Assessment of dose to Lacrimal Glands in Carcinoma Nasopharynx, Nasal Cavity and Paranasal Sinuses and its clinical importance

[1]S.K.Azharuddin, [2]Piyush Kumar

[1]Senior Resident, [2]Professor and Head
[1,2]Department of Radiation oncology, Shri Ram Murti Smarak Institute of Medical sciences, Bareilly,UP.

Background:
Head and Neck cancers comprises of heterogenous group of tumors with significant mortality and morbidity causing all around the world. The optimal management of these tumors include multi-modality approach of surgery, radiotherapy and chemotherapy. Radiotherapy treatment planning for head and neck tumors are complex owing to number of organs at risk located in the vicinity of Planning target volumes. Carcinoma Nasopharynx, Nasal cavity and Para-nasal sinuses tumors are a distinct group of tumors within head and neck cancers with slight variation in treatment approach. Recent trends in conformal techniques of radiotherapy led to exploration of long-term toxicities caused by the various Organs at risk (OAR's) and further development of planning techniques in such a way to limit dose to OAR's. Lacrimal glands as an Organ at risk (OAR) is being evaluated recently due its ocular toxicities which was usually under-evaluated and unaccounted in most of clinical settings.

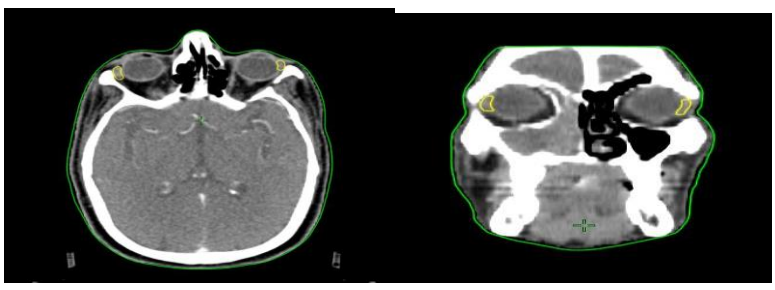
Lacrimal gland produces the majority of tear fluid.It is located in the superio-temporal part of the orbit. The tear fluid continuously moistens and lubricates the eye and also protects the eye by providing immunityagainst the surface pathogens and minute dustparticles. Histo-pathologically, the gland is composed of several lobules separated by loose connective tissue[1]. The lacrimal glands are sensitive to radiation. 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.
Dry eye syndrome is a complication of radiotherapy to the periorbital region. It is defined by International Dry Eye Workshop 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 accompanied by increased osmolarity of the tear film and inflammation of the ocular surface"[2]. Kerato-conjunctivitis is one of the commonest consequences in Carcinoma Nasopharynx (NPX), Nasal cavity (NC), Para-nasal sinuses (PNS) patients who receive radiotherapy as the lacrimal gland is in close proximity to the target volumes. Treatment of dry eyes is only a temporary measure and is treated by using artificial tears which are synthetic polymers that increase viscosity and retention time of tears[3].

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[4].

Materials and Methods:
Twenty-three patients of Carcinoma NPX, NC and PNS already treated with IMRT/3DCRT in our Institute from 2017 to 2021 were included.The patients were immobilized using a fixed 5 point thermoplastic cast system. After CT simulation the images were transferred through Digital Imaging and Communications in Medicine (DICOM-CT) into the Eclipse treatment planning system version 13.6.The clinical target volume (CTV) was defined as per RTOG Guidelines. The OARs were also contoured. A margin of 5 mm was taken for PTV. Ppatients were planned by IMRT/3DCRT. Dose to PTV was 60-70Gy with/without concurrent chemotherapy. Retrospectively, Right and left lacrimal gland was contoured according to the guidelines by Freedman et al. starting from the axial slice at the level of widest part of lens[5]. The width extended from zygomatic bone to globe of the eye.

The Dmin, Dmax and Dmean along with V10, V20, V30 to the lacrimal glands were evaluated. Patient's were evaluated for any ocular signs and symptoms of Dry eyes (using any artificial tears), burning sensation in eyes, Visual disturbances (diplopia, poor vision) and also ophthalmological examination done with Schirmers tests, Tear Break Up Time (TBUT) and visual acuity tests.

FIGURE 1 & 2: Contouring and location of lacrimal glands in axial and coronal sections of CT scan



The above images depict the location of lacrimal glands. They can be seen in superior-lateral aspect of orbit as suggested in the literature.

Statistical Analysis:
Statistical analysis was done with Pearson Correlation Coefficient to establish and evaluate relationship between the dose parameters and clinical data.

Results:

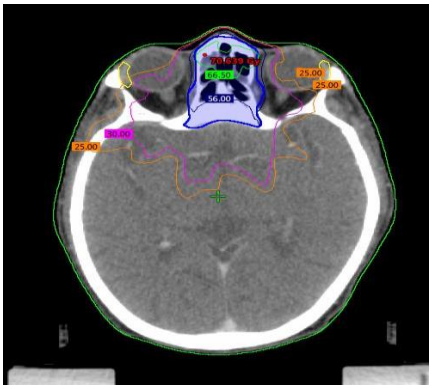
Tumor location and corresponding number of patients:
The division of percentage of patients in each subsite shows that there is almost an equal distribution of patients in each subsite with 39% patients have carcinoma Nasopharynx as primary with 35% and 36% of patients belong to carcinoma Para-nasal sinuses and Nasal cavity tumors respectively.

Table-1: Table showing Mean values of dosimetric parameters of Left and right lacrimal glands

MEAN						
Parameters	**Dmean**	**Dmax**	**Dmin**	**V10**	**V20**	**V30**
Left lacrimal gland	9.46Gy	15.2Gy	5.65Gy	29.7%	8.9%	4.75%
Right lacrimal gland	11.58Gy	18.57Gy	6.9Gy	81.4%	12.8%	4.4%

The mean, max and min doses to left lacrimal gland are 9.46Gy, 15.2Gy, 5.65Gy respectively, where as for right lacrimal gland they were 11.58Gy,18.57Gy, 6.9Gy respectively. The volumetric doses of V10, V20 and V30 for left side are 29.7%, 8.9%, 4.75% and 81.4%, 12.8% and 4.4% for right side as can be observed in **Table-1**.

FIGURE 3: Isodose levels corresponding to PTV showing isodose lines of V25 and V30 near Lacrimal glands



The above image shows the iso-dose lines of V25 and V30. The dose volumes of V25 and lower than that, can be seen intersecting at the right lacrimal gland, how-ever no dose of V25 can be observed at left lacrimal gland.

Table-2: Table showing clinical data and number/percentage of patients

Clinical data	***Number***	***Percentage***
Visual disturbances/dry eyes	7	31%
Clear vision	5	21%

No follow up since 1 year	5	21%
Death	6	27%

In the **Table-2**, the visual difficulties including dryness, conjunctivitis and vision disturbances reported in approximately 31% patients (n=7) with only 21% (n=5) patients having clear vision with no ocular difficulties. How-ever, there was no follow up data in 21% (n=5) patients with death reported in another 27% (n=6) patients.

Clinical examination findings:
Total 7 patients underwent ophthalmological tests in which 2 patients underwent TBUT and Schirmers test, 3 patients of TBUT and Visual Acuity tests, 1 patient underwent Visual acuity and Schirmers test each with 5 patients having clinically relevant notes of no ocular difficulties.

Table-3: Pearson Correlation coefficient between Dosimetric parameters and visual problems/Conjunctivitis/Keratitis

PARAMETERS	Dmean	Dmax	Dmin	V10	V20	V30
Pearson Correlation coefficient	0.0121	0.059	-0.119	0.03	0.16	-0.07

There is a positive correlation although with weak relationship between the visual problems and dosimetric parameters of mean, max and V10 and V20 with no correlation for V30.

Discussion:
A study by Tejaswi P et al, analyzing the dose to lacrimal glands in Carcinoma Nasopharynx reported the minimum dose, maximum dose and mean dose received by right lacrimal gland as 3.86Gy, 19.20Gy and 9.34Gy respectively and by left lacrimal gland as 3.84Gy, 23.02Gy and 9.94Gy respectively. Similar results were obtained in our study with doses of 6.9Gy, 18.5 Gy and 11.5 Gy in right side and 5.6Gy, 15.2Gy and 9.4Gy in left side. They also concluded that 8(40%) patients developed dry eyes and V30 Gy as a significant parameter[6]. How-even in our study 7(30.4%) patients developed visual problems and no significant dose for V30. This can be explained because most patients were planned by IMRT and distance to PTV and lacrimal glands was significant with higher percentage volume at V20 only.

A study published by Bath S et al, on Clinical-dosimetric relationship between lacrimal gland dose and ocular toxicity after intensity-modulated radiotherapy for sino-nasal tumors concluded that V20 and Dmax are the strong predictors of late ocular toxicities. They also suggested that no patient developed late toxicity with a maximum dose, 15.1Gy or mean dose, 8.0Gy and for every 1% observed increase in V20, the odds of ocular toxicity increased by 7%[7]. In our study the max dose and V20 for left eye is 15.2Gy and 8.9% with 18.5Gy and 12.8% for right eye respectively. Both these parameters in our study showed positive correlation with clinical toxicity profile corresponding to above literature.

Another study by Bhandare N et al, investigating severe dry eye syndrome after radiotherapy in head and neck cancers concluded that the incidence of dry eyes syndrome increased steadily from 6% at 35–39.99 Gy to 50% at 45–49.99 Gy and 90% at 60–64.99 Gy with a mean latency for late complications of 0.9 years[8]. In our study also the mean of Dmax was 15.2 Gy (left) and 18.5 Gy (right) with a V30 values of less than 5%. However total 7 patients Dmax of more than 20 Gy out of which 4 patients had clinically relevant ophthalmologic problems corresponding to the literature that complications may steadily increase at higher doses.

Parsons et al. from the University of Florida demonstrated sigmoid dose–response curve with a 0% incidence of severe dry eye syndrome at lacrimal gland doses of 30Gy, which increased to a 100% incidence at doses 57Gy. In our present study, no patient received doses to a range of 30Gy which resulted in very less chances of developing dry eyes[9].

The present study in our opinion adds to the limited literature, characterisingthe relationship between lacrimal gland dose andocular toxicities. Specifically, we foundthat the maximum dose as well as V20 to the lacrimal gland can be a better predictor of late toxicity. It is been mentioned in the above studies that late toxicities seems to increase ata maximum dose of 30Gy. Our preliminary data based on our study also suggest that IMRT planning guidelines should aim to limit themaximum lacrimal gland dose to 30Gy, while prioritising adequate dose to thetumour.

It's our opinion that the present study was has some limitations which may have created an unintended bias in results. The lacrimal gland being a very small structure have a potentialeffect of interobserver variability in delineation which has the potential to skew our dosimetric finding. Lastly the limited available patient pool, no data on base line ophthalmological tests and also no standard tests may have inadvertently introduced some bias in the results. Prospective studies which include adequate ophthalmological examination are necessary to validate the above findings inthe future.

Conclusion:

This study demonstrates that the dose received by lacrimal gland may have resulted in visual difficulties with significant parameters being Dmax and V20. However further large scale studies with long term follow up may help in further concluding the relationship between dose and clinical outcomes.

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