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Research Article

Analysing the dose to lacrimal glands in Carcinoma Nasopharynx: Is there a need for Ophthalmic prophylaxis?

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Abstract
Objective: *To evaluate the relationship between lacrimal gland dose and ocular toxicity among the patients treated by Intensity Modulated Radiotherapy (IMRT) for Carcinoma Nasopharynx.*
Material and Methods: *20 patients of Carcinoma Nasopharynxwere treated by IMRT techniqueto a curative dose of 70Gy. The lacrimal glands were contoured as Organ at risk (OARs) and the minimum dose, maximum dose, mean dose and V_{30} were evaluated. Radiation Therapy Oncology Group (RTOG) toxicity criteria was used to report on conjunctivitis, corneal ulceration and keratitis.*
Results: *The minimum dose, maximum dose and mean dose received by right lacrimal gland was 3.86Gy, 19.20Gy and 9.34Gy respectively and by left lacrimal gland was 3.84Gy, 23.02Gy and 9.94Gy respectively. PTV volume (in cc) was evaluated. The minimum, maximum and mean PTV volumes were 193.9cc, 1444.6 cc and 550.6 cc respectively. In the patients who developed ocular toxicity, the mean PTV volume was 835.3cc. The mean distance between lacrimal gland and PTV was found to be 0.6cm. 8 patients reported with Grade-I ocular toxicity. In all these patients, the lacrimal gland was found to be in close proximity to the PTV.V30 of left lacrimal gland was 11.87% and V30 of right lacrimal gland was 6.2% respectively in the patients who developed ocular toxicities.*
Conclusion: *This study documents that the mean dose and maximum dose to lacrimal gland is important for analysing the acute and late ocular toxicities. Hence, lacrimal gland should be contoured as Organ at risk in Carcinoma Nasopharynx and dose constraints should be given to minimise the toxicity and prevent Dry Eye Syndrome.*
Keywords: *Lacrimalgland, Nasopharynx, Keratitis sicca, Intensity Modulated Radiotherapy, Radiation Therapy Oncology Group.*

Introduction

Lacrimal gland produces the majority of tear fluid. It is located in the superio-temporal part of the orbit. Lacrimal gland is bilobed and has a large orbital and a small palpebral part. Lacrimal gland is approximately 20mm long and 12 mm wide. The orbital lobe is 5mm thick and the palpebral lobe is 3mm in thickness. The glands of Krause

and Wolfring are accessory lacrimal glands in the orbit [1].

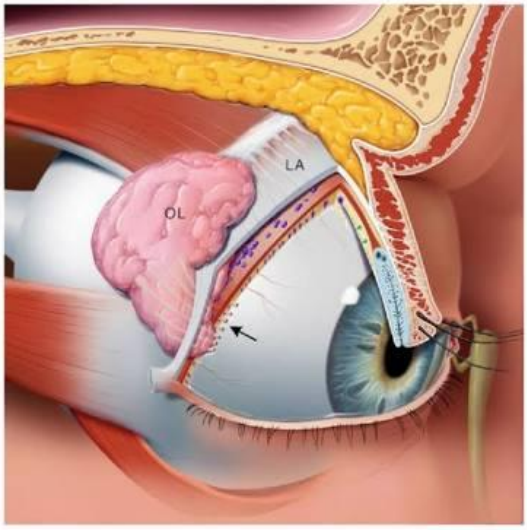

Figure 1: Lacrimal gland: Location and structure

The tear fluid continuously moistens and lubricates the eye. The tear film has three layers: inner mucin coating layer, middle aqueous component layer and outer lipid layer. The inner mucin layer is produced by goblet cells of the conjunctiva, the aqueous component layer by paired lacrimal glands and the lipid layer by meimobian glands.

Tear film protects the eye by providing immunity against the surface pathogens and minute dust particles (IgA and IgM producing cells) [2]. It also provides an air tissue interface for gas exchange. It provides nutrients and metabolites to the avascular cornea and maintains its transparency.

Histopathologically, the gland is composed of several lobules separated by loose connective tissue. Lobules consist of multiple acini lined by columnar secretory cells which secretes mucopolysaccharides. Multiple interlobular ducts drain into 8-12 excretory ducts. The ducts of orbital lobe pass through the parenchyma of palpebral lobe making the proximal secretory ducts susceptible to damage distally [3].

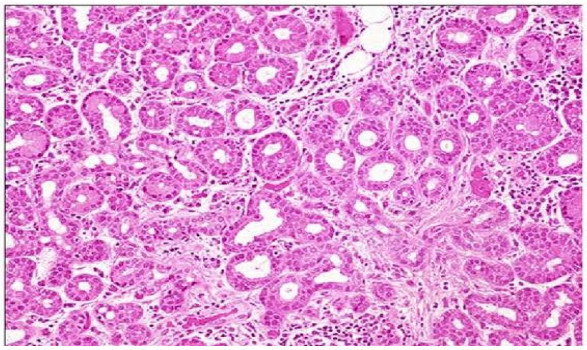

Figure 2: Normal lacrimal gland

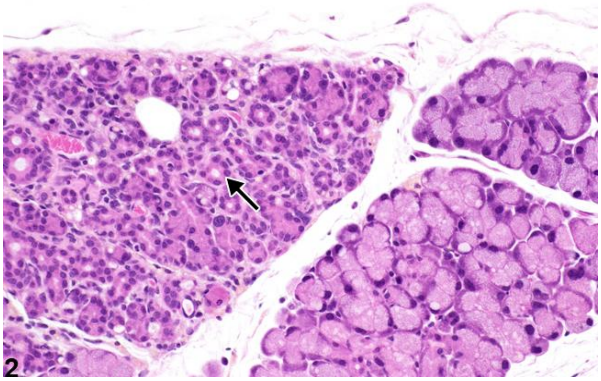

Figure 3: Atrophic glands on the left

The functions of the lacrimal glands are altered due to aging, smoking, infections, autoimmune diseases, comorbid conditions and radiation exposure. These changes are histopathologically found to be due to atrophy of glandular parenchyma, increased interstitial connective tissue, increased fat content within the glandular tissue and epithelial secretory cells.

Obata et al found statistically significant difference in incidence of diffuse fibrosis, atrophy and periductal fibrosis of lacrimal gland in post-menopausal women as compared to men. Similar histological changes are hypothesised to occur post radiotherapy as well, causing keratitis sicca, although the exact pathogenesis is unclear [4].

The lacrimal glands are sensitive to radiation. There can be transient or permanent dysfunction of the glands post radiotherapy. Orbital radiotherapy is associated with near total destruction of the histology of the human lacrimal gland with negligible number of viable acini, loss of cellular integrity, and gross reduction of secretory function. The ductal cells also appear to be damaged with extensive periductal and

intralobular fibrosis and lymphocyte inundation [5].

Dry eye syndrome is a complication of radiotherapy to the periorbital region. It is defined by International Dry Eye Workshop as "multi-factorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" [6].

Keratitis sicca is one of the commonest consequences in Carcinoma Nasopharynx patients who receive radiotherapy as the lacrimal gland is in close proximity to the target volumes. Treatment of Keratitis sicca is only a temporary measure and is treated by using artificial tears which are synthetic polymers that increase viscosity and retention time of tears. It doesn't provide important nutrients and immunity for ocular health [7]. Artificial tears, betamethasone cream, ketorolac drops, antibiotic ointments are being used in the treatment of Keratitis sicca.

Punctal plugs have been tried but has poor retention rates and they migrate into lacrimal system predisposing to infections or causes epiphora. Punctal cautery may not be acceptable to patients and is difficult to reverse when patients become intolerant. To prevent the complications of Keratitis sicca, the dose to lacrimal gland has gained significance with the advancement of radiotherapy treatment delivery. It is critical to avail ophthalmic prophylaxis in Carcinoma Nasopharynx patients who are at risk of Keratitis sicca.

The standard of care in Carcinoma Nasopharynx is Radiotherapy with or without chemotherapy. Intensity Modulated Radiation Therapy is a novel radiation delivery technique and is the standard treatment delivery method [8] in which the prescribed dose to Planning Target Volume (PTV) is 70Gy for curative treatment.

Lacrimal gland is in close proximity to the treatment fields during radiotherapy as it is located in the lacrimal fossa of the orbital plate of frontal bone. Studies have shown that the tolerance of lacrimal gland is V30 less than 50% and Dose maximum (Dmax) less than 40Gy [9].

In this study, dosimetry of lacrimal gland in Carcinoma Nasopharynx patients treated with IMRT technique was assessed and the clinical outcome using RTOG toxicity was evaluated.

Materials and methods

20 patients of Carcinoma Nasopharynx treated with IMRT technique from 2016 to 2018 in our Institute was included.CT simulation scan with 3 mm slice thickness from Vertex to T4 vertebra was obtained and imported to our treatment planning system.

GTV, CTV and PTV was contoured according to the RTOG guidelines[10]. Right and left lacrimal gland was contoured as OARs along with other structures and target volumes. The lacrimal gland was contoured starting from the axial slice at the level of widest part of lens. The width extended from zygomatic bone to globe of the eye. The length was contoured from the retina posteriorly to the lens anteriorly.

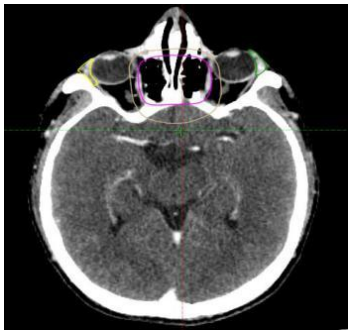

Figure 4: Contouring of target volumes and OARs

Dose to PTV was 70Gy and all the patients were planned with Eclipse version 13.1 for IMRT.

The minimum dose, maximum dose and mean dose to the lacrimal gland was evaluated.

RTOG toxicity criteria was used to report on conjunctivitis, corneal ulceration and keratitis [11].

Results

Statistical analysis was done with 'R' software and Independent T – test was done to corelate the significance.

Patients were in the age group of 35-60 years, of which 17 patients were male and 3 were female. The majority of the patients in the study had major bulk of disease in the left side (70%) of the nasopharynx.

Table 1: Gender wise distribution of cases

GENDER		
Sex	Number	Percentage (%)
Male	17	85.0
Female	3	15.0
Total	**20**	**100**

Table 2: Side of tumor bulk

TUMOR BULK		
Side of Nasopharynx	Number	Percentage (%)
Right	6	30.0
Left	14	70.0
Total	**20**	**100**

15 patients (75%) belong to stage III and 5 patients (25%) belong to stage IVA according to AJCC 7th edition and 4 patients (20%) belong to stage II and 16 patients (80%) belong to stage III according to AJCC 8th edition.

Table 3: Staging comparison of cases

7th Edition AJCC	**Number**	**8th Edition AJCC**	**Number**
Stage I	0	Stage I	0
Stage II	0	Stage II	4
Stage III	15	Stage III	16
Stage IVA	5	Stage IVA	0
Stage IVB	0	Stage IVB	0
Stage IVC	0	Stage IVC	0

The mean volume of right and left lacrimal gland was 1.3cc and 1.2cc respectively.

Table 4: Lacrimal Gland Volumes

Volumes	**Minimum (in cc)**	**Maximum (in cc)**	**Mean (in cc)**	**S.D. (in cc)**
Right lacrimal gland	0.7	1.8	1.3	0.3
Leftlacrimal gland	0.7	2.0	1.2	0.3

The minimum dose, maximum dose and mean dose received by right lacrimal gland was 3.86Gy, 19.20Gy and 9.34Gy respectively and by left lacrimal gland was 3.84Gy, 23.02Gy and 9.94Gy respectively.

Table 5: Lacrimal Gland Doses

Dose Received (in cGy)	**Lacrimal Gland**	
	Right	**Left**
Minimum	386.7	384.8
Maximum	1920.4	2302.1
Mean	934.4	994.2

PTV volume (in cc) was evaluated. The minimum, maximum and mean volumes were 194cc, 1445cc and 550.6 cc respectively. The distance between the lacrimal gland and PTV was also evaluated.On correlating the distance between the lacrimal gland and PTV, it was found that p-value was less than 0.001 which is statistically significant.

Table 6: PTV and lacrimal gland distance

Volumes	**Minimum**	**Maximum**	**Mean**	**S.D.**
PTV	194.0	1445.0	550.6	340.6
Distance b/w LG & PTV	0.0	2.0	0.6	0.8

V30 of right and left lacrimal gland was 1.6 % and 3.8 % respectively.

Table 7: V30 of Lacrimal Gland

Volume (%)	**Right**				**Left**			
	Minimum	**Maximum**	**Mean**	**S.D.**	**Minimum**	**Maximum**	**Mean**	**S.D.**
V30	0.0	14.0	1.6	3.9	0.0	21.0	3.8	7.1

On correlating PTV with dose to lacrimal gland, it was not statistically significant. (p-value = 0.056)
Only 8 patients complained of mild dry eye (RTOG Grade-I toxicity) and all of them were managed conservatively.

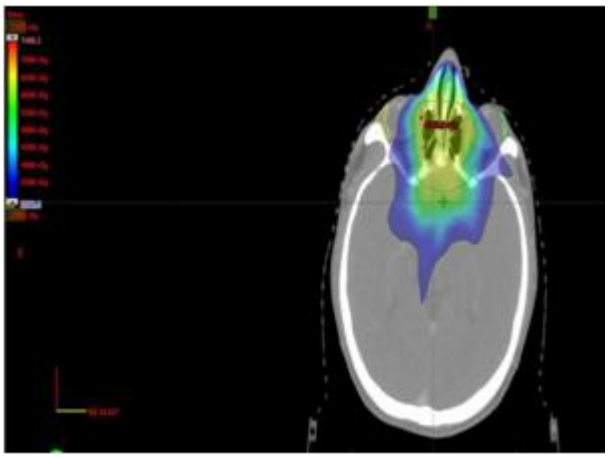

Figure 5: Dose colour wash of Target Volume

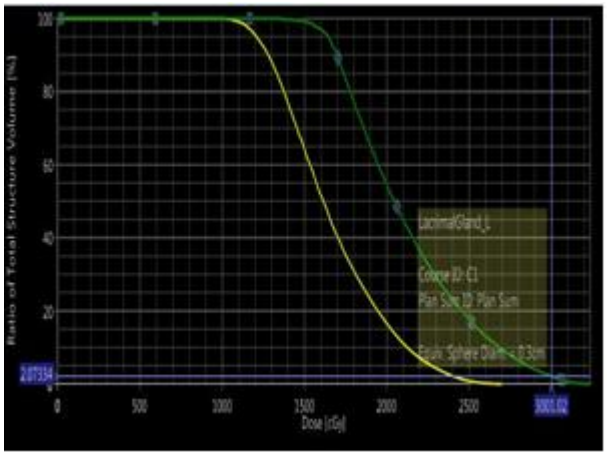

Figure 6: DVH of Lacrimal Gland

Discussion

In the present study, a dose response relationship for Keratitis sicca in Carcinoma Nasopharynx patients treated by IMRT technique was analysed.
Majority of the patients had tumour bulk in the left side of the nasopharynx.
We found that the minimum, maximum and mean distance between lacrimal gland and PTV was 0.0, 2.0, 0.6 cm respectively.
8 patients had Grade-I toxicity and in all the 8 patients, the lacrimal gland and PTV were in very close proximity.
The minimum dose, maximum dose and mean dose to right lacrimal gland was 3.86Gy, 19.20Gy and 9.34Gy respectively and by left lacrimal gland was 3.84Gy, 23.02Gy and 9.94Gy respectively.
12 patients received maximum dose of greater than 30Gy to the lacrimal gland and 7 patients who developed Keratitis sicca had received maximum dose of greater than 30Gy.
In the study by S.S. Bath et al, the observed incidence of higher acute and late toxicities significantly increased at a maximum dose of 30Gy, suggesting a threshold with a dose response relationship that was more prominent for acute toxicity[(12)].A mean dose of 67.8Gy and maximum dose of 75.4Gy to lacrimal gland resulted in severe conjunctivitis, periorbital oedema, keratitis sicca syndrome and transient loss of vision.
In the study by Bhandare et al, the incidence of dry eye syndrome increased steadily from 6% at 35-39.99Gy to 50% at 45-49.99Gy and 90% at 60-64.99Gy. The latency of dry eye syndrome was observed to be a function of total dose and dose per fraction[(13)].
In the present era of advanced treatment planning system and precision radiotherapy delivery techniques, the lacrimal gland must be contoured and dose constraints given to the organs at risk, to all patients of Carcinoma Nasopharynx, Sinonasal tumours and Brain tumour patients to avoid the complications of dry eye syndrome. Ophthalmic Prophylaxis must be considered before starting the radiation to these sites.

Conclusion

This study demonstrates the doses received by lacrimal gland in carcinoma nasopharynx patients using IMRT technique. It shows that the farther the distance between lacrimal gland and PTV, the dose received by lacrimal gland was very minimal.
12 patients (60%) received maximum dose of more than 30Gy to the lacrimal gland. Keratitis sicca was found in 8 patients (40%) and all the patients were managed conservatively.
Ophthalmic prophylaxis must be done for Carcinoma Nasopharynx patients before the start of radiotherapy. It must also be considered for

Sinonasal and Frontal lobe tumours to reduce the toxicity to the lacrimal gland. Lacrimal gland must also be contoured as organ at risk in Carcinoma Nasopharynx. Future studies with high number of patients is required to redefine the dose constraints and other organs at risk using conformal techniques. The mean dose and the maximum dose to lacrimal glands is important for analysing the acute and late toxicity respectively.

Detailed clinical evaluation of even mild symptoms should be done according to RTOG toxicity grading in Carcinoma Nasopharynx patients to corelate with doses received by lacrimal gland.

The effect of chemotherapy with radiotherapy, altered dose fractionation, differential dosing and precision radiation delivery techniques needs to be investigated.

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