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Prospective assessment of patient-reported dry eye syndrome after whole brain radiation

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Abstract

Purpose—Dry eye is not typically considered a toxicity of whole brain radiation (WBRT). We analyzed dry eye syndrome as part of a prospective study of patient-reported outcomes after WBRT.

Methods—Patients receiving WBRT to 25–40 Gy were enrolled on a study with dry mouth as the primary endpoint and dry eye syndrome as a secondary endpoint. Patients received 3-dimensional WBRT using opposed lateral fields. Per standard practice, lacrimal glands were not prospectively delineated. Patients completed the Subjective Evaluation of Symptom of Dryness (SESoD, scored 0–4, higher representing worse dry eye symptoms) at baseline, immediately after WBRT (EndRT), one month (1M), three months (3M), and six months. Patients with baseline SESoD ≥ 3 (moderate dry eye) were excluded. The endpoints analyzed were ≥ 1 point and ≥ 2 point increase in SESoD score at 1M. Lacrimal glands were retrospectively delineated with fused MRI's.

Results—100 patients were enrolled, 70 were eligible for analysis, and 54 were evaluable at 1M. Median bilateral lacrimal V20Gy was 79%. At 1M, 17 patients (32%) had a ≥ 1 point increase in SESoD score, and 13 (24%) a ≥ 2 point increase. Lacrimal doses appeared to be associated with an increase in SESoD score of both ≥ 1 point (V10Gy: $p=0.042$, OR 1.09/Gy, V20Gy: $p=0.071$, OR 1.03/Gy) and ≥ 2 points (V10Gy: $p=0.038$, OR 1.15/Gy, V20Gy: $p=0.063$, OR 1.04/Gy). The proportion with increase in dry eye symptoms at 1M for lacrimal V20Gy ≥ 79% vs. <79% was

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Conflicts of Interest:

None

46% vs. 15%, respectively, for 1 point SESoD increase ($p=0.02$), and 36% vs. 12%, respectively, for 2 point SESoD increase ($p=0.056$).

Conclusions—Dry eye appears to be a relatively common, dose/volume-dependent acute toxicity of WBRT. Minimization of lacrimal gland dose may reduce this toxicity, and patients should be counseled regarding the existence of this potential side effect and treatments for dry eye.

Introduction

Whole brain radiation (WBRT) is a standard of care treatment for patients with widespread brain metastases. Despite increasing adoption of stereotactic radiosurgery (SRS), the majority of patients undergoing radiation for brain metastases still receive WBRT.^{1–3} Although the prognosis of patients who receive WBRT varies by clinical scenario, patients who require this therapy may have limited life expectancies. Thus, it is important to minimize both the acute and late toxicities of WBRT, which is often a palliative treatment.

Although neurocognitive effects, fatigue, and hair loss are known to be common side effects of WBRT,^{4–6} salivary toxicity is generally not acknowledged to occur. In a prospective observational study, we recently reported that patients receiving standard WBRT developed clinically significant xerostomia associated with parotid dose.⁷ In that study, we also sought to analyze the effects of radiation on another secretory organ: the lacrimal glands.

We herein report the results of our study's secondary analysis on dry eye syndrome. Though the lacrimal glands receive near-prescription doses during WBRT,^{8,9} there are no published articles to our knowledge that describe dry eye syndrome in this setting. We hypothesized that dry eye occurs after WBRT and is associated with lacrimal dose.

Methods

Study Design

Adult patients planned to receive WBRT to a dose of 25–40 Gy in 10–20 fractions, 2–3 Gy per fraction for any diagnosis were eligible for this IRB-approved prospective observational study ([ClinicalTrials.gov #NCT02682199](https://clinicaltrials.gov/ct2/show/study/NCT02682199)) with xerostomia as the primary endpoint and dry eye syndrome as a secondary endpoint. Patients were treated at one academic center and two affiliated community hospitals. Patients with a history of prior parotid radiation exposure or altered mental status were ineligible. Enrolled patients who did not complete WBRT, did not complete at least one post-baseline questionnaire, or had baseline xerostomia were excluded from prospective follow-up. The current report describes the study's secondary analysis of dry eye syndrome; the primary analysis of xerostomia and sample size calculations have been published previously.⁷

Treatment

All patients received CT simulations and 3D-conformal treatment with headcast immobilization. WBRT was delivered using standard “opposed lateral” fields with a lower border at the inferior aspect of the C1 or C2 vertebrae. The parotids and lacrimal glands were *not* prospectively delineated, although some providers delineated the lenses or globes

for treatment planning. For the latter cases, the radiation fields were often angled slightly in the axial plane to provide a non-divergent anterior field edge in the vicinity of the globes to reduce lens and conjunctival dose. Patients did not receive concurrent systemic therapy during WBRT.

Assessments

Patients completed study assessments at baseline, immediately after WBRT (EndRT), then at one month (1M), three months (3M), and six months (6M) post-WBRT. The primary analyzed endpoint for this paper was the Subjective Evaluation of Symptoms of Dryness (SESoD).^{10–12} The SESoD is a single question assessing the presence and significance of dry eye and is scored on a 5-point Likert scale:

0: None – I do not have dry eye.

1: Minimal – I seldom have dry eye and it does not make me uncomfortable.

2: Mild – I sometimes have dry eye that makes me uncomfortable, but it does not interfere with activities.

3: Moderate – I frequently have dry eye that makes me uncomfortable, and it sometimes interferes with activities.

4: Severe – I always have dry eye that is uncomfortable, and it usually interferes with activities.

Dosimetric Analysis

Patients were treated *without* prospective delineation of the lacrimal glands. The lacrimal glands were retrospectively delineated with the aid of fused brain MRI's. Individual lacrimal contours (left and right) were combined, and the lacrimal mean, and volume receiving 10 Gy (V10Gy), V15Gy, V20Gy, and V25Gy were recorded. Because these are collinear metrics, and the lowest standard WBRT dose is 20 Gy, we chose lacrimal V20Gy for additional analyses and presentation in the accompanying figures. We also analyzed bilateral globe dose to assess whether it could be used as a surrogate for lacrimal dose, given that it is challenging to identify and delineate the lacrimal glands using CT alone.¹³

Statistical Analysis

We chose 1M as the primary time point because we were interested in analyzing acute toxicity in a patient population at high risk of death and loss to follow-up. The dry eye endpoints analyzed were 1 point increase and 2 point increase in SESoD score. We excluded from analysis patients with a baseline SESoD score of 3 (moderate or worse dry eye). We used logistic regression to analyze the association between SESoD score increase with factors including lacrimal dose analyzed as a continuous variable. No multivariable analyses were performed due to the relatively low number of events and covariates associated with dry eye. Overall change in dry eye from baseline within the study population was analyzed using the Wilcoxon signed-rank test. Statistical analyses were performed using SPSS version 21 (Armonk, NY).

Results

100 patients were enrolled on the study between 2015 and 2018. Of these patients, 27 were prospectively excluded from analysis (18 due to baseline xerostomia, 4 who did not complete WBRT, and 5 who did not complete any follow-up questionnaires). 3 additional patients with baseline SESoD score ≥ 3 were retrospectively excluded, leaving 70 patients in the final analysis of dry eye syndrome. Patient characteristics for these 70 patients are shown in Table 1. Of these 70 patients, 54 (77%) completed the 1M primary assessment, 32 (46%) completed the 3M assessment, and 27 (39%) completed the 6M assessment. The most common fractionation scheme was 30 Gy in 10 fractions (59%). Median lacrimal mean dose was 25 Gy and median lacrimal V20Gy was 79%. Median follow-up was 7 months and median overall survival was 8 months.

Figure 1A shows the distribution of dry eye scores at each time point and Figure 1B shows the proportion of evaluable patients at each time point with an increase in dry eye symptoms compared to baseline. At baseline, SESoD score was 0 (no dry eye), 1 (minimal dry eye), and 2 (mild dry eye) in 61%, 20%, and 19%, respectively. There was a trend towards worse dry eye compared to baseline at 1M (1-sided $p=0.083$), but not 3M (1-sided $p=0.20$) or 6M (1-sided $p=0.54$).

By the end of WBRT, 13/66 patients (20%) already had an increase in dry eye symptoms. At the 1M primary time point, 17/54 patients (32%) had a ≥ 1 point increase in SESoD score, and 13/54 (24%) a ≥ 2 point increase. Analyses of factors associated with SESoD score increase of ≥ 1 and ≥ 2 at 1M are shown in Table 2. Lacrimal doses, specifically V10Gy and V15Gy, were significantly associated with 1M increase in SESoD score of both of ≥ 1 and ≥ 2 . There was also a trend toward an association between Lacrimal V20Gy and SESoD score increase. No other factors, including medications or globe doses, were associated with an increase in dry eye symptoms at 1M. At 3M, 11/32 patients (34%) had a ≥ 1 point increase in SESoD score from baseline, though only 2/32 patients (6%) had a ≥ 2 point increase. Analysis of factors associated with SESoD score increase of ≥ 1 at 3M is shown in Appendix Table 1. None of the examined covariates, including lacrimal dose, were associated with increase in SESoD score at 3M.

Figure 2 shows the proportion with a ≥ 1 point increase (Figure 2A) or ≥ 2 point increase (Figure 2B) in SESoD score at all time points for patients with lacrimal V20Gy above vs. below the median, 79%. For patients with lacrimal V20Gy $\geq 79\%$ vs. $<79\%$, the proportion with an increase in dry eye symptoms (by ≥ 1 point SESoD increase) at 1M was 46% vs. 15%, respectively ($p=0.02$). For a ≥ 2 point SESoD increase, the proportion was 36% vs. 12%, respectively ($p=0.056$). At 3M, the proportion with a ≥ 1 point SESoD increase for lacrimal V20Gy $\geq 79\%$ vs. $<79\%$ was 47% vs. 20%, respectively, but this was not statistically significant ($p=0.15$). Results were unchanged when using median V10Gy or V15Gy for these cutpoint analyses.

Figure 3A shows the SESoD score increase at 1M for each patient plotted against lacrimal V20Gy, with Figures 3B and 3C showing the fitted logistic regression for probability of SESoD score increase of ≥ 1 point and ≥ 2 points, respectively.

Discussion

Almost a third of patients receiving WBRT reported some degree of worsening of dry eye symptoms 1 month after radiation, with 32% reporting a 1 point increase and 24% reporting a 2 point increase in SesoD score. Dry eye symptoms were observed as early as the last day of WBRT, and appeared to be associated with lacrimal gland dose. The severity/incidence of dry eye appeared to be lower at 3 and 6 months, though analyses of later time points were underpowered. These findings support the exploration of methods to lower lacrimal doses to reduce this toxicity. Furthermore, patients should be counseled that dry eye may occur after WBRT and made aware of treatments for dry eye such as lubricating eye drops.¹⁴

Though SRS is used with increasing frequency, WBRT will likely continue be used for patients with widespread brain metastases and in centers without SRS capabilities.^{1–3,15} Accordingly, there has been great interest in the mitigation of WBRT toxicity. Most of the current research, however, pertains to preventing moderate-long term neurocognitive sequelae of WBRT.^{16,17} Although these efforts have the potential to improve outcomes, patients receiving WBRT in the SRS era are increasingly those with worse prognoses (eg, widespread, leptomeningeal, or bulky/symptomatic intracranial disease), many of whom may die before realizing a clinical benefit from neurocognitive protection. When WBRT is delivered with palliative intent, prevention of *acute* toxicity is equally important as protection from late toxicity.

In this and our previous report,⁷ we show that dry eye and dry mouth are relatively common acute toxicities of WBRT. Although dosimetric studies have shown that WBRT delivers substantial dose to the lacrimals and parotids,^{8,9,18–21} these organs are not typically considered at risk nor routinely delineated for avoidance during WBRT. One reason may simply be the lack of reports of these side effects. Other reasons include lack of routine follow-up after palliation, under-reporting of toxicity by patients approaching end of life, and perhaps misconceptions regarding the timing or dosimetric predictors of salivary toxicity. For instance, although most studies on radiation-induced xerostomia commonly use late endpoints, acute toxicity is often more severe (as it precedes later salivary recovery).²² Similarly, dry eye syndrome follows a similar trajectory, with acute toxicity followed by late recovery.^{23,24} These acute effects have meaningful impacts on quality of life in patients receiving palliative treatments.

Lacrimal and other ocular toxicities are well described after radiation for orbital lymphomas and head and neck cancer.^{24–29} The majority of published data analyze late (eg, years after radiation) occurrence of dry eye syndrome. In the setting of 1.8–2 Gy/fraction treatment, the risk of severe late toxicity appears low with lacrimal doses of <30–40 Gy. For instance, Bhandare et al reported that the risk of severe, persistent dry eye syndrome in 78 patients exposed to orbital radiation for head and neck cancer was 6%, 50%, and 90% for lacrimal doses of 35–40 Gy, 45–50 Gy, and 60–65 Gy, respectively.²⁵ In patients receiving lower total doses (eg, 24–30 Gy) for orbital lymphoma, symptoms are often mild. For example, in a series of 54 patients treated to 24–25.5 Gy, 50% reported mild acute symptoms, with 33%

reporting mild late symptoms.²⁴ Consistent with the head and neck data, other lymphoma series report an increasing risk of severe late complications with doses >35 Gy.^{27–29}

However, the published lacrimal dose limits may not apply to *acute* toxicity, which is often of equal importance for patients receiving WBRT. Given that radiation-induced secretory dysfunction manifests with an acute “peak” in symptoms that improve over time,²² the doses required to cause significant acute toxicity are likely lower than published constraints that are based on later endpoints. Patients receiving WBRT in our study reported dry eye as early as their final day of radiation. This is consistent with both clinical,^{22,26} and animal studies, where apoptosis of serous acinar cells has been shown to occur as early as 24–48 hours after a single dose of radiation.^{23,30,31}

Further, dose limits for secretory organs must also consider that a comparable dose delivered during WBRT is typically both accelerated and hypofractionated (eg, 2.5–4 Gy/fraction, delivered in 5–10 days) compared to standard 1.8–2 Gy/fraction treatment. Take for example a report of 72 patients treated with SBRT (50 Gy in 5 fractions) for uveal melanoma, where a mean lacrimal dose of 40 Gy (8 Gy/fraction) was associated with a 50% risk of late dry eye syndrome.³² This is substantially higher than the 6% risk reported for comparable mean lacrimal doses of 35–40 Gy in the Bhandare et al series utilizing conventional fractionation,²⁵ and supports the intuitive notion that secretory organs may be more sensitive to accelerated/hypofractionated treatments such as WBRT. Thus, it is likely that lacrimal dose tolerance for WBRT is lower than in other contexts.

We were only able to find one other study on lacrimal toxicity after WBRT. A 2014 abstract from Avkshtol et al. analyzed 40 patients receiving WBRT to a total dose 25 Gy. Acute grade 1–2 ocular toxicity occurred in 15% of patients. Ocular toxicity was associated with lacrimal gland dose, and occurred in 36% vs. 4% of patients with mean lacrimal dose >30.6 Gy vs. <30.6 Gy, respectively.⁹ Although it does not appear that this study was published in final form, its results are consistent with the findings of our prospective study.

Standard WBRT techniques have not changed appreciably for decades, and the routine practice of designing radiation fields to encompass the upper cervical vertebrae and the cribriform plate results in dose to the parotid and lacrimal glands, respectively.^{8,18–21} Figure 4A shows the radiation fields used to treat a study patient who developed persistent dry eye symptoms. In Figure 4B, the radiation fields were re-designed to spare the lacrimal glands. Given the small size of the glands, small variations in field design can have large impacts on lacrimal dose. In addition, dose to the globes was not associated with dry eye, suggesting that the lacrimals themselves must be spared to prevent symptoms. However, avoidance of the lacrimals may result decreased radiation coverage of the brain above the cribriform plate. The risk of lacrimal toxicity must therefore be weighed against the risk of a marginal miss above the cribriform plate, especially for those with gross disease near this location. Nonetheless, the adoption of SRS for increasing numbers of lesions and interest in hippocampal-sparing techniques supports the prioritization of quality of life over full elective brain coverage in most cases.

Our study has several limitations. First, many patients were ineligible for analysis after prospective exclusion or lost to follow-up due to death or other causes, which may confound analyses of toxicity. Second, other comorbid conditions or medications could influence outcomes; for instance longitudinal data were not available regarding usage of anticholinergic or other medications after WBRT, and we were unable to account for usage of lubricating eye drops. Third, the SESoD study instrument is a single question with five possible responses that has not been validated in cancer patients. We also did not objectively measure toxicity and the results may be susceptible to “open-label” bias from subjective patient reports. However, we attempted to measure severity by reporting two different levels of symptom worsening (1 point and 2 point increase in SESoD score). Furthermore, the SESoD score has been shown to correlate well with longer questionnaires despite its simplicity.^{10–12} Fourth, the lacrimal glands are small and difficult to delineate on CT. However, we minimized uncertainty by using MRI to assist in lacrimal delineation for all patients. Fifth, our analysis was underpowered to analyze toxicity at later time points, which may be of greater importance for patients receiving WBRT with better prognoses, such as those with hormone-positive breast cancer or EGFR/ALK-mutated lung adenocarcinoma. Finally, our analysis did not consider radiation effects on minor salivary glands in the eyelid and/or the conjunctiva which may also contribute to dry eye symptoms. Nevertheless, lacrimal irradiation appears to be the dominant determinant of dry eye symptoms in other settings.^{25,26}

In conclusion, dry eye appears to be an acute toxicity of WBRT associated with lacrimal dose. Unlike dry mouth, which is notoriously difficult to treat, a solution for this problem could be as simple as counseling patients regarding the risk of this toxicity and recommendation of lubricating eye drops.¹⁴ Clinicians could also consider methods to minimize lacrimal dose. These results complement ongoing efforts to identify and minimize other types of toxicity associated with WBRT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(A) Distribution of dry eye scores at baseline and each time point amongst evaluable patients. (B) Proportion of evaluable patients with an increase in dry eye score from baseline at each time point.

Figure 2. Proportion of patients with (A) 1 point increase and (B) 2 point increase in dry eye score (SESoD score from baseline, divided by lacrimal V20Gy the median 79% (solid lines, circles), or V20Gy $< 79\%$ (dashed lines, squares).

Figure 3.

(A) SESoD score increase at 1 month, plotted against parotid V20Gy. (B) Logistic regression probability of a ≥ 1 point SESoD score increase at 1M. (C) Logistic regression probability of a ≥ 2 point SESoD score increase at 1M. Note: Dashed lines indicate the 95% confidence interval.

Figure 4.

(A) WBRT fields for an enrolled patient who received 35 Gy in 14 fractions and developed significant dry eye syndrome at 1 month that persisted to the final 6 month time point. The lacrimal glands were *not* prospectively delineated and received a V20Gy of 100%. (B) Alternative plan with fields adjusted to reduce lacrimal dose, resulting in a lacrimal V20Gy of only 17%. With lacrimal sparing, there may be underdosing of the brain overlying the cribriform

plate. Nonetheless, the volume of brain covered by 95% of prescription dose was still 99.77% for the lacrimal-sparing replan, vs. 99.99% for the original fields.

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Table 1.**Patient and Treatment Characteristics (n = 70)**

Patient Characteristics		
Age (med., range)	61	(23 – 88)
Diagnosis		
Breast cancer	11	16 %
Lung cancer	48	69 %
Melanoma	5	7 %
Other	6	9 %
ECOG PS		
0	21	30 %
1	32	46 %
2	13	19 %
3	4	6 %
Baseline Steroid Use	41	59 %
Baseline Narcotic Use	31	44 %
Baseline Anticholinergic Use	30	43 %
Post-RT Chemo Before 1 Month	35	50 %
Number Completing Study Assessments		
Baseline	70	100 %
EndRT	66	94 %
1 month post-RT	54	77 %
3 months post-RT	32	46 %
6 months post-RT	27	39 %
Treatment Characteristics		
Fractionation Scheme		
2.5 Gy x 10 = 25 Gy	7	10 %
3 Gy x 10 = 30 Gy	41	59 %
2 Gy x 15 = 30 Gy	1	1 %
2.5 Gy x 14 = 35 Gy	19	27 %
2 Gy x 20 = 40 Gy	2	3 %
Lacrima Mean (med., range)	25 Gy	(10 – 40 Gy)
Lacrima V10Gy (med., range)	94 %	(40 – 100 %)
Lacrima V15Gy (med., range)	87 %	(25 – 100 %)
Lacrima V20Gy (med., range)	79 %	(11 – 100 %)
Lacrima V25Gy (med., range)	67 %	(0 – 100 %)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; RT, radiation; Gy, gray; VxGy, percentage of organ receiving “x” Gy.

Table 2.

Univariable Analyses of Factors Associated With Increase in Dry Eye (SESoD) Score at 1 Month

Covariate	1 Point Increase		2 Point Increase	
	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)
Age (years)	0.56	1.02 (0.96 – 1.08)	0.65	0.99 (0.93 – 1.05)
ECOG PS	0.87	0.94 (0.45 – 1.98)	0.74	0.87 (0.38 – 1.98)
Baseline Steroid Use	0.30	0.54 (0.17 – 1.73)	0.35	0.55 (0.16 – 1.93)
Baseline Narcotic Use	0.65	1.30 (0.41 – 4.15)	0.35	1.82 (0.52 – 6.41)
Baseline Anticholinergic Use	0.46	0.64 (0.20 – 2.10)	0.73	0.80 (0.22 – 2.86)
Post-RT Chemo Before 1M	0.29	0.53 (0.17 – 1.71)	0.27	0.49 (0.14 – 1.75)
Prescription Dose >30 Gy	0.99	1.01 (0.30 – 3.35)	0.78	1.21 (0.33 – 4.38)
Globe Mean (Gy)	0.62	0.97 (0.86 – 1.10)	0.69	0.97 (0.85 – 1.11)
Globe V20Gy (%)	0.67	0.99 (0.95 – 1.03)	0.78	0.99 (0.95 – 1.04)
Lacrimal Mean (Gy)	0.25	1.06 (0.96 – 1.17)	0.20	1.07 (0.96 – 1.19)
Lacrimal V10Gy (%)	0.042	1.09 (1.003 – 1.19)	0.038	1.15 (1.008 – 1.32)
Lacrimal V15Gy (%)	0.046	1.05 (1.001 – 1.10)	0.048	1.06 (1.001 – 1.13)
Lacrimal V20Gy (%)	0.071	1.03 (0.997 – 1.07)	0.063	1.04 (0.998 – 1.08)
Lacrimal V25Gy (%)	0.14	1.02 (0.993 – 1.05)	0.10	1.03 (0.995 – 1.06)

Abbreviations: SESoD, Subjective Evaluation of Symptom of Dryness; OR, odds ratio; ECOG PS, Eastern Cooperative Oncology Group Performance Status; RT, radiation; VxGy, percentage of organ receiving “x” Gy. Note: Dry eye (SESoD) is scored on a 5-point Likert scale ranging from “none” to “severe.”