### Title

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### Journal

British Journal of Radiology, 86(1032)

### ISSN

0007-1285



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### Publication Date

2013-12-01

### DOI

10.1259/bjr.20130459

Peer reviewed

BJR


Received: 27 July 2013 | Revised: 28 September 2013 | Accepted: 21 October 2013

doi: 10.1259/bjr.20130459

Cite this article as:
Batth SS, Sreeraman R, Dienes E, Beckett LA, Daly ME, Cui J, et al. Clinical-dosimetric relationship between lacrimal gland dose and ocular toxicity after intensity-modulated radiotherapy for sinonasal tumours. Br J Radiol 2013;86:20130459.

FULL PAPER

# Clinical-dosimetric relationship between lacrimal gland dose and ocular toxicity after intensity-modulated radiotherapy for sinonasal tumours

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Presented at the Multidisciplinary Head and Neck Cancer Symposium, 26–28 January 2012, Phoenix, AZ.

**Objective:** To characterise the relationship between lacrimal gland dose and ocular toxicity among patients treated by intensity-modulated radiotherapy (IMRT) for sinonasal tumours.
**Methods:** 40 patients with cancers involving the nasal cavity and paranasal sinuses were treated with IMRT to a median dose of 66.0 Gy. Toxicity was scored using the Radiation Therapy Oncology Group morbidity criteria based on conjunctivitis, corneal ulceration and keratitis. The paired lacrimal glands were contoured as organs at risk, and the mean dose, maximum dose, $V_{10}$, $V_{20}$ and $V_{30}$ were determined. Statistical analysis was performed using logistic regression and the Akaike information criterion (AIC).
**Results:** The maximum and mean dose to the ipsilateral lacrimal gland were 19.2 Gy (range, 1.4–75.4 Gy) and 14.5 Gy (range, 11.1–67.8 Gy), respectively. The mean $V_{10}$, $V_{20}$ and $V_{30}$ values were 50%, 25% and 17%, respectively. The incidence of acute and late Grade 3+ toxicities was 23% and 19%, respectively. Based on logistic regression and AIC, the maximum dose to the ipsilateral lacrimal gland was identified as a more significant predictor of acute toxicity (AIC, 53.89) and late toxicity (AIC, 32.94) than the mean dose (AIC, 56.13 and 33.83, respectively). The $V_{20}$ was identified as the most significant predictor of late toxicity (AIC, 26.81).
**Conclusion:** A dose–response relationship between maximum dose to the lacrimal gland and ocular toxicity was established. Our data suggesting a threshold relationship may be useful in establishing dosimetric guidelines for IMRT planning that may decrease the risk of acute and late lacrimal toxicities in the future.
**Advances in knowledge:** A threshold relationship between radiation dose to the lacrimal gland and ocular toxicity was demonstrated, which may aid in treatment planning and reducing the morbidity of radiotherapy for sinonasal tumours.

The majority of tear fluid is produced by the paired lacrimal glands, which are located in the superior temporal quadrants of the orbits. Each bilobed lacrimal gland is anatomically divided into the larger orbital and smaller palpebral parts, both of which contain excretory components consisting of ductal cells that mechanically assist in the secretion of tears on to the ocular surface by modifying the fluid secreted by acinar and myoepithelial cells [1]. The glands of Krause and Wolfring are smaller accessory lacrimal glands located in the superior fornix that secrete additional tear fluid. Functionally, the lacrimal gland is responsible for the secretion of fluid that continually moistens, lubricates and protects the surface of the eye.

An increasingly recognised complication of radiotherapy to the periorbital region is dry eye syndrome, defined by the International Dry Eye WorkShop as a "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" [2]. Although previous research has suggested a variable association between radiation dose to the lacrimal gland and incidence of dry eye syndrome [3–11], the exact nature of this dose–response relationship remains undetermined. This is particularly relevant given the ability of intensity-modulated radiotherapy (IMRT) to limit dose to normal structures designated as organs at risk (OARs). The aim of the present study was to characterise this relationship between various dosimetric parameters related to the lacrimal gland and ocular toxicity in patients treated with IMRT for sinonasal tumours.

## METHODS AND MATERIALS

### Patients

All relevant institutional review boards approved this study. Between January 2005 and August 2011, 40 consecutive patients with head and neck cancer with involvement of the nasal cavity or paranasal sinuses were treated with IMRT. The median age was 59 years (range, 11–89 years). Patient characteristics are described in Table 1. 14 patients underwent gross total tumour resection followed by postoperative radiotherapy; 26 patients were treated by primary radiotherapy. Axial imaging of the head and neck as a component of the initial evaluation was performed using CT and MRI. None of the patients had evidence of distant metastatic disease at diagnosis.

Table 1. Patient characteristics ($n$=40)

| Patient characteristics | No. of patients |
|---|---|
| Gender | |
| Male | 23 |
| Female | 17 |
| T-stage | |
| T1 | 1 |
| T2 | 9 |
| T3 | 4 |
| T4 | 20 |
| Other[a] | 6 |
| Histological type | |
| Squamous cell carcinoma | 20 |
| Adenocarcinoma | 4 |
| Melanoma | 4 |
| Non-Hodgkin lymphoma | 2 |
| Adenoid cystic carcinoma | 1 |
| Basal cell carcinoma | 1 |
| Esthesioneuroblastoma | 2 |
| Extramedullary plasmacytoma | 1 |
| Juvenile angiofibroma | 1 |
| Lymphoepithelial carcinoma | 1 |
| Merkel cell carcinoma | 1 |
| Mucoepidermoid carcinoma | 1 |
| Sarcoma | 1 |
| Primary site | |
| Nasopharynx | 12 |
| Nasal cavity | 10 |
| Maxillary sinus | 9 |
| Ethmoid sinus | 3 |
| Skin or soft tissue | 3 |
| Frontal sinus | 1 |
| Hard palate | 1 |
| Sphenoid sinus | 1 |

[a]Non-Hodgkin lymphoma, 2; esthesioneuroblastoma, 2; extramedullary plasmacytoma, 1, and melanoma, 1.

### Intensity-modulated radiotherapy technique

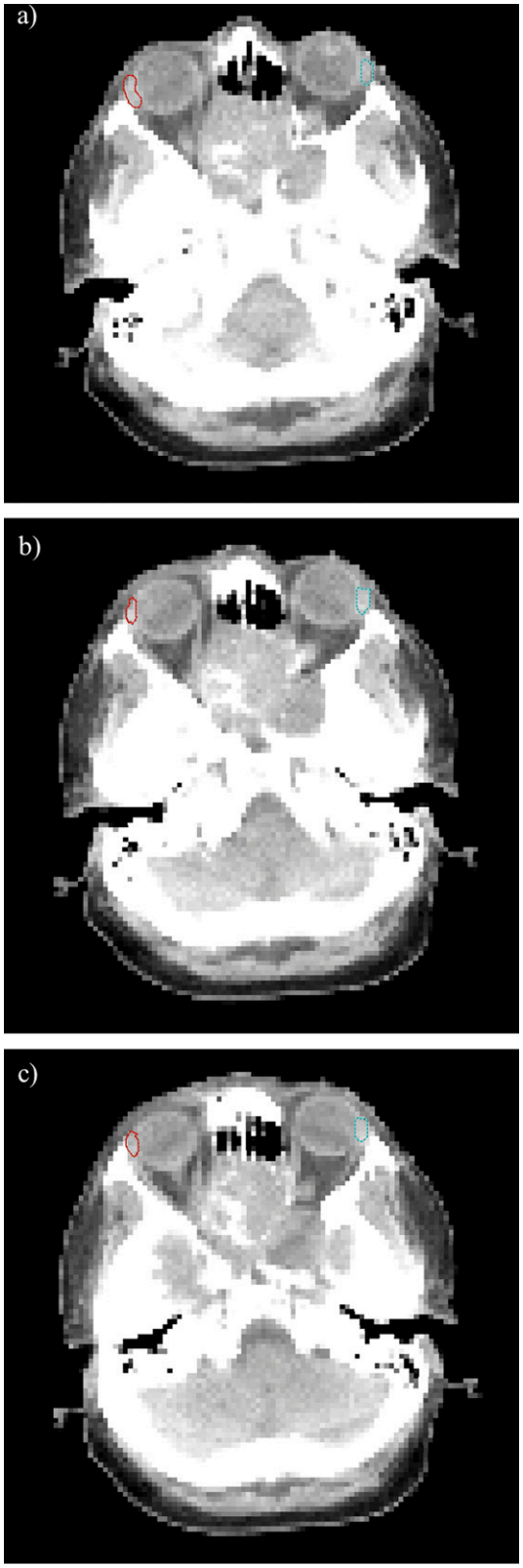
At simulation, the head, neck and shoulders were immobilised using a perforated thermoplastic mask with a Timo cushion mounted on carbon fibre board (Type-S™; MEDTEC®, Orange City, IA). Axial images with contiguous 3 mm slice thickness were obtained on a CT simulator (Picker PQ2000; Philips Medical Systems, Andover, MA) and transferred to a contouring workstation, where delineation of target and normal tissue structures was performed. Fusion with MRI was performed in all cases.

For patients treated by primary radiotherapy, the gross tumour volume (GTV) was specified as the gross extent of a tumour as demonstrated by imaging and physical examination. The clinical target volume (CTV) was the GTV plus a margin of 0.5–1 cm, to account for microscopic disease spread. For patients treated postoperatively, the CTV encompassed all areas at highest risk for disease recurrence, including the surgical bed and all clips. Elective neck irradiation was not routinely performed. The planning target volume (PTV) contained an automated 0.3–0.5 cm expansion of the CTV to account for patient set-up error. The median prescribed dose of 66.0 Gy (range, 30.6–70.0 Gy) was delivered to at least 95% of the PTV at a median dose of 2.0 Gy per fraction (range, 1.8–2.1 Gy). Radiation was delivered using the TomoTherapy® HI-ART® treatment planning system (Accuray, Inc., Sunnyvale, CA) with the following planning parameters: 2.5 cm jaw (field width in the longitudinal direction of couch); pitch, 0.3; and an initial modulation factor of 3.0. Planning with heterogeneity corrections was calculated using convolution/superposition-based dose calculation algorithm. The dose calculation grid size was 2 mm. The plans were normalised to achieve adequate target coverage without excessive dose inhomogeneity (dose prescription to 90–93% isodose lines).

The following ocular symptoms were noted at baseline: 9 (23%) with impaired visual acuity (including diplopia or visual obstruction), 4 (10%) with proptosis or orbital swelling, 3 (7.5%) with dry eye (burning, tearing or use of artificial tears), 3 (7.5%) with impaired ocular movement, 1 (2.5%) with epiphora, and 1 (2.5%) with Salzmann's nodular corneal degeneration. Because most patients with ocular symptoms had multiple complaints at baseline, a total of 30 patients were devoid of any symptoms at baseline. Dose to the contralateral lacrimal gland was analysed for the four patients who underwent ipsilateral orbital exenteration prior to IMRT. 9 (23%) patients received cisplatin chemotherapy concurrently during radiotherapy, which was typically administered for 3 cycles (100 mg $m^{-2}$ intravenously on Days 1, 22, and 43 of radiotherapy).

The paired lacrimal glands were defined as being located in the superior temporal quadrants of the orbits. The lacrimal gland was identified as an almond-shaped structure in the lacrimal fossa of the orbital plate of the frontal bone and retrospectively contoured as OARs on the treatment planning CT as shown in Figure 1. The lacrimal gland was contoured on the axial slice at

Figure 1. Representative contours of the paired lacrimal glands on axial CT imaging at (a) the level closest to the widest part of the lens, (b) mid-gland and (c) the superior aspect.




the level of the widest part of the lens. The width extended from the zygomatic bone to the globe of the eye and the length from the retina posteriorly to the lens anteriorly. This was repeated for the two axial slices located superiorly as well. The following dosimetric parameters were evaluated: mean dose, maximum dose, $V_{10}$, $V_{20}$, and $V_{30}$. The dose to the lacrimal gland was analysed only because the cornea was too thin and the Krause and Wolfring glands too small to be reliably identified by axial CT or MRI. Notably, no effort was made to spare the lacrimal glands during IMRT.

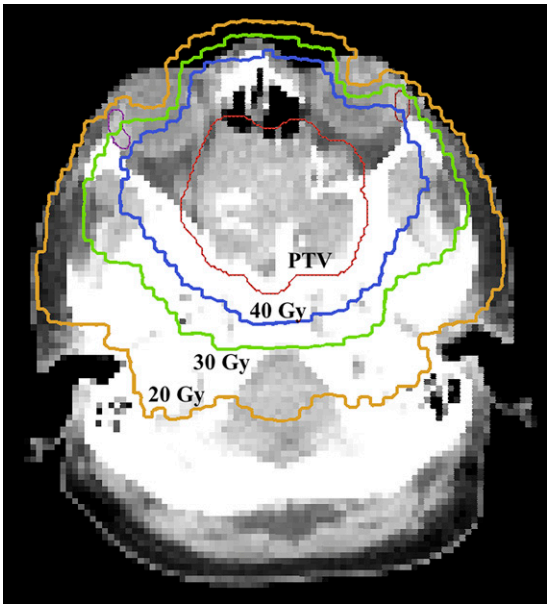
## Follow-up

Patients were asked to return for follow-up visits 2–3 weeks after the completion of radiation therapy and then every 2–3 months during the first year, every 4–6 months in the second and third years and annually thereafter. Follow-up was calculated from the first day of radiotherapy, and follow-up data were obtained from clinic notes from the Departments of Radiation Oncology, Ophthalmology and Otolaryngology, University of California, Davis, Sacramento, CA. Acute and late ocular toxicities were retrospectively graded according to the radiation toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) [12]. This rating was based on the degree of conjunctivitis, keratitis, corneal ulceration, retinopathy or detachment and visual loss.

## Statistical analysis

Ordinal logistic regression was undertaken to characterise the relationship between the ipsilateral lacrimal gland dose and acute toxicity. Logistic regression was then performed to characterise the effect of ipsilateral dose on late toxicity. The Akaike information criterion (AIC) was used to determine which measure of ipsilateral lacrimal gland dose, mean or maximum dose and

Figure 2. Isodose lines representing 20, 30, and 40 Gy for a patient who developed Grade 3 acute and late ocular toxicities after the treatment of a sphenoid sinus tumor.



which partial volume dose was the most useful predictor of toxicity. Logistic regression was applied to statistically model the relationship between toxicity and ipsilateral dose, age, gender and use of concurrent chemotherapy. A $p$-value of 0.05 was considered to indicate statistical significance.

The AIC measures the goodness of an estimated statistical model and selects a model from a set of candidate models. The chosen model is the one that is expected to minimise the difference between the model and the truth. Given a data set, several competing models may be ranked according to their corresponding AIC, and the one having the lowest AIC will be the best. In the general case, the AIC is defined as $\mathrm{AIC} = 2k\,(2\ln L)$, where $k$ is the number of parameters in the statistical model and $L$ is the maximised value of the likelihood function for the estimated model. An advantage of the AIC is that it penalises the number of parameters less strongly than does the Bayesian information criterion (BIC).

## RESULTS

The median follow-up among the 27 patients alive at the time of analysis was 28.5 months (range, 2.3–74 months). The incidence of acute Grades 1, 2, 3 and 4 ocular toxicities was 3 (8%), 5 (13%), 6 (15%) and 1 (3%) patient(s), respectively, among the entire patient population. 23 (58%) patients experienced no acute ocular symptoms. The incidence of late Grades 1, 2, and 3 ocular toxicities was 4 (10%), 3 (8%) and 5 (13%) patients, respectively. 23 patients (70%) reported no late ocular symptoms. Of the 30 patients without baseline ocular symptoms at presentation, 7 (23%) and 5 (18%) patients developed Grade 2 or higher acute and late ocular toxicities, respectively (2 of these 30 patients were not evaluable for late toxicity because of inadequate length of follow-up).

The mean lacrimal gland volume was 0.40 $cm^3$(range, 0.16–0.74 $cm^3$). The average maximum dose to the ipsilateral lacrimal gland was 19.2 Gy (range, 1.43–75.4 Gy). The average mean lacrimal dose was 14.5 Gy (range, 1.1–67.8 Gy). The mean lacrimal gland $V_{10}$, $V_{20}$, and $V_{30}$ were 50% (range, 0–100%), 25% (range, 0–100%) and 17% (range, 0–100%), respectively. Figure 2 illustrates the isodose lines for one of the patients.

No patient developed an acute toxicity grade >1 or late toxicity grade >0 with a maximum dose <15.1 Gy or mean dose <8.0 Gy. The mean and maximum dose of the lacrimal gland ranges with the corresponding incidences of Grade 2 or higher toxicity are listed in Tables 2 and 3, respectively.

Table 2. Lacrimal gland mean dose ranges and Grade 2 or higher ocular toxicity

| Lacrimal gland mean dose (Gy) | Incidence of Grade 2+ acute toxicity | Incidence of Grade 2+ late toxicity |
|---|---|---|
| 1.00–4.99 | 0% (0/17) | 0% (0/17) |
| 5.00–14.99 | 13% (1/8) | 13% (1/8) |
| 15.00–24.99 | 57% (4/7) | 29% (2/7) |
| 25.00–34.99 | 80% (4/5) | 60% (3/5) |
| ≥35.00 | 100% (3/3) | 100% (2/2) |

Table 3. Lacrimal gland maximum dose ranges and Grade 2 or higher ocular toxicity

| Lacrimal gland maximum dose (Gy) | Incidence of Grade 2+ acute toxicity | Incidence of Grade 2+ late toxicity |
|---|---|---|
| 1.00–9.99 | 0% (0/19) | 0% (0/19) |
| 10.00–19.99 | 20% (1/5) | 20% (1/5) |
| 20.00–29.99 | 43% (3/7) | 14% (1/7) |
| 30.00–39.99 | 80% (4/5) | 80% (4/5) |
| ≥40.00 | 100% (4/4) | 50% (2/4) |

Based on ordinal logistic regression, the maximum dose to the ipsilateral lacrimal gland (AIC, 53.89) emerged as a more useful predictor of acute toxicity than mean dose (AIC, 56.13). Figure 3a shows the relationship between maximum dose and the corresponding acute toxicity grades. The goodness-of-fit model derived from the AIC for acute toxicity indicated that for every 1.0 Gy increase in maximum dose, the probability of a higher toxicity grade increased by 23% ($p<0.001$). Also, $V_{20}$ (AIC, 65.07) was identified as a more useful predictor of acute toxicity than $V_{10}$ (AIC, 68.68) or $V_{30}$ (AIC, 76.31). For every 1% observed increase in $V_{20}$, the odds of a higher grade acute toxicity increased by 7% ($p<0.001$). Based on the AIC values, the maximum dose was identified as a more useful predictor of acute toxicity than any partial volume metric.

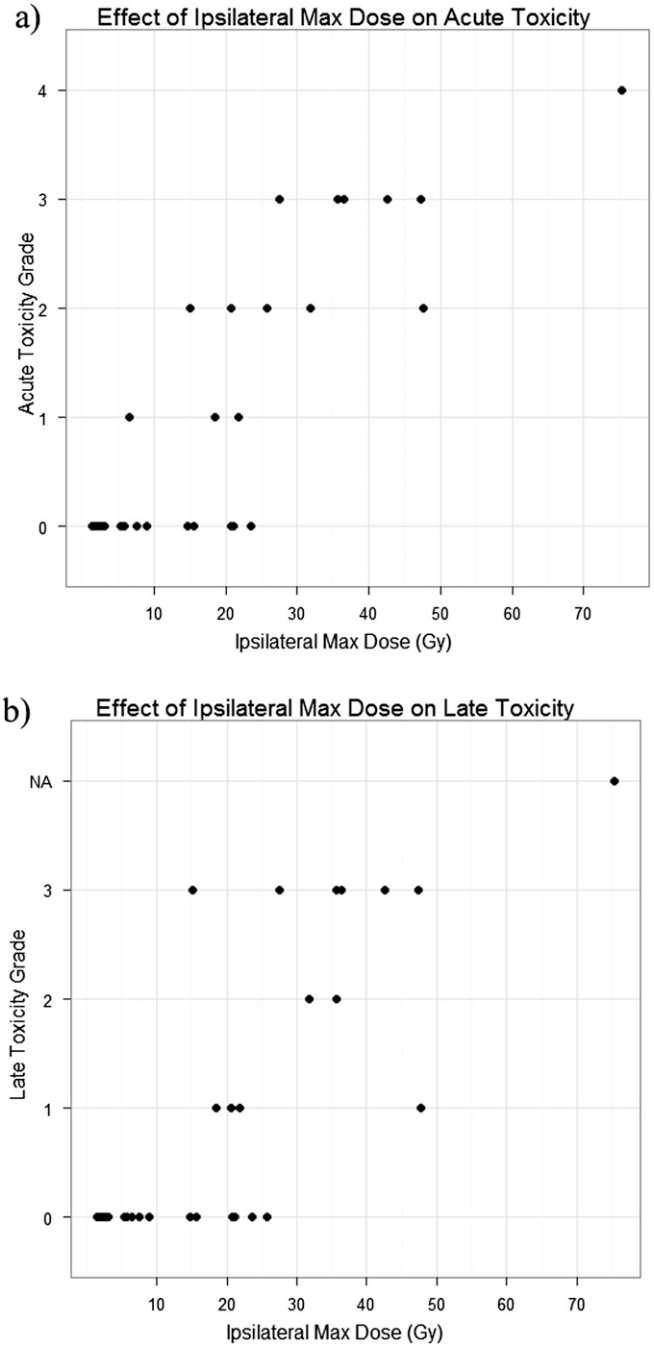
Similarly, maximum dose (AIC, 32.94) was a more useful predictor of late toxicity than mean dose (AIC, 33.83) based on logistic regression. Figure 3b shows the relationship between maximum dose and the corresponding late toxicity grades. The goodness-of-fit model derived from the AIC for late toxicity demonstrated that as the maximum dose increased by 1.0 Gy, the odds of developing Grade 1+ late complication increased by approximately 7% ($p=0.02$). Also, $V_{20}$ (AIC, 26.81) was identified as a more useful predictor of late toxicity than $V_{10}$ (AIC, 30.71) or $V_{30}$ (AIC, 32.48). For every 1% increase in $V_{20}$, the odds of developing Grade 1+ late toxicity increased by 4% ($p=0.002$). Based on the calculated AIC values, $V_{20}$ was thus identified as the most useful predictor of late toxicity. Figure 4 demonstrates the relationship between acute toxicity and subsequent late toxicity among the patient population.

Logistic regression demonstrated that age, gender and concurrent chemotherapy were not significant predictors of acute or late toxicity ($p>0.05$, for all). None of the nine patients treated with concurrent chemotherapy had an acute or late toxicity >Grade 1. However, Fisher's exact test demonstrated a significant association between the acute toxicity grade and whether the patient received concurrent chemotherapy ($p=0.02$).

## DISCUSSION

The results of the present study suggest a dose–response relationship for lacrimal gland toxicity among a cohort of patients treated by IMRT for sinonasal tumours. Specifically, we demonstrated that

Figure 3. Dot plots illustrating the relationship between maximum dose to the lacrimal gland and corresponding (a) acute and (b) late toxicity grades. Max, maximum.



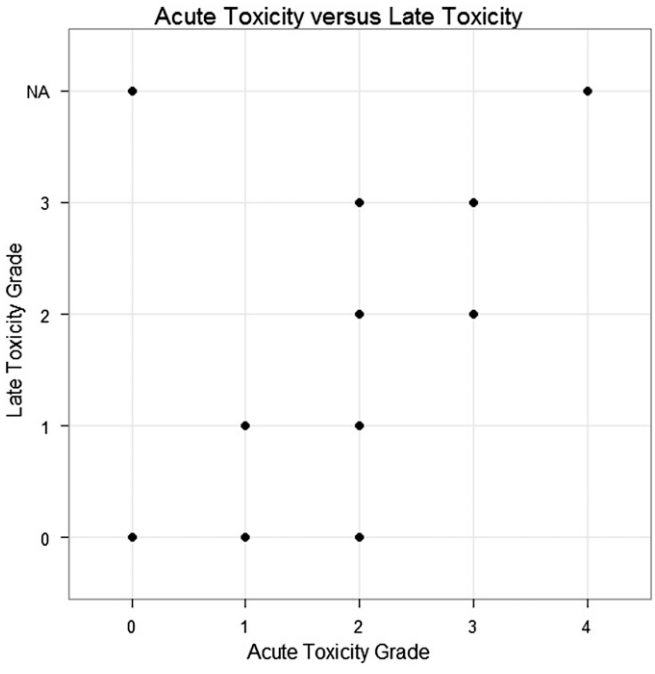

the maximum dose to the ipsilateral lacrimal gland is a more meaningful predictor of acute and late toxicities than mean dose and that $V_{20}$ is the most useful predictor of late toxicity. Notably, the observed incidence of higher acute and late toxicities significantly increased at a maximum dose of 30.0 Gy, suggesting a threshold with a dose–response relationship that was more prominent for acute toxicity.

The only observed case of acute Grade 4 toxicity was for a patient with skin cancer invading the maxillary sinus who had poor baseline visual acuity and a complicated ocular history of cataract extraction with intraocular lens, laser-treated retinal tear, branch retinal vein occlusion and untreated glaucoma of the affected eye. Following a mean dose of 67.8 Gy and maximum dose of 75.4 Gy to the lacrimal gland, the patient experienced severe conjunctivitis and periorbital oedema, and developed transient loss of vision requiring the use of artificial tears, Aquaphor (Beiersdorf Inc., Wilton, CA), betamethasone cream, ketorolac drops and erythromycin ointment.

The pathogenesis of radiation-induced lacrimal gland toxicity is unclear. Radiation-induced lacrimal gland damage has previously been demonstrated by histopathology. Cogan et al [13] originally reported a decrease in lacrimal gland size with increasing radiation dose ranging from 10.0 to 40.0 Gy in rabbits. Karp et al [14] studied human specimens from orbital exenterations and found persistent involutional atrophy of the lacrimal gland in a patient who had received 69.0 Gy with chronic keratoconjunctivitis, cataract, entropion and decreased tear fluid production on Schirmer's test. Studies in rhesus monkeys demonstrated that serous acinar cells of irradiated lacrimal glands undergo selective death after receiving a total dose of 2.5–20 Gy [15,16]. These serous acinar changes were found to far exceed those in the meibomian and zeisian glands, sweat glands of Moll and goblet cells. Such damage to the lacrimal gland likely affects tear film production and contributes functionally to dry eye syndrome.

Most studies reporting the incidence of ocular toxicity and dry eye syndrome after radiotherapy are limited by small patient numbers, older techniques and lack of CT planning, which thus makes it difficult to determine the actual delivered dose with certainty [3–6]. Nakissa et al [3] studied 30 patients treated using a Cobalt-60 source for paranasal sinus cancer and reported

Figure 4. Dot plot illustrating the relationship between acute toxicity and subsequent late toxicity.



5 patients who subsequently developed keratitis who had received a total dose of 34.0–75.0 Gy, 20 patients who developed conjunctivitis who had received 55.0–75.0 Gy and 1 patient who developed xerophthalmia causing visual impairment who had received 60.0 Gy . Morita and Kawabe [4] similarly observed that all patients receiving >53.0 Gy to the cornea and 58.0 Gy to the lens and retina developed panophthalmia with painful corneal ulceration, and 18 of 21 patients receiving 28.0–54.0 Gy experienced visual impairment. Notably, none of the patients receiving <28.0 Gy experienced such visual complications. Bessell et al [5] further explored lower dose ranges in patients with orbital or conjunctival lymphoma and found that only 5 patients developed late dry eye symptoms, 2 of 43 who received a total dose to the orbit of 30.0–39.0 Gy and 3 of 13 who received 40.0–49.0 Gy . Letschert et al [6] studied similar dose ranges in lymphoma patients and also demonstrated a threshold dose of approximately 40.0 Gy, with 0% of patients receiving <40.0 Gy developing sicca syndrome compared with 33–39% who received >40.0 Gy. Most of these earlier studies suggested a dose threshold of 30.0–40.0 Gy associated with a significant rise in orbital complications; however, they did not specifically analyse dose to the lacrimal gland or include patients treated using IMRT.

More limited data exist characterising the relationship between lacrimal gland dose and the incidence of ocular complications, including dry eye syndrome, using modern radiation techniques [7–11]. Jiang et al [7] observed a significant increase in visual impairment with lacrimal gland doses >56.0 Gy, with only a 17% incidence among patients receiving 42.0–55.0 Gy compared with >80% among patients receiving >56.0 Gy . Claus et al [8] reported that none of the 32 patients treated with IMRT to 40.0 Gy for sinonasal cancer developed dry eye syndrome. Parsons et al [10] from the University of Florida demonstrated a sigmoid dose–response curve with a 0% incidence of severe dry eye syndrome at lacrimal gland doses <30.0 Gy, which increased to a 100% incidence at doses >57.0 Gy . More recently, this data set was expanded by Bhandare et al [11] who showed a similar dose–response relationship for lacrimal gland dose and severe dry eye syndrome, with an incidence of 6% at 35.0–40.0 Gy, 50% at 45.0–50.0 Gy and 90% at 60.0–65.0 Gy. Most of the previous studies suggested that the rate of dry eye syndrome begins to increase at a lacrimal gland threshold dose of 30.0 Gy. These data are compatible with the present study, which demonstrates an increase in both acute and late ocular toxicities as the lacrimal gland mean dose rises >15.0–24.9 Gy and the maximum dose rises >20.0–29.9 Gy. Notably, our observed threshold doses may be more sensitive because the toxicity was evaluated according to the RTOG/EORTC morbidity criteria, which is broader than the strict definition of severe dry eye syndrome.

The clinical implications of this study need to be considered in context. High-grade ocular toxicity and severe dry eye syndrome are potentially debilitating complications associated with sinonasal malignancies treated by external beam radiotherapy and can detrimentally affect the quality of life in patients. The incidence of these complications has been shown to increase with higher doses to the lacrimal gland, especially above a threshold level, and can be significant. Dry eye syndrome can be chronically painful and lead to corneal vascularisation and opacification, keratoconjunctivitis sicca and, ultimately, visual loss [3,17,18]. Treatment is largely conservative, and options include topical lubricants, moist chamber goggles, cautery to retain tears, and tarsorrhaphy, all of which are inconvenient to the patient, often only providing partial relief, and can have negative cosmetic outcomes [18]. In extreme cases, enucleation is necessary, which is both cosmetically disfiguring and causes a significant loss of function [8].

The limitations of this study relate to its retrospective nature. Our conclusions could have been strengthened by standardisation of ophthalmological assessments (both pre- and post-treatment) to include evaluation of dry eye syndrome with Schirmer's testing. Along these lines, not all patients were formally evaluated by an ophthalmologist prior to beginning radiation, and the presence of pre-existing lacrimal symptoms and/or ophthalmological co-morbidities may have confounded results. Also, using the National Cancer Institute's Common Terminology Criteria for Adverse Events and Common Toxicity Criteria may have allowed for increased discrimination between different types of ocular toxicities [19]. Also, the pathogenesis of radiation-induced dry eye syndrome is almost certainly a multifactorial process attributed to damage from not only the lacrimal glands themselves but also to numerous other structures of the ocular apparatus. In this sense, a weakness of this study was that we were unable to account for the relative contributions of radiation-induced damage to the conjunctiva, minor lacrimal glands of the globe, uvea or cornea itself. Ongoing work at our institution is analysing how dose to the anterior chamber and cornea contribute to the symptoms from lacrimal gland toxicity.

Lastly, the lacrimal gland is a very small structure, and the potential effect of interobserver variability in delineating the lacrimal glands has the potential to skew our dosimetric finding, especially because 3 mm axial sections were used for contouring. However, this may have been mitigated by the fact that MRI fusion was routinely performed and that this OAR was reviewed independently by at least three physicians in all cases, typically with the assistance of a board-certified neuroradiologist. Along these lines, the uncertainty associated with calculation of grid size has been an issue, particularly with highly conformal IMRT planning systems.

Nonetheless, the present study adds to the limited data characterising the relationship between lacrimal gland dose and ocular toxicity, especially dry eye syndrome. Specifically, we found that the maximum dose to the lacrimal gland is a better predictor of acute and late ocular toxicities than mean dose, and $V_{20}$ is the best predictor of late toxicity. We also demonstrated that the incidence of severe acute and late toxicities seems to increase at a maximum dose >30.0 Gy. Based on our preliminary data, we have established IMRT planning guidelines aiming to limit the maximum and mean lacrimal gland dose to 30.0 Gy and 25.0 Gy, respectively, while prioritising adequate dose to the tumour. Prospective studies that include thorough ophthalmological assessment are necessary to validate these findings in the future.

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