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# Evaluation of Toxicity Profiles of Lacrimal Glands in Nasopharyngeal Carcinoma Patients Treated with Volumetric Modulated Arc Therapy

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## Abstract
**Background:** Lacrimal gland forms the integral part of tear film production. In view of close proximity to treatment portals, the present study aimed to investigate the relationship between lacrimal gland radiotherapy dose and its toxicity among patients treated with volumetric modulated arc therapy for carcinoma nasopharynx.
**Method:** A total number of 50 nasopharynx cancer patients treated with 70Gray included in this mono-centric, prospective, observational study. The lacrimal glands contoured as part of organs at risk. Impact of planned target volume, distance of gland to this volume, dose received by glands and V30 are assessed. Slit-lamp examination and Schirmer-I test were used pre-treatment and post-treatment up to a period of 2-years. Radiation Therapy Oncology Group toxicity criteria were used to provide information on conjunctivitis, corneal ulceration, and sicca-keratitis. 'R' software v4.4 was used for statistical analysis and independent T-test to correlate the significance with *P*-value <0.05.
**Results:** The minimum, maximum, and mean dose (Gray) received by the right lacrimal gland, comparable with the dose delivered to left lacrimal gland, was 2.58, 17.44 and 10.01, respectively. The minimum, maximum and mean planned target volumes (cubic centimetre) were 188.12, 1612.33 and 893.45, respectively. The mean distance between lacrimal gland and planned target volume is 0.51 centimetre and found to be statistically significant with *P*-value <0.001. Ten Grade-I and three Grade-II toxicity were reported in the study.
**Conclusion:** Based on the findings of the present study, contouring lacrimal gland as organ at risk in carcinoma nasopharynx is recommended and dose constraints to be advised, to minimize the toxicity and to prevent dry eye syndrome.

***Keywords:*** Nasopharyngeal neoplasms, Conformal radiotherapy, Volumetric modulated arc therapy, Lacrimal gland, Dry eye syndrome

## Introduction

The lacrimal gland is situated superotemporally in the orbit within the lacrimal fossa of the frontal bone. The gland is divided into two lobes, orbital and palpebral lobes, by the lateral horn of levator aponeurosis. It is bound anteriorly by orbital septum and pre-aponeurotic fat pad, posteriorly by orbital fat, medially by intermuscular membrane between the superior and lateral recti, and laterally by bone. The gland averages approximately 20 millimetre (mm) long and 12-mm wide with the orbital and palpebral lobes having a thickness of 5-mm and 3-mm, respectively.[1]

The lacrimal gland is an exocrine gland similar to the mammary gland and salivary gland. Each gland lobule consists of many acini and intralobular ducts that drain into approximately 8–12 excretory ducts or tubules. The ducts of both orbital and palpebral lobes drain into the superotemporal conjunctival fornix, approximately 5-mm superior the lateral tarsal border.[1]

The tear film production by lacrimal gland is critical in several processes related to ocular surface health.[2] It protects ocular surface from invading pathogens with local population of IgA-secreting plasma cells. It also secretes several bactericidal and fungicidal agents into the tear film, thereby greatly reducing susceptibility of the ocular surface to invading pathogens due to cytotoxicity.[3] The high volumes of water from the gland helps to keep ocular surface moist and maintain light refraction in the air-water-corneal interfaces, and dilute proteins within the tears to keep them solubilised.[4] Retinol, a vitamin-A derivative, is also secreted by the lacrimal gland and is required in maintenance of goblet cells within the conjunctiva and controls corneal epithelial desquamation, keratinization, and metaplasia.[5,6]

Due to close proximity of lacrimal glands to nasopharynx, radiation induced toxicity is high in the treatment of malignancies.[7] The nasopharynx, positioned between the base of skull and soft palate, is an integral segment of pharynx. Carcinoma of this site, usually presents with locally advanced, non-metastatic stage accounting upon 70% of nasopharyngeal cancers. In most cases, the most effective means of treatment is radiotherapy (RT) with or without concurrent chemotherapy.[8]

Prior to the advent of conformal methods of RT treatment, carcinoma nasopharynx conventional RT portal encompassed a lateral parallel-opposed pair of fields or three-field techniques (laterals and an anterior field), resulting in acute and late ocular toxicities.[9]

As per the guidelines of International Dry Eye Workshop, dry eye is defined as multifactorial 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. It is accompanied by increased osmolarity of tear film and inflammation of ocular surface.[10]

Stress to the ocular surface (environmental factors, infection, endogenous stress, antigens, genetic factors) is postulated as the pathogenetic triggering mechanism for dry eye syndrome (DES). The ocular surface (cornea, conjunctiva, accessory lacrimal glands), meibomian glands (specific sebaceous glands of the eyelid margin, which produce the outer lipid film of the tear film), the main lacrimal gland, and the innervation between them form a functional unit. Any or all of these structures may be affected in dry eye disease.[11] The pathogenetic mechanism of ocular dryness by irradiation is the result of reduction or absence of the lipid layer of the tear film and evaporation, or damage to the acinar cells of the lacrimal glands.[11]

After a latent period of roughly 6-months, RT to the lacrimal gland may cause persistent inflammation and eventually, fibrosis and atrophy. The incidence of severe acute and late toxicities seems to increase at a maximum dose >30.0 Gray (Gy).[12-17]

The limited data on lacrimal gland toxicity profile is derived from treatments of overall

head and neck malignancy, brain tumours and sino-nasal tumours.[12-17] The present study being site-specific can bring more perspective in this regard. Given the capacity of volumetric modulated arc therapy (VMAT) to restrict radiation to normal structures classified as organs at risk (OARs), the purpose of present study was to investigate the association between several dosimetry parameters related to lacrimal gland and its toxicity with clinical result using Radiation Therapy Oncology Group (RTOG) toxicity criteria,[18] in patients receiving VMAT for nasopharyngeal malignancies.

## Materials and Methods

### *Study criteria*

This is a Mono-centric, prospective, observational study approved from institutional ethics committee of Karnataka cancer therapy and research institute, Hubli, Karnataka and assigned as KCTRI/IEC/03/21. Written informed consent was taken from all study participants. From 2021 to 2023, 50 patients aged above 18 years, with carcinoma nasopharynx underwent VMAT treatment at our institute. The computed tomography (CT) simulation scan from Vertex to T4 vertebra with 3-mm slice thickness was obtained and put into our treatment planning system. According to RTOG recommendations, gross tumour volume, clinical target volume, and planning target volume (PTV) were contoured.[19] Along with additional structures and these target volumes, the right and left lacrimal glands were contoured as organ-at-risk (OAR). The entire length of the lacrimal gland was contoured from the lens's anterior to the retina's posterior, starting at the axial slice at the level of the broadest section of the lens and the breadth included from zygomatic bone to the eyeball (Figure 1).

All of the patients were treated with concurrent chemotherapy (cisplatin-40mg/$m^2$) and RT, since it is the standard of care in head and neck malignancy. Dose to PTV is 70Gy in 35 fractions and planned with Monaco5.11 for VMAT. The minimum dose, maximum dose and mean dose to the lacrimal gland was evaluated along with V30. PTV volumes and its distance from lacrimal glands are also assessed to determine its contribution to toxicity profile. RTOG toxicity criteria was used to report on conjunctivitis, corneal ulceration and keratitis. The patients are assessed with slit-lamp examination and Schirmer-I test for lacrimal gland toxicities, both pre-treatment and post-treatment with intervals of 3-months up to period of 2-years.

### *Statistical method*

Data were entered into Microsoft (MS) excel data sheet and analysed using 'R' software version 4.4. The Yamane formula and confidence interval method were used for sample size estimation. Categorical data are presented as frequency and proportion. Continuous data are presented as mean and standard deviation (SD). Independent T-test used to correlate the significance. *P*-value <0.05 was considered as statistically significant.

## Results

The mean age of the 50 patients included in the study was 45.61 ± 9.31 years, of which 33 (66%) were male and 17 (34%) were female. It was observed that the majority of the patients had a disease bulk on the right side 34 (68%) whereas 16 (32%) had disease in the left side. Also, 37 patients (74%) belonged to stage III and 6 patients (12%) belonged to stage IVA, according to American Joint Committee on Cancer (AJCC) 8$^{th}$ edition. None of the patients reported DES or lacrimal gland related illness prior to treatment.

The mean volume of right and left lacrimal gland was 1.28 cubic-centimetres (cc) and 1.22cc, respectively. There was no statistically significant difference (*P* = 0.731).

The minimum dose, maximum dose, and mean dose received by the right lacrimal gland was 2.58Gy, 17.44Gy and 10.01Gy,

whereas on the left side, it was slightly higher, 3.11Gy, 22.71Gy, and 11.23Gy, respectively. The V30 of right and left lacrimal gland was 1.6% and 3.8 %, respectively. However, the difference was not statistically significant ($P = 0.619$).
The distance between the lacrimal gland and PTV was evaluated, along with minimum, maximum and mean values of PTV volumes (in cc) (Table 1).

On correlating the distance between the lacrimal gland and PTV, it was found that the *P*-value was less than 0.001 which is statistically significant. Similarly, higher treatment volumes to lower treatment volumes correlated to the dose received by lacrimal gland, it was found not statistically significant ($P = 0.056$).
In the patients who developed ocular toxicities, the mean PTV was 994.81cc, which was higher in comparison with those who did not develop complications. V30 of left and right lacrimal gland was 9.13% and 5.98%. In 16 individuals (32%), lacrimal gland got a maximal dose of more than 30Gy and among them ten patients (20%) had keratitis sicca (RTOG Grade-I toxicity) whereas 3(6%) had Grade-II toxicity. Also, 9(18%) patients with toxicity had PTV in close proximity to lacrimal gland and had conservative treatment.

**Discussion**

The study result shows there is no comparable dose difference between right and left lacrimal gland with no statistical impact shown by variations in the volume size of PTV. Whereas the distance from PTV to lacrimal gland showed statistical significance, indicating more the treatment volume proximity to the gland, more will be the lacrimal gland toxicity. While V30 was assessed in this study for accurate analysis of toxicity profile and to limit dose delivered to lacrimal glands, conformal therapy like VMAT could result in desirable V30. The present study also shows conformal treatment limited toxicity to maximum extent, which can be managed conservatively.
The observed incidence of more severe acute and late ocular toxicities increases dramatically with a dosage of 30 Gy, indicating a threshold with a dose-response relationship that was more pronounced for acute toxicity.[20,21] Ahmad et al.,[22] did a review on radiation induced xerophthalmia and observed a significantly lower rate of DES of 7.7% with intensity modulated radiotherapy in comparison with 31.6% with conventional technique and reported a significant correlation between V30Gy >50% and risk for acute and late grade 2 or more ocular toxicity. The incidence of DES leading to visual loss increased from 6.7% for doses between 35-40 Gy to 25% for 40-45 Gy, 50% for 45-50 Gy, and 90% for doses greater than 60Gy.[22] Patients receiving doses ranging from 42-55Gy, 17% experienced toxicity whereas 56-74.5Gy caused toxicity in 81%, due to damage to corneal-lacrimal complex, as per the 2-year incidence assessment for impairment in vision.[22]
Taking note from these evidence, we have analysed the dose contribution to lacrimal gland and assessed V30 in our study, which was found to be well within an acceptable norm. Since our study included conventional technique, we analysed patients treated with VMAT, a conformal and advanced treatment modality, so as to assess its safety profile in terms of achieving acceptable doses to OAR.
Soni M. et al.[23], analysed 90 post RT patients of head and neck malignancy and found a strong positive correlation between tumour location and incidence of DES. Thus, a dose-response connection for Keratitis sicca in patients with carcinoma nasopharynx treated with VMAT technique was examined in the present study. In fact, the distance from PTV to lacrimal gland, has a significant bearing on the level of ocular toxicity, inferenced from our study results.
New evidence shows the prevalence of DES with systemic chemotherapy in breast

cancer patients.[24] Since concurrent chemo-radiation is standard of care in head and neck malignancy, we have not assessed the effect of radiation alone in our study. Due to institutional protocol, we have treated all our patients with conformal technique only. Therefore, we could not compare it with conventional treatment technique. Also, none of the patients received a fractionated radiation dose above 2 Gy per fraction; thus, the correlation between DES and radiation per fraction could not be assessed. The present study also serves as indirect evidence to consider lacrimal gland as OAR to lessen toxicity in Sino-nasal and frontal lobe malignancies, due to its close proximity to the target volume but warrants further investigation in these sites to ascertain conclusively.

Our study results show that contouring lacrimal glands as organ-at-risk helps to assess the impact of VMAT in carcinoma nasopharynx, and provides necessary information about the need for prophylactic and curative measures in case of lacrimal gland toxicity. The main limitation of the present study is that we did not compare the results with other radiotherapy delivery techniques.

## Conclusion

Our study demonstrates that the lacrimal gland toxicity in nasopharyngeal cancer can be decreased by conformal techniques like VMAT achieving acceptable V30 levels and the dose received by lacrimal gland is minimised when it is further away from PTV.


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## Authors' Contributions

Sridhar Poojar: Conception of the work, study design, drafting, data approval and draft review.

Poornachandra Tejaswi Siddappa: Study design, data gathering, drafting and reviewing the manuscript.

Vinay Desai: Data analysis and data interpretation, draft review.

Naveen Thimmaiah: Data analysis and data interpretation, draft review.

All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.


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## Conflict of Interest

None declared.

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Table 1. Standard deviations of planned target volume and its distance from lacrimal gland recorded from the study, while the latter bearing impact on toxicity

| Volumes | Minimum | Maximum | Mean | S.D. |
|---|---|---|---|---|
| PTV (in cc) | 188.12 | 1612.33 | 493.45 | 340.61 |
| Distance between lacrimal gland and PTV (in cm) | 0.00 | 2.00 | 0.51 | 0.80 |

PTV: Planned target volume; cc: Cubic centimetre; cm: Centimetre; S.D: Standard deviation

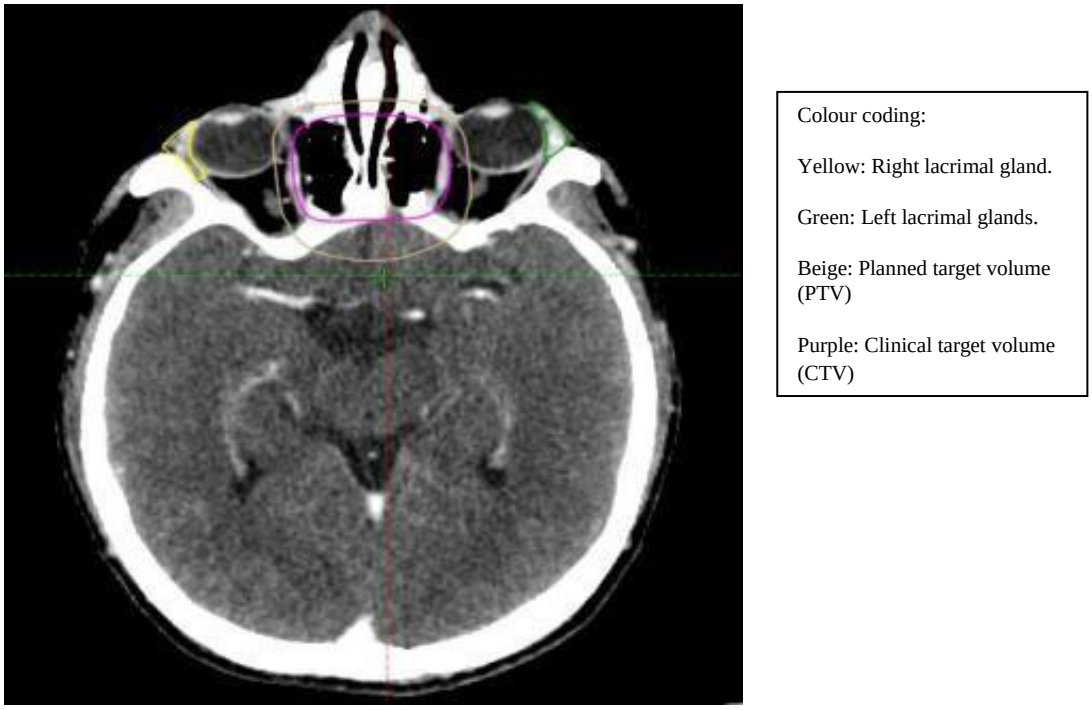


Figure 1. Lacrimal glands contoured as organ at risk. The above axial view of CT slice, clearly depicts the proximity of planned target volume and lacrimal glands, thus indicating the need to assess lacrimal gland toxicity profile.

CT: Computed tomography; PTV: Planned target volume; CTV: Clinical target volume