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Lacrimal Gland and Radiotherapy

Ebtisam R Qasem, Abbas Sarhan, Salma Khaled Abd El-Maksoud, Doaa Mandour

Clinical Oncology & nuclear medicine Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Salma Khaled Abd El-Maksoud

Email: Sk2681689@gmail.com,

Abstract:

The lacrimal gland plays a crucial role in maintaining ocular surface integrity by secreting the aqueous layer of the tear film. Radiation therapy (RT) targeting intracranial, sinonasal, or orbital tumors often leads to incidental irradiation of the lacrimal glands. This exposure can result in reduced tear secretion, tear film instability, and the development of dry eye syndrome (DES), which significantly impairs patient quality of life. Several clinical-dosimetric studies have reported a dose–response relationship between lacrimal gland radiation dose and the incidence or severity of ocular toxicity. As advanced techniques such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) become widely applied, reducing lacrimal gland dose while ensuring adequate tumor coverage has become a clinical priority.

Keywords: Lacrimal gland; Radiotherapy; Dry eye syndrome; Ocular toxicity; Dosimetric analysis; Quality of life.

Introduction:

The lacrimal gland is the main source of the aqueous layer of the tear film, which is essential for ocular surface homeostasis. Damage or dysfunction of the lacrimal gland leads to instability of the tear film and the development of dry eye syndrome (DES), characterized by discomfort, photophobia, and potential corneal complications **(1).**

Radiotherapy is widely used for the treatment of intracranial and head-and-neck tumors. However, incidental irradiation of the lacrimal gland during whole-brain or periocular radiotherapy has been associated with dose-dependent ocular toxicity, particularly DES **(2).**

Several dosimetric analyses have shown that higher lacrimal gland doses are correlated with increased risk and severity of dry eye. Prospective studies in whole-brain radiotherapy have demonstrated a measurable rise in DES prevalence after treatment **(3, 4).**

Clinical reports on sinonasal and nasopharyngeal carcinoma patients indicate that sparing the lacrimal gland through advanced techniques such as intensity-modulated radiotherapy (IMRT) reduces the incidence of ocular toxicity **(5).**

Moreover, periocular irradiation has also been linked to meibomian gland dysfunction, which exacerbates tear film instability and contributes to long-term ocular surface morbidity **(6).**

Overall, minimizing lacrimal gland dose has become an important goal in radiotherapy planning, with ongoing prospective studies highlighting its significance in patient-reported outcomes and survivorship quality of life **(7).**

Lacrimal gland (LG) is considered an important risk organ in the pathway of radiation beam during radiotherapy of various tumors like head and neck cancers (HNC), orbital tumors and brain tumors.

Effect of radiotherapy depends on multiple factors:

- **Normal Tissue Toxicity:**

Normal tissue complications that occur during or after radiotherapy are caused by the death of critical target cells that are essential for structural and functional tissue integrity.

Complications arise from complex and dynamic processes such as oxidative stress, radiation-induced gene expression, and cellular signaling cascades, various modes of cell death (such as mitotic cell death, apoptosis, senescence, etc.) and compensatory proliferative responses are all involved. **(8)**

- **Tolerance Dose:**

The radiosensitivity of the different cells in a given tissue, the proliferative organization of the tissue (which determines whether the toxicity is early or late) are all important considerations in determining tolerance doses for different tissues.

The severity of the complication is determined by the radiosensitivity of the target cell whose death causes the complication, as well as the time- dose-fractionation schedule used. While the dose is typically expressed in Gy, particle therapy requires a corrective radiobiological factor to account for increased linear energy transfer (LET) and radiobiological effectiveness (RBE). **(9)**

- **Lacrimal gland dose constraints:**

$D_{max} < 40$ Gy **(10)**

$D_{mean} \leq 26$ Gy **(11)**

At doses greater than 40 Gy, a steeply increasing risk of dry eye syndrome has been reported, whereas irradiation of the lacrimal gland with doses greater than 57 Gy results in a 100% rate of atrophy and fibrosis of the lacrimal gland, with permanent loss of tear secretion, using twice-a-day fractionation (1.2 Gy twice daily) reduces the risk of these complications. **(11)**

- **Volume Effects:**

By analogy with electrical circuits, normal organs can be thought of as having "serial" or "parallel" structural organization. A serial organ is one in which an injury to any anatomic point in the structure results in severe functional loss, such as optic chiasma. Radiation injury to a portion of one of the parallel organs, such as the lacrimal gland, will generally only reduce its function by the proportion of the organ that is destroyed by mean of it will not cause a significant functional deficit unless the irradiated volume is large, resulting in dry-eye syndrome, which can lead to vision loss. **(8)**

- **Fractionation Sensitivity:**

Early and late-responding normal tissues and tumors respond differently to fractionation patterns.

Acute/early reactions are normal tissue damage that occurs weeks to months after radiation exposure. It may occur during therapy and persist after treatment is completed. Late reaction is tissue damage that occurs months or years after radiation exposure. Acute reactions, if mild, typically resolve on their own and are not permanent. Late reactions, on the other hand, develop gradually and become permanent. Late-reacting tissues are typically considered dose-limiting during radiotherapy. **(12)**

Dose fractionation effectively protects normal tissues. Some DNA radiation damage from the first fraction can be repaired before the second fraction if given enough time (6-24 hours, depending on tissue type).Different tissues have varying fractionation sensitivity, which is linked to their ability to repair DNA radiation damage. **(12)**

Early responding tissues have limited DNA repair capacity. Variations in fraction size have a moderate effect on the tolerance dose of early responding tissues (ranging from 1.5 to 4 Gy). **(12)**

Late-responding tissues have a high DNA repair capacity. Late responding tissues are highly sensitive to fractionation. However, the tolerance dose varies greatly based on the fraction size. **(12)**

The LQ model calculates the surviving fraction (SF) of clonogenic or stem cells as a function of radiation dose (D): $SF(D) = e^{-\alpha*D - \beta*D2}$.

This model's main parameters, α and β, represent the intrinsic radiosensitivity of irradiated cells. Higher α and β values indicate greater radiation sensitivity. The α/β ratio indicates a cell's sensitivity to fractionation. Higher α/β values indicate less sensitivity to fractionation's sparing effect. **(13)**

Lacrinal gland is considered a late responding tissue with low α/β ratio=3 **(14)** So we can spare its toxicity by reducing fraction size.

- **Precautions to be taken into consideration during radiotherapy:**

The golden role of radiotherapy is to "give the maximum, possible and lethal dose to the tumor while protecting the normal healthy tissue around"

It has been accepted that the human eyes are radiosensitive and radiovulnerable organ. **(10)**

It is now clear that adverse effects can occur at these levels even at low and/or chronic ionizing radiation doses. **(10)**

To reduce the incidence of DED in brain tumor patients receiving RT

- **Patient preparation:**

Referral of the patient to the ophthalmologist for examination of eye- dryness before starting radiotherapy and giving proper management if there is pre-existing dry eye.

- **Eye shielding and patient position:**

an adequate eye shielding block must be used, not only in patients whose field of radiation clearly includes the orbit, but also in patients whose field of radiation is near the orbit, proper patient positioning and patient immobilization during radiation delivery, will help reduce the incidence of radiation-induced toxicity. **(15)**

- **Proper lacrimal gland contouring and delineation:**

The lacrimal gland is situated superolateral to the globe. It consists of two parts: the larger orbital region and the smaller palpebral portion. The two parts cannot be distinguished on CT so the gland is contoured as one part. It is small, with a mean volume of approximately 0.680 cm3 in men and 0.662 cm3 in women. The average axial length of the lacrimal gland is 14.7-14.9 mm, with coronal lengths ranging from 20.7-20.9 mm and coronal widths of 3.6-3.8 mm2. **(16)**

The gland typically well appears with the administration of intravenous contrast, so performing the CT for simulation with intravenous contrast is recommended when the lacrimal gland is an important organ at risk. since the gland is small, it is recommended that CT slice intervals of 2mm or less. **(16)**

1) Begin by identifying the middle portion of the lacrimal gland, which is located inferior to the orbital rim between the eye and the bone. It will appear as a soft-tissue region that is slightly more dense than the rest of the eye.
2) The superior lateral corner of the orbit will be the most cranial, with a contour along the bone's edge. This volume will go between the lateral aspect of the eye and the bone.
3) Inferiorly, you will find the gland between the lateral orbital wall and the upper border of the lateral rectus muscle, but not at its insertion.
4) The anterior-most part of the gland fuses with the orbital septum.
5) Superomedially, the gland spreads to the lateral aspect of the superior rectus/levator palpebral superiosis complex.
6) It makes contact with the globe posteroinferiorly.
7) Cross-reference the contour with a coronal image. A normal gland has a crescentic shape on coronal cuts as it extends from the superomedial to the inferomedial aspects. **(16)**

Figure 1: lacrimal gland contouring and delineation (17)

- **Evaluation of OAR dose constraints:**

The evaluation of the calculated dose distribution is frequently based on dose volume histograms (DVHs), making sure that the lacrimal gland and other risk organs receives doses of radiation within their tolerance. **(18)**

- **Follow up the patient during radiotherapy:**

Weekly evaluation of radiotherapy toxicity in the form of dry eye and grades for early detection and proper management of any complications.

Case study:

Case (1): female patient 23 years old diagnosed with frontal low grade glioma underwent incomplete surgical resection then started adjuvant 3D- radiotherapy 54Gy / 1.8 fraction on Linear accelerator machine. Baseline evaluation of dry eye before starting Rth shows no dryness with SESoD less than 3 and TBUT > 10 sec, on follow up at 6th month after Rth dry eye evaluation shows decline in TBUT result Rt eye = 8 sec while left eye 5 sec , SESoD evaluation =2 (mild dryness).

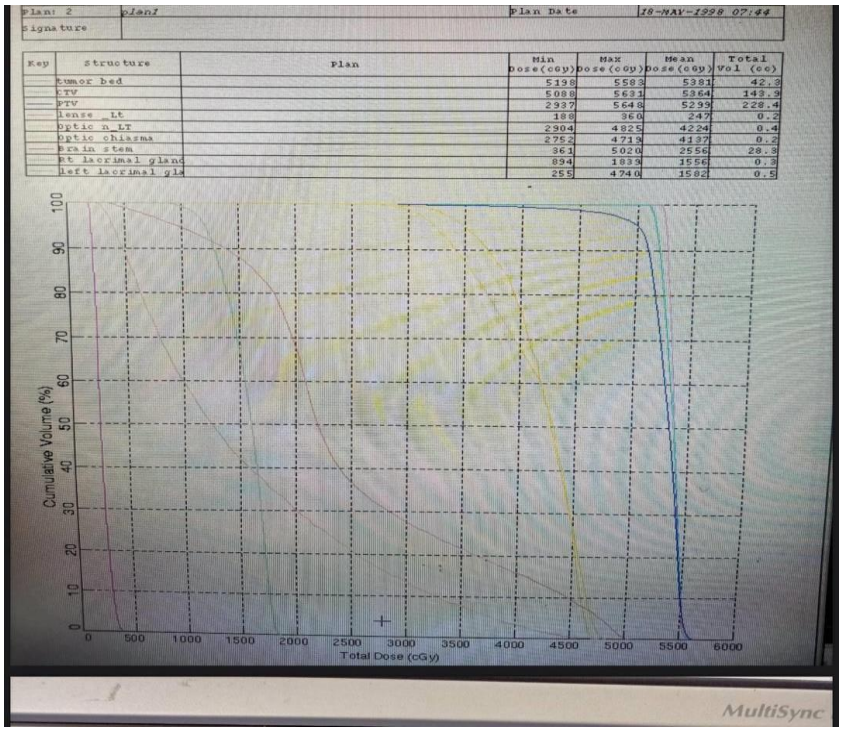

Figure 2: DVH parameters of patient's plan

Case (2): male patient 62 years old diagnosed with metastatic bladder cancer to brain received palliative whole cranial radiotherapy 3oo cGy

/10 fractions on cobalt 60 machine. Baseline evaluation of dry eye before starting Rth shows no dryness with SESoD less than 3 and TBUT >10 sec, on follow up at 6th month after Rth dry eye evaluation shows decline in TBUT result of Rt eye =5:10 sec and normal left eye TBUT=10sec , SESoD.

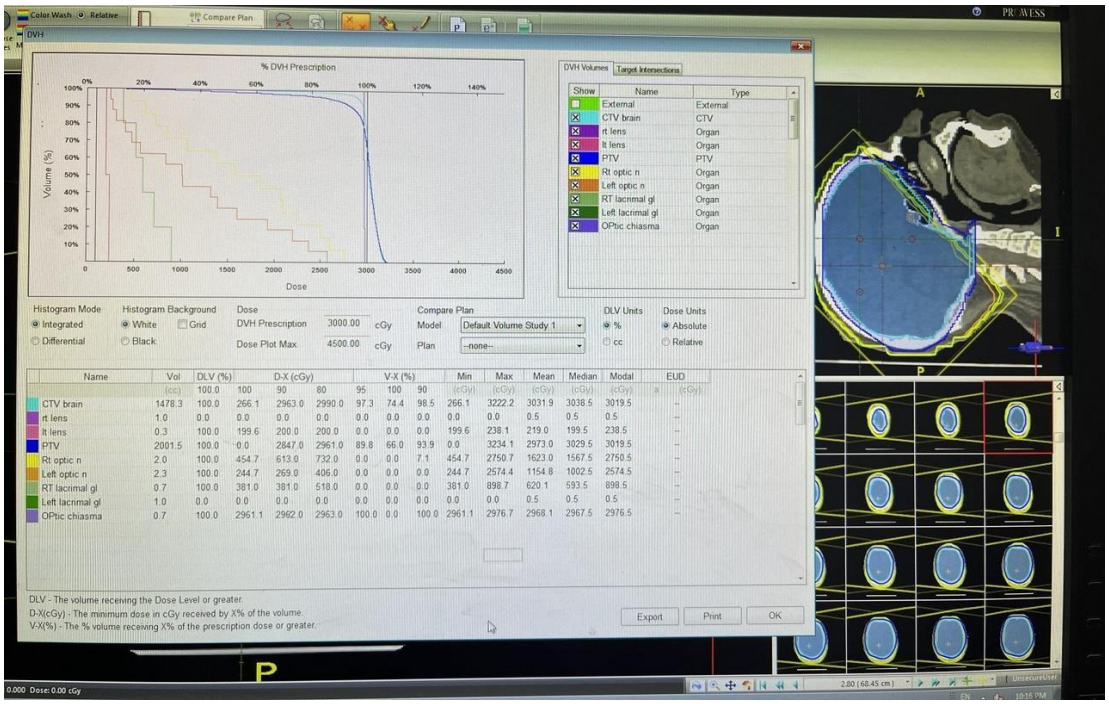

Figure 3: DVH parameters of patient's plan

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