to fractionated EBRT, 40 developed severe DED leading to visual compromise. The incidence of DED increased steadily from 6% at 35-39.99 Gy to 50% at 45-49.99 Gy and 90% at 60-64.99 Gy. They concluded that the risk of severe DES increased and the latency decreased with an increase in the total dose and dose per fraction to the lacrimal gland. [11]

Similar results were found by Jain K et al (2021) in their study. They concluded that 59% of the patients of HNC who had undergone radiotherapy for its treatment developed dry eye; the severity of which is directly proportional to the total radiation dose delivered during the therapy. The study also suggested the importance of total dose as well as dose per fraction in causing DES in such patients. [12]

Radiation also damages the limbal stem cells and can cause limbal ischemia in such patients leading to chronic non healing epithelial defect. In our study we found one patient who developed limbal ischemia.

Ours is a short duration study with patients not receiving fractionated radiation dose above 2 Gy. Further studies with longer duration period recruiting more number of patients and those receiving higher fractionated radiation dose are required in order to study relationship between DED and fractionated radiation dose and other chronic toxic effects of RT on ocular and adnexal tissues.

CONCLUSION:

Among the various acute radiation induced ocular and adnexal toxicities, dry eye disease is one of the most common. It can occur as an acute or delayed toxic effect. Also, the incidence of DED in patients undergoing radiotherapy for head and neck cancers increases with the increase in total radiation dose and has a positive correlation. Limbal ischemia, although an uncommon effect of radiation toxicity, is resistant to treatment by medical methods and may need a surgical intervention thereby further increasing the burden on the cancer patients.

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