



Not All Tears Imply Sadness: A Concise Review on the Impact of Modern Radiotherapy Techniques in Preventing Radiation Induced Xerophthalmia

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Short Comunication

The orbit is a complex region with respect to its architectural anatomy and physiological function. The tissues of the eye and orbit are trigeminal in embryonic origin and are composed of several discrete structures functioning in harmony [1]. Consequently, a diverse spectrum of neoplasms can arise within and around this relatively small region and damage to even a single normal structure leads to consequential adverse effects. While surgical intervention is often necessary to manage neoplasms arising in and around this region, Radio Therapy (RT) and chemotherapy are also indicated in selected cases [1]. Due to the small size and multitude of normal structures, a wide range of side-effects can occur as a result of intentional or unintentional irradiation of the orbit, which is further complicated by varying radiation sensitivity of each structure. The purpose of this article is to summarize the literature on radiation induced xerophthalmia (dry eye syndrome) and the impact of modern radiotherapy techniques to prevent this complication.

Dry Eye Syndrome (DES) is 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]. Damage to the lacrimal functional unit is implicated as the cause of DES [3,4]. It is comprised of the main lacrimal gland, accessory lacrimal glands (Krause & Wolfring), conjunctival goblet cells and epithelial cells of the cornea and conjunctiva. The overall physiological function of these structures is to produce the tear film, which is composed of aqueous, mucinous and lipid components, as shown in (Figure 1). Radiation induced damage to the lacrimal functional unit leads to tear film instability and reduced surface tension resulting in an evaporative dry state [4,5]. This results in xerophthalmia, secondary damage to cornea and conjunctiva, which if not addressed could also lead to loss of vision or ocular perforation (Figure 2) [4,5,6].

The probability of DES is dose-dependent and increases with increasing radiation dose (Table 1). This may be related to varying radiation sensitivities of the different subunits of the lacrimal functional unit. Atrophy of meibomian glands and conjunctival goblet cells occurs at doses less than 30 Gy, whereas the lacrimal gland atrophy occurs at higher doses [7,8]. Till date, researchers have attempted to correlate the dose received by the main lacrimal gland and DES but there is a growing appreciation of the multi-factorial process involved in the pathogenesis of DES attributable not just to the main lacrimal gland but also to numerous other structures of the ocular apparatus [6,7,8]. A few series have reported on rate of RT induced DES in patients treated for ocular lymphoma and these provide data on the lower end of the dose spectrum. In the series reported by Kennerdell et al, 54 patients were treated with RT dose between 24-25.5 Gray (Gy) utilizing conventional fractionation [9]. They reported acute and chronic DES in 50% and 33% of patients, respectively. Another series by Stafford et al composed of 48 patients, reported mild chronic DES in 25% of patients and severe chronic DES in a single patient. However, the range of RT dose prescribed was quite variable (15-53.8 Gy) [10]. Older series reported by Bessel et al and Letschert et al also report a threshold dose of 30-40 Gy beyond which the probability of DES rises significantly [11,12].

The incidence for severe DES (defined as sufficient enough to produce vision loss) resulting with higher doses used in the treatment of carcinomas in and around the orbit, in which the eye was included in the treatment field, was reported by Parsons et al [13]. 33 patients were treated with conventional radiation techniques and dose to the lacrimal gland was estimated retrospectively with

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Table 1: Summary of the literature on radiation induced dry eye syndrome. Abbreviations: DES, Dry Eye Syndrome; Gy, Gray; Fr, Fractions; FSRT, Fractionated Stereotactic Radiotherapy; IMRT, Intensity Modulated Radiotherapy; RT, Radiotherapy; SRS, Stereotactic Radio Surgery.

Author, Year (in order of publication date)	N	Patient population	RT dose delivered	Technique	Toxicity (Dry Eye Syndrome)
Bessel et al, 1987 [11]	115	Orbital Lymphoma	40 Gy in 20 Fr or 30 Gy in 15 Fr	Conventional	Late DES rate with 6-29 Gy: 0%. Late DES rate with 30-39 Gy: 4.5%. Late DES rate with 40-49 Gy: 23%
Letschert et al, 1991 [12]	30	Orbital Lymphoma	40 Gy in 20 Fr (20 of 30 patients). The other patients received doses ranging from 20 Gy in 10 Fr to 60 Gy in 30 Fr.	Conventional	DES rate with less than 40 Gy: 0%. DES rate with 40-43 Gy: 39%. DES rate with greater than 43 Gy: 33%
Parsons et al, 1994 [13]	33	Nasal cavity, paranasal sinuses, eye, orbit, nasopharynx, upper gum or skin tumors (in whom the eye was included within the treatment fields)	Variable (as per primary location and histology)	Conventional	Severe DES with less than 30 Gy: 0%. Severe DES with 30-40 Gy: 25%. Severe DES with 40-57 Gy: 50%. Severe DES with greater than 57 Gy: 100%
Jiang et al, 1994 [15]	219	Nasal and paranasal sinus tumors	Variable (as per primary location and histology)	Conventional	Visual impairment due to DES with 42-55 Gy (without chemotherapy): 17%. Visual impairment due to DES with 42-55 Gy (with chemotherapy) or 56-74.5 Gy (without chemotherapy): 81%. Visual impairment due to DES with 56-74.5 Gy (with chemotherapy): 88%
Kennerdell et al, 1999 [9]	54	Orbital Lymphoma	24 Gy in 12 Fr or 25.5 Gy in 17 Fr	Conventional	Acute: 50% Chronic: 33%
Stafford et al, 2001 [10]	48	Orbital Lymphoma	15-53.8 Gy (fractionation pattern NR)	Conventional, Orthovoltage X-rays, Electrons	Acute: 4% Mild chronic: 25% Severe chronic: 2%
Claus et al, 2002 [16]	32	Nasal and paranasal sinus tumors	60-70 Gy in 30-35 Fr	IMRT	Acute DES Grade 1-2: 100%. Acute DES Grade 3+: 0%. Late DES Grade 1-2: 35%. Late DES Grade 3+: 0%.
Daly et al, 2007 [17]	36	Nasal and paranasal sinus tumors	70 Gy in 33 Fr	IMRT	Acute DES: 0% Chronic DES: 2%
Duthoy et al, 2005 [18]	39	Nasal and paranasal sinus tumors	60-70 Gy in 30-35 Fr	IMRT	Acute DES grade 1-2: 100%. Acute DES grade 3+: 0%. Chronic DES grade 1-2: 12.8%. Chronic DES grade 3+: 5%
Sreeraman et al, 2009 [21]	18	Nasal and paranasal sinus tumors	60-70 Gy in 30-35 Fr	IMRT	Acute grade 2+ ocular toxicity (including DES): 33%. Late grade 2+ ocular toxicity (including DES): 17%
Muller et al, 2009 [24]	72	Uveal Melanoma	50 Gy in 5 Fr	FSRT	Late DES rate: 13.9%. Acute DES grade 1-2: 30%. Acute DES grade 3+: 0%. Late DES grade 1-2: 7.7%. Late DES grade 3+: 0%.
Dirix et al, 2010 [20]	84	Nasal and paranasal sinus tumors	60-66 Gy in 30-33 Fr.	IMRT	Acute DES grade 1-2: 37%. Acute DES grade 3+: 0%. Late DES grade 1-2: 11.5%. Late DES grade 3+: 0%.
Weigner et al, 2011 [19]	52	Nasal and paranasal sinus tumors	60-66 Gy in 30 Fr. SRS Boost for gross residual disease: 8 Gy in single Fr or 10 Gy in 2 Fr	IMRT	DES with less than 35 Gy: 0%. DES with 35-39.9 Gy: 6%. DES with 45-49.9 Gy: 50%. DES with 60-64.99 Gy: 90%. DES with greater than 65 Gy: 100%
Bhandare et al, 2012 [14]	78	Nasal cavity, paranasal sinuses, eye, orbit, nasopharynx, upper gum or skin tumors (in whom the eye was included within the treatment fields)	Variable (as per primary location and histology)	Conventional	Acute DES grade 1-2: 27%. Acute DES grade 3+: 1%. Late DES grade 1-2: 25.6%. Late DES grade 3+: 0%.
Duprez et al, 2012 [22]	130	Nasal and paranasal sinus tumors	70 Gy in 33 Fr	IMRT	Acute grade 1-2 ocular toxicity (including DES): 21%. Acute grade 3+ ocular toxicity (including DES): 18%. Late grade 1-2 ocular toxicity (including DES): 18%. Late grade 3+ ocular toxicity (including DES): 13%.
Batth et al, 2013 [23]	40	Nasal and paranasal sinus tumors	66 Gy in 33 Fr	IMRT	All grades DES incidence at 1 yr, 2 yr & 5 yr: 6%, 11.2 % & 23%, respectively. Severe DES incidence at 1 yr, 2 yr & 5 yr: 2.1%, 4.8% & 10.9%, respectively.
Thariat et al, 2017 [25]	853	Uveal Melanoma	52 Gy in 4 Fr	Proton Therapy	

appropriate dosimetric corrections. They reported that all patients receiving a dose greater than 57 Gy developed dry eye syndrome with vision loss, while 20% of patients receiving a dose less than 45 Gy developed this complication and the latency of developing dry eye was inversely proportional to the total dose received. They also generated a dose effect curve (incorporating data from three other authors who reported on dry eye syndrome), which revealed a 0% complication probability at doses less than 30 Gy, and 100% probability at doses greater than 57 Gy. In an update of the data from Parsons et al, Bhandare et al reported on 78 patients with paranasal sinus cancer and the incidence of severe DES with conventional radiation techniques [14]. The dose to lacrimal gland was estimated from conventional treatment plans using CT or CT-MR imaging studies for 54 patients and from phantom dosimetry for remaining patients treated earlier in the series. 51% (40/78) patients developed dry-eye syndrome leading to visual loss with the latency of developing dry eye syndrome being inversely related to dose per fraction and total dose in a continuous relationship. 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 60 Gy. Kaplan-Meier analysis showed a significant decrease in the freedom from DES from 93% for doses less than 45 Gy to 29% for doses between 45–59.9 Gy and 3% for doses greater than 60 Gy. Normal Tissue Complication Probability (NTCP) modeling showed a 5% incidence for a dose of 34 Gy and 10% incidence for a dose of 38 Gy. Another series reported by Jiang et al, evaluated 219 patients treated for nasal and paranasal cancers by conventional treatment techniques, with some patients receiving corneal and/or lacrimal shielding.[15] Dose to the corneal-lacrimal complex was estimated from CT scans or reconstructed from isodose curves on patient contours. The 2 year incidence of visual impairment due to damage to corneal-lacrimal complex was 17% when the lacrimal gland received 42-55 Gy and 81% when the lacrimal gland received 56-74.5 Gy. These studies laid the foundation for understanding RT induced damage to the lacrimal functional unit, but are not without limitations. The data primarily corresponds to the era of conventional radiotherapy, consequently the biggest limitation being that either the dose received by the whole orbit or point dose estimates were correlated with incidence of DES.

A few series have reported on the incidence of DES with Intensity Modulated Radiotherapy (IMRT) used in the management of nasal and paranasal carcinomas, without explicitly defining constraints for main lacrimal gland during treatment planning [16,17,18,19,20]. In these series the incidence of any grade of DES ranged from 2% to 35% and the rate of DES leading to vision loss was nil. Dirix et al reported on a retrospective comparison between IMRT and conventional RT technique for post-operative management of nasal cavity/paranasal sinus cancers [20]. They observed a significantly lower rate of DES of 7.7% with IMRT (compared to 31.6 % with conventional technique, $p=0.007$). While fortuitous lacrimal gland sparing may be considered a feature of IMRT due to rapid dose fall-off beyond the planning target volume, objective data on the dose-response relationship of the lacrimal gland is needed. Three studies have reported on incidence of DES after delineating the main lacrimal gland during treatment planning for IMRT. Sreeraman et al analyzed grade 2 or higher ocular toxicity (including DES) and dose volume histograms for lacrimal gland [21]. They reported a significant correlation between $V30\text{ Gy} > 50\%$ and risk for acute and late grade 2 or more ocular toxicity. Duprez et al have reported on incidence of DES after delineating and placing a constraint ($D50\% < 30\text{ Gy}$) on the main lacrimal gland [22].

They reported acute grade 2 or less DES in 27% of patients and late grade 2 or less DES in 25.6% of patients. Batth et al reported on the dose response relationship between dose to bilateral lacrimal glands and ocular toxicity [23]. A significant relationship was demonstrated between maximum dose (D_{max}) and acute ocular toxicity, with every 1 Gy increase in D_{max} increasing the probability for a higher toxicity grade by 23% ($p < 0.001$). Similarly, a significant relationship was demonstrated between $V20\text{ Gy}$ and late ocular toxicity, with every 1% increase in $V20\text{ Gy}$ increasing the probability of developing grade 1+ late toxicity by 4% ($p=0.002$).

At the higher end of the dose spectrum, a few series have explored the incidence of DES with hypofractionated radiotherapy for uveal melanomas. Muller et al reported on incidence of DES and abnormal schirmer test in patients with uveal melanoma treated with Fractionated Stereotactic Radiotherapy (FSRT) [24]. Lacrimal gland mean dose (D_{mean}) exceeding 8 Gy/fraction and median dose ($D50\%$) exceeding 10 Gy/fraction resulted in 50% probability of DES. Similarly, lacrimal gland mean dose (D_{mean}) exceeding 6 Gy/fraction and median dose ($D50\%$) exceeding 7 Gy/fraction resulted in 50% probability of abnormal schirmer test. Thariath et al have recently reported on the single largest series of patients with uveal melanoma treated with proton therapy [25]. The 5 year incidence of DES and severe DES was 23% and 10.9%, respectively. The median dose to lacrimal gland in patients with severe DES was 50.7 Gy.

While the data on dose-response relationship of ocular toxicity with lacrimal gland dose are valuable, they are susceptible to inter-observer variations in delineation of very small structures [26]. Additionally, due to its relatively superficial location and small size, calculated dose parameters are susceptible to various technical issues (e.g. differences in the dose calculation algorithm, CT slice thickness, pixel width, dose grid voxel width, dose-volume histogram calculation resolution and surface dose calculation inaccuracies) [27,28]. To counteract the issue of inter-observer a delineation guide on CT images is available [29]. (Figure 3) demonstrates delineation of lacrimal gland with the aid of MRI. (Figure 4) demonstrates the variation in delineating the main lacrimal gland on MRI versus CT and examples of lacrimal gland sparing achieved with Volumetric Modulated Arc Therapy (VMAT).

The authors recommend that D_{max} to orbit be limited to 40 Gy when delivering treatment with conventional techniques. For IMRT/VMAT treatment the authors recommend lacrimal gland delineation on CT (with MRI co-registration if available). If feasible, D_{max} should be limited to 30 Gy and emphasis should be placed to minimize $V20\text{ Gy}$ as much as possible. If D_{max} cannot be kept below 30 Gy, then planning should aim to limit D_{max} to 40 Gy and achieve $D50\% < 30\text{ Gy}$.

In conclusion, radiation induced damage to the lacrimal functional unit is an important complication of radiotherapy directed at or in proximity to the orbit, with the potential to reduce functional vision. Advances in modern radiotherapy have resulted in significantly lower rates of DES, requiring meticulous attention to detail in every step of the treatment planning process.

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