Published in final edited form as:

Radiother Oncol. 2018 January ; 126(1): 100–106. doi:10.1016/j.radonc.2017.08.008.

Brainstem dose is associated with patient-reported acute fatigue in head and neck cancer radiation therapy

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Abstract

Background and purpose—Radiation (RT) dose to the central nervous system (CNS) has been implicated as a contributor to treatment-related fatigue in head and neck cancer (HNC) patients undergoing radiation therapy (RT). This study evaluates the association of RT dose to CNS structures with patient-reported (PRO) fatigue scores in a population of HNC patients.

Materials and methods—At pre-RT (baseline), 6th week of RT, and 1-month post-RT time points, Multidimensional Fatigue Inventory (MFI-20) scores were prospectively obtained from 124 patients undergoing definitive treatment for HNC. Medulla, pons, midbrain, total brainstem, cerebellum, posterior fossa, and pituitary dosimetry were evaluated using summary statistics and dose-volume histograms, and associations with MFI-20 scores were analyzed.

Results—Maximum dose (Dmax) to the brainstem and medulla was significantly associated with MFI-20 scores at 6th week of RT and 1-month post-RT time points, after controlling for baseline scores ($p < 0.05$). Each 1 Gy increase in medulla Dmax resulted in an increase in total MFI-20 score over baseline of 0.30 ($p = 0.026$), and 0.25 ($p = 0.037$), at the 6th week of RT and 1-month post-RT, respectively. Each 1 Gy increase in brainstem Dmax resulted in an increase in total MFI-20 score over baseline of 0.30 ($p = 0.027$), and 0.25 ($p = 0.037$) at the 6th week of RT, 1-month post-RT, respectively. Statistically significant associations were not found between dosimetry for the other CNS structures and MFI-20 scores.

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Conflict of interest statement: All authors certify that they have no financial, professional, or ethical conflicts of interest to declare.

Appendix A. Supplementary data: Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2017.08.008>.

Conclusions—In this analysis of PRO fatigue scores from a population of patients undergoing definitive RT for HNC, maximum dose to the brainstem and medulla was associated with a significantly increased risk of acute patient fatigue.

Keywords

Head and neck cancer; Fatigue; Radiation therapy; Quality of life; Brain dose

Intensity modulated radiation therapy (IMRT) has become the standard of care in head and neck cancer (HNC) due to the increased ability to spare critical normal tissues. The PARSPORT trial, however, noted increased fatigue in the patients who had parotid-sparing IMRT—presumed to be due to a shift in dose distribution [1]. A subsequent dosimetric analysis of the trial was conducted to investigate this rare instance in which a side-effect was not improved with IMRT, and it found that higher doses were delivered to the posterior fossa, brainstem, and cerebellum in the patients who reported worse acute fatigue [2]. These authors later analyzed the evolution of fatigue levels in a series of patients undergoing IMRT for nasopharyngeal cancer and found correlation between fatigue and increased doses to the basal ganglia, pituitary, and cerebellum; they suggest disruption of the pituitary axis and activating pathways associating the basal ganglia, cerebellum, and higher cortical centers as possible contributors to RT-induced fatigue [3]. These suggestions connecting central nervous system (CNS) structure damage to fatigue have correlates in studies using functional brain imaging to analyze fatigue in multiple sclerosis, depression and chronic fatigue syndrome [4–13].

Fatigue is one of the most common quality of life (QoL) effects experienced during RT for HNC, and affects virtually all patients [14–19]. QoL, besides being a concern in its own right, has been demonstrated to contribute to improved disease control outcomes in HNC [20,21]. It has been recognized that physician assessments are suboptimal for assessing QoL in cancer therapy; patient reported outcomes (PRO) are a superior means of evaluating treatment-related toxicities compared to physician assessments—including in HNC [16,22–28]. To our knowledge there has been no study to prospectively describe the relationship between patient-reported fatigue and CNS structure dose. Here, using a PRO metric, we investigate the presence of such a relationship in a series of patients undergoing definitive RT for HNC.

Materials and methods

Patient characteristics

This study was conducted after approval from our institutional review board. Patients included were all enrolled in the Department of Radiation Oncology at either Winship Cancer Institute of Emory University or Winship at Emory University Hospital Midtown. Disease was staged per the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th Edition [29]. Patients enrolled in this study had histological proof of locoregionally confined squamous cell carcinoma of the head and neck (T1-4, N0-3). Patients with simultaneous primaries or metastatic disease were excluded. Patients who were

disease-free for less than three years from a previous invasive malignancy were also excluded.

Patients filled out questionnaires at pre-RT, 6th week of RT and 1-month post-RT time points. The primary questionnaire assessing fatigue was the Multidimensional Fatigue Inventory (MFI-20). The MFI-20 has been established as a reliable metric in patients with numerous diseases, including specifically those with cancer and receiving RT [30,31]. The MFI-20 is a 20-item self-report questionnaire that consists of five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity [31]. Each dimension includes the sum of four items that are each rated on a 1- to 5-point scale. The total score is calculated as the sum of the five dimensions, with scores ranging from 20 to 100. The MFI-20, as a PRO metric, was used on-study as the primary outcome measure for fatigue. The study protocol did not dictate treatment paradigms, and patients were treated per our typical institutional practice for each clinical scenario. A portion of patients was treated in the post-operative setting, a portion was treated with definitive radiation alone to intact disease, and a portion was treated with concurrent chemoRT.

Treatment characteristics

All patients were treated with definitive intent. After immobilization in custom-made thermoplastic head, neck, and shoulders mask, all patients underwent computed tomography (CT) simulation, followed by treatment planning using the Eclipse treatment planning software. All but two patients then received highly conformal treatment via IMRT or Volumetric Modulated Arc Therapy (VMAT); the remaining two patients were treated with opposed laterals for early-stage glottic lesions.

CNS structure delineation and dosimetry

The medulla, pons, and midbrain, total brainstem, cerebellum, posterior fossa and pituitary were retrospectively delineated as separate structures on each patient's treatment planning scan. The brainstem structure was a union of the medulla, pons, and midbrain structures. The posterior fossa structure was a union of the medulla, pons, and cerebellum structures. For consistency, contours were delineated using a uniform methodology by the same radiation oncologist (MJF). Mean dose (Dmean), maximum dose (Dmax), and near maximum dose (D2) were recorded. D2 was recorded because the ICRU 83 has recommended D2 (the highest contiguous dose received to 2% of structure volume) as a preferred metric for assessing maximum dose received by a structure [32].

Statistical analysis

Descriptive statistics were generated for patient demographics, dosimetry variables, and fatigue variables. Several studies suggest treatment-related fatigue peaks not during the RT course but in the several weeks following its completion [18,33]. Thus the time points focused upon in this analysis were pre-RT (as a baseline metric), 6th week of RT, and 1-month post-RT. Additionally, a combined—or fatigue at any acute time point—score was created for each patient, which was taken as the highest value of either the patient's 6th week of RT score or 1-month post-RT score. Using multivariable linear regression (with 95% confidence intervals) and handling MFI-20 scores as a continuous variable, total fatigue

(MFI-20 score) at 6th week of RT, 1-month post-RT, and combined time points was modeled as a function of each CNS dosimetry variable, while controlling for baseline fatigue. To control for baseline fatigue, pre-RT scores were subtracted from 6th week of RT, 1-month post-RT scores, and combined scores, respectively, during analysis. As medulla Dmax and D2, and brainstem Dmax and D2 were found to be statistically associated with total MFI-20 score, we then performed further analysis of these dosimetry variables by breakdown of the MFI-20 score into each of its five dimensions. We modeled general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity scores with medulla Dmax, medulla D2, brainstem Dmax, and brainstem D2, again controlling for the respective pre-RT scores at all time points. General fatigue, physical fatigue, and reduced activity were found to yield statistically significant results, and as such, these three individual components, in addition to total MFI-20 score, were included in a further multivariable model that assessed the impact at all time points of the implicated dosimetry variables but also the most likely confounding factors: (A) chemotherapy use and (B) primary/intact versus post-operative use of RT. Significance was assessed at the 0.05 level. Statistical analyses were performed using the SAS 9.4 statistical package (SAS Institute Inc., Cary, NC).

Results

From March 2013 to January 2017, 124 patients enrolled on our institutional HNC fatigue protocol were treated in the definitive setting with RT and had fatigue scores available at the appropriate time points. Patient and tumor characteristics are summarized in Table 1. Thirty-seven patients received postoperative RT. Twenty-four of the post-operative patients underwent concurrent chemoRT. The remaining 87 patients received definitive radiotherapy to intact disease, all but four of these concurrent with chemotherapy. Of the 107 total patients who received chemotherapy, 80 received cisplatin, 19 received carboplatin/paclitaxel, 6 received cisplatin initially but were switched to carboplatin/paclitaxel after toxicity, and 2 received concurrent cetuximab. Patient MFI-20 total fatigue scores, including breakdown into each of the five dimensions of the MFI-20, at pre-RT, 6th week of RT, and 1-month post-RT intervals, are summarized in Table 2.

CNS dosimetry variables and respective associations with total MFI-20 scores at the different time points are shown in Table 3. Medulla Dmax, medulla D2, and brainstem Dmax were significantly associated with higher MFI-20 score at each of the 6th week of RT, 1-month post-RT, and combined time points (all $p < 0.05$). Brainstem D2 was significantly associated with higher fatigue at only the combined time point, however, there was a trend toward significance at the 6th week of RT ($p = 0.090$) and 1-month post-RT individual time points ($p = 0.053$). Each 1 Gy increase in medulla Dmax resulted in an increase in total MFI-20 score over baseline of 0.30, 0.25, and 0.27 at the 6th week of RT, 1-month post-RT, and combined time points, respectively. Each 1 Gy increase in medulla D2 resulted in an increase in total MFI-20 score over baseline of 0.31, 0.26, and 0.29 at the 6th week of RT, 1-month post-RT, and combined time points, respectively. Each 1 Gy increase in brainstem Dmax resulted in an increase in total MFI-20 score over baseline of 0.30, 0.25, and 0.26 at the 6th week of RT, 1-month post-RT, and combined time points, respectively. Each 1 Gy increase in brainstem D2 resulted in an increase in total MFI-20 score over baseline of 0.24

at the combined time point. No other statistically significant associations between CNS structure dosimetry and total MFI-20 scores were found.

Table 4 demonstrates the associations between medulla and brainstem Dmax and D2 to the individual components of the MFI-20. Significant associations were demonstrated at varying specific time points for each dosimetry variable for general fatigue, physical fatigue, and reduced activity. No significant associations were demonstrated between the dosimetry variables and the other MFI-20 dimensions of mental fatigue or reduced motivation.

Table 5 displays results of the multivariable analyses that include the effect on MFI-20 scores of medulla and brainstem Dmax or D2, use of chemotherapy, and intact versus post-operative status of RT. In summary, use of chemotherapy was not demonstrated to impact MFI-20 scores. RT in the intact setting appeared to be associated, in general, with higher MFI-20 scores. The reduction in statistical power inherent to these multivariable analyses led to many of the previously significant dosimetry relationships just falling out of the 0.05 significance level; however, in general strong trends remained associating medulla and brainstem Dmax and D2 to MFI-20 scores. Medulla and brainstem Dmax and D2 remained statistically significant for physical fatigue at the 1-month post-RT time point.

Discussion

This study has found a link between one of the most important QoL concerns in HNC—fatigue—and potentially modifiable aspects of a patient's treatment—maximum medulla and brainstem RT dose. Patient QoL has been predictive of outcome data across disease sites, including HNC, further increasing its importance [20,21,34]. The development of fatigue in HNC treatment is assuredly multifactorial, and explanations range from the intuitive—the need to travel back and forth to treatment every day, compromised nutritional status, metabolic changes induced by the malignancy, general malaise from the congregation of disease and treatment related side-effects—to the complex. For example, numerous studies have described altered levels of circulating inflammatory markers as a contributor to fatigue in cancer therapy [30,34–40]. Our group has previously prospectively correlated changes in HNC patients' inflammatory markers to MFI-20 scores [41]. Additionally, chemotherapy has been implicated as a likely contributor; patients undergoing RT for breast cancer, for example, have been demonstrated to experience worse fatigue if they had previously undergone chemotherapy [42–44]. Finally, mental health comorbidities and other complex psychobehavioral factors have been associated with persistent fatigue following cancer therapy [42,43,45].

Curative courses of radiation for HNC have the capacity to cause brain structure damage. Wang et al. describe such damage by correlating RT courses for nasopharyngeal carcinoma to metabolic brain changes using diffusion tensor imaging and proton magnetic resonance spectroscopy [46]. Other functional imaging studies in the neurology realm have directly correlated changes in brain activity with fatigue. Again, the root of fatigue is complex. The basal ganglia, frontal cortex, thalamus, limbic system, amygdala have all been implicated [4–7,11]. Discrete structural areas entwined in interconnections and feedback loops characterize the brain, and as such identifying one distinct area for which damage can be

unequivocally linked to fatigue has proven elusive. Moreover, there are different facets to fatigue, subtleties that the MFI-20, in its inclusion of the five different dimensions, attempts to capture. Interestingly, our study demonstrated associations between three separate dimensions of the MFI-20 score—general fatigue, physical fatigue and reduced activity—and maximum medulla and brainstem RT dose. Given the criticality of brainstem—and notably, medulla—involvement to motor function, perhaps focal damage has the capacity to instill a sense of physical weakness, which might correlate to the MFI-20 dimensions of physical fatigue and reduced activity. Since cognition is a higher cortical function, the demonstration of an association between medulla or brainstem damage and the MFI-20 dimensions of mental fatigue or reduced motivation, would have been more challenging to interpret.

The dosimetric analysis of the PARSPORT study showed significantly higher Dmax and Dmean to the posterior fossa, brainstem, and cerebellum among patients who reported provider-assessed acute grade 2 or higher fatigue [2]. Our study was discordant with these results in that we found no association between brainstem Dmean or cerebellum or posterior fossa dosimetry and fatigue. One explanation for these differences is that the patient population in that analysis received considerably higher doses to the brainstem and cerebellum compared to the patient population in our study. Similarly, our study did not concord with the results of Powell et al. which described associations between provider-assessed grade 2 or higher fatigue and increased RT dose to the pituitary, cerebellum, and basal ganglia [3]. Their study consisting of only patients with nasopharyngeal cancer may be related to their demonstration of a relationship between fatigue and pituitary and cerebellum dosimetry—again, their patient population typically received higher doses to both structures than the patient population in our study, which contained mixed HNC primary sites. It is possible that our patient population as a whole did not receive an adequate threshold of dosing to demonstrate a relationship between the pituitary or cerebellum and fatigue. An alternative possibility for the differences between studies might be a susceptibility of provider-assessed fatigue grading to variability, which may impede inter-study comparisons [16,24–27]. Falchhook et al. describe a lower severity of provider-assessed side-effects compared to PRO side-effects in a population of patients undergoing chemoRT for HNC, and cite fatigue as being especially prone to underestimation due to the inability to rely on the physical examination [28]. Correspondingly, we believe one of the core strengths of our study is that CNS dosimetry was compared to PRO fatigue scores.

Our inclusion of a population of mixed HNC primary sites helps to generalize our results, but simultaneously made the statistical analyses more challenging. Patients included received either intact/primary RT or post-operative RT, with or without chemotherapy. Additionally, the population of patients in this study had cancers with varying stages and primary sites, which inherently means that some of these patients—particularly those with larger or more advanced tumors, and especially those with tumors extending more superiorly—may have simultaneously been prone to greater fatigue and higher brainstem dose. By that effect though, they would have also been prone to higher doses to the other CNS structures, for which no associations between dosimetry and fatigue were demonstrated. While it would have been possible to include tumor staging into our multivariable analysis, we ultimately elected to proceed with including only chemotherapy and intact/post-operative status of RT

into the model. We viewed these as two of the most likely factors that would have the capacity to contribute to fatigue, and also viewed these as factors that would translate across a patient population composed of mixed HNC primary sites—especially considering the implications of staging differences between sites.

Chemotherapy did not seem to contribute to treatment-related fatigue in our multivariable analyses, which seems to inherently suggest that RT plays the more prominent role as a contributor to fatigue during definitive HNC treatment. RT in the primary/intact setting did seem to impact patient fatigue on multivariable analysis (Table 5), likely as a surrogate of higher RT doses and more advanced tumors than the post-operative group. While these multivariable analyses did cause some of the previously significant associations to fall out of significance, we believe that this is largely a function of sample size between groups, which is supported by the strong statistical trends that remain. Additionally statistical significance associating medulla and brainstem maximum dose to the MFI-20 component of physical fatigue did persist on these multivariable analyses. In summary, given our multiple analyses taken as a whole, we conclude that medulla and brainstem maximum dose have a genuinely significant, but small, effect on treatment-related patient fatigue. Any time several tests are performed using numerous parameters, as in our study, there is a risk of overfitting with the modeling; however, each of the models performed in our study was fairly straightforward, though of course there were multiple iterations that needed to be performed given the nature of our data. In summary, our results could be considered primarily hypothesis generating at present, as the robustness of our analyses could be further improved upon by greater patient numbers, or perhaps by limiting a future study to a more homogenous patient population.

Our study was limited by the absence of inclusion of dosimetry data for the basal ganglia, which is implicated in the literature as an at-risk structure for causing fatigue. While we do believe the basal ganglia is likely to be an at-risk structure, our patient population did not, by our estimation, receive high enough doses to this area of the brain so that an effect might have been demonstrated. Again, this is due to our inclusion of mixed HNC primary sites; Powell et al's study population [3], which included only patients with nasopharyngeal cancers, received higher doses to the basal ganglia in general, and thus they were able to demonstrate a relationship between dose and fatigue.

As our experience with IMRT advances, further description of any unintentional consequences of dosimetric choices is warranted. We believe that our data suggest that maximum dose to the medulla and brainstem has a small but significant effect on treatment-related patient fatigue, and should be considered during the RT planning process. It seems possible that in at least some cases, utilizing in the treatment planning process a stricter brainstem optimization goal than the routine 54 Gy or less may translate to a tangible clinical benefit, provided target coverage is not compromised. The gold standard for establishing CNS fatigue constraints would be a prospective study in which at-risk CNS structures would be constrained in an attempt to improve fatigue outcomes. A study of this nature we would hope to see in the future.

In this large analysis of prospectively-gathered PRO fatigue scores from a population of patients undergoing definitive RT for HNC, maximum medulla and brainstem dose was

associated with a significantly increased risk of treatment-related patient fatigue. Future investigation might establish a guideline for a brainstem dose constraint that could contribute to a decreased risk of patient fatigue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by NIH/NINR K99R00NR014587 and the Oncology Nursing Society Foundation. Research reported in this publication was also supported in part by the Biostatistics and Bioinformatics Shared Resource of Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 1Patient and tumor characteristics ($n = 124$).

Age; n	
Median	59
Range	38–89
Sex; n (%)	
Male	96 (77.4)
Female	28 (22.6)
Radiation setting	
Intact	87 (70.2)
Post-operative	37 (29.8)
Concurrent chemotherapy	
Yes	107 (86.3)
No	17 (13.7)
Primary tumor	
Oropharynx	68 (54.8)
Larynx	18 (14.5)
Oral cavity	16 (12.9)
Hypopharynx	10 (8.1)
Maxillary sinus	4 (3.2)
Nasopharynx	3 (2.4)
Unknown primary	3 (2.4)
Nasal cavity/ethmoid	2 (1.6)
Stage	
1	6 (4.8)
2	2 (1.6)
3	20 (16.1)
4	96 (77.4)
TNM staging	
T	
x	3 (2.4)
1	22 (17.7)
2	33 (26.6)
3	25 (20.2)
4	41 (33.1)
N	
0	22 (17.7)
1	15 (12.1)
2	84 (67.7)
3	3 (2.4)

Table 2

MFI-20 fatigue scores^{*}; median (range).

Time	Total fatigue	General fatigue	Physical fatigue	Mental fatigue	Reduced motivation	Reduced activity
Pre-RT	47.5 (22–90)	10 (4–20)	10 (4–20)	8 (4–19)	8 (2–18)	10 (3–19)
6th week of RT	65 (20–98)	14 (4–20)	14 (4–20)	11 (4–20)	12 (4–20)	14 (4–20)
1-month post-RT	59 (20–93)	12 (4–20)	13 (4–20)	9 (4–20)	10 (4–18)	12 (4–20)

^{*} MFI-20 total fatigue score (maximum possible score 100) composed of five dimensions (each with maximum score of 20): general fatigue, physical fatigue, mental fatigue, reduced motivation, reduced activity.

Table 3

Central nervous system dosimetry and associations with total MFI-20 scores.

Dosimetry variable	Median value in Gy (SD; range)	Total fatigue 6th week of RT*	Total fatigue 1-month post-RT*	Total fatigue, combined time points* [†]
<u>Medulla</u>				
Dmax	33.2 (10.8; 0.2–62.7)	0.026 (0.04–0.57)	0.037 (0.02–0.48)	0.022 (0.04–0.50)
D2	29.6 (10.7; 0.3–55.9)	0.028 (0.03–0.58)	0.031 (0.02–0.49)	0.017 (0.05–0.13)
Dmean	16.9 (10.0; 0.2–45.9)	0.224 (–0.12 to 0.50)	0.299 (–0.12 to 0.39)	0.209 (–0.09 to 0.42)
<u>Pons</u>				
Dmax	15.7 (14.0; 0.1–59.3)	0.545 (–0.16 to 0.30)	0.579 (–0.13 to 0.23)	0.600 (–0.13 to 0.23)
D2	11.5 (12.3; 0.1–54.1)	0.283 (–0.12 to 0.41)	0.498 (–0.13 to 0.28)	0.499 (–0.14 to 0.28)
Dmean	5.7 (9.4; 0.1–60.6)	0.273 (0.00–0.00)	0.247 (0.00–0.00)	0.190 (0.00–0.00)
<u>Midbrain</u>				
Dmax	2.7 (9.4; 0.1–50.1)	0.448 (–0.24 to 0.53)	0.371 (–0.14 to 0.36)	0.927 (–0.25 to 0.28)
D2	2.6 (9.8; 0.1–42.8)	0.849 (–0.39 to 0.48)	0.836 (–0.27 to 0.33)	0.506 (–0.42 to 0.21)
Dmean	5.7 (5.3; 0.1–29.8)	0.644 (–0.59 to 0.94)	0.653 (–0.36 to 0.57)	0.650 (–0.60 to 0.38)
<u>Brainstem</u>				
Dmax	33.2 (10.7; 0.2–62.7)	0.027 (0.03–0.57)	0.037 (0.01–0.48)	0.028 (0.03–0.49)
D2	26.0 (10.9; 0.2–53.7)	0.090 (–0.04 to 0.52)	0.053 (0.0–0.46)	0.044 (0.01–0.47)
Dmean	6.9 (7.2; 0.1–35.8)	0.255 (0.20–0.73)	0.347 (–0.18 to 0.51)	0.535 (–0.24 to 0.46)
<u>Cerebellum</u>				
Dmax	43.2 (16.7; 0.1–72.8)	0.920 (–0.17 to 0.19)	0.526 (–0.11 to 0.21)	0.465 (–0.10 to 0.21)
D2	31.0 (13.2; 0.1–61.1)	0.685 (–0.18 to 0.27)	0.716 (–0.16 to 0.23)	0.537 (–0.13 to 0.25)
Dmean	9.9 (7.3; 0.1–34.8)	0.118 (–0.09 to 0.78)	0.275 (–0.15 to 0.54)	0.405 (–0.20 to 0.50)
<u>Posterior Fossa</u>				
Dmax	44.0 (14.1; 0.1–72.8)	0.498 (–0.14 to 0.28)	0.149 (–0.05 to 0.31)	0.131 (–0.04 to 0.32)
D2	30.4 (12.7; 0.2–60.0)	0.620 (–0.18 to 0.30)	0.727 (–0.17 to 0.24)	0.567 (–0.14 to 0.26)
Dmean	9.9 (7.2; 0.1–32.6)	0.110 (–0.08 to 0.81)	0.446 (–0.21 to 0.48)	0.381 (–0.20 to 0.51)
<u>Pituitary</u>				
Dmax	3.7 (15.0; 0.1–70.4)	0.208 (–0.08 to 0.37)	0.757 (–0.14 to 0.19)	0.811 (–0.15 to 0.19)
D2	3.6 (14.8; 0.1–68.0)	0.201 (–0.08 to 0.39)	0.710 (–0.13 to 0.20)	0.822 (–0.15 to 0.19)
Dmean	3.1 (12.8; 0.1–63.1)	0.202 (–0.10 to 0.46)	0.809 (–0.17 to 0.21)	0.914 (–0.19 to 0.21)

Abbreviations: MFI-20 = Multidimensional Fatigue Inventory-20; SD = Standard deviation; Dmax = maximum point dose to the structure; D2 = dose received to 2% of structure volume; Dmean = mean dose to the structure

* Multivariable linear regression p-value (95% confidence interval); controlled for pre-radiation scores. Bolded values are significant.

[†] Association tested between dosimetry variable and highest value of either 6th week of RT or 1-month post-RT score.

Table 4

Association between brainstem and medulla dosimetry to MFI-20 individual components.*

MFI-20 component and time point	Medulla Dmax	Medulla D2	Brainstem Dmax	Brainstem D2
<u>General fatigue</u>				
6th week of RT	0.022 (0.01–0.14)	0.011 (0.02–0.15)	0.024 (0.01–0.14)	0.046 (0.0–0.13)
1-month post-RT	0.022 (0.01–0.14)	0.011 (0.02–0.15)	0.024 (0.01–0.14)	0.046 (0.0–0.13)
Combined [†]	0.026 (0.01–0.11)	0.017 (0.01–0.12)	0.032 (0.0–0.11)	0.046 (0.0–0.10)
<u>Physical fatigue</u>				
6th week of RT	0.015 (0.02–0.15)	0.025 (0.01–0.15)	0.016 (0.02–0.15)	0.058 (0.0–0.14)
1-month post-RT	0.005 (0.03–0.15)	0.004 (0.03–0.15)	0.005 (0.03–0.15)	0.006 (0.03–0.15)
Combined	0.019 (0.01–0.12)	0.009 (0.02–0.13)	0.024 (0.01–0.12)	0.019 (0.01–0.12)
<u>Mental fatigue</u>				
6th week of RT	0.409 (–0.04 to 0.10)	0.434 (–0.04 to 0.10)	0.444 (–0.04 to 0.10)	0.527 (–0.05 to 0.09)
1-month post-RT	0.379 (–0.03 to 0.08)	0.345 (–0.03 to 0.08)	0.390 (–0.03 to 0.08)	0.542 (–0.04 to 0.07)
Combined	0.362 (–0.03 to 0.08)	0.334 (–0.03 to 0.09)	0.414 (–0.03 to 0.08)	0.495 (–0.04 to 0.08)
<u>Reduced motivation</u>				
6th week of RT	0.172 (–0.02–0.11)	0.188 (–0.02–0.11)	0.167 (–0.02–0.11)	0.276 (–0.03–0.11)
1-month post-RT	0.379 (–0.03 to 0.08)	0.345 (–0.03 to 0.08)	0.390 (–0.03 to 0.08)	0.542 (–0.04 to 0.07)
Combined	0.148 (–0.01 to 0.10)	0.118 (–0.01 to 0.10)	0.173 (–0.02 to 0.09)	0.223 (–0.02 to 0.09)
<u>Reduced activity</u>				
6th week of RT	0.143 (–0.02 to 0.12)	0.158 (–0.02 to 0.13)	0.136 (–0.02 to 0.13)	0.495 (–0.05 to 0.10)
1-month post-RT	0.034 (0.01–0.12)	0.020 (0.01–0.13)	0.031 (0.01–0.12)	0.023 (0.01–0.13)
Combined	0.039 (0.0–0.13)	0.030 (0.01–0.13)	0.046 (0.0–0.12)	0.071 (0.0–0.12)

Abbreviations: MFI-20 = Multidimensional Fatigue Inventory-20; Dmax = maximum point dose to the structure; D2 = dose received to 2% of structure volume; Dmean = mean dose.

* Multivariable linear regression p-value (95% confidence interval); controlled for pre-radiation scores. Bolded values are significant.

[†] Association tested between dosimetry variable and highest value of either 6th week of RT or 1-month post-RT score.

Table 5

Multivariable analyses controlling for chemotherapy and intact versus post-operative radiation therapy. *

MFI-20 component and time point	6th week of RT	1-month post-RT	Combined [†]
<u>Total fatigue</u>			
1) Medulla Dmax	0.085 (−0.04 to 0.54)	0.209 (−0.09 to 0.40)	0.132 (−0.06 to 0.43)
Intact [‡] vs. post-op	0.009 (2.22–15.37)	0.092 (−0.84 to 11.02)	0.030 (0.67–12.59)
Chemotherapy	0.693 (−8.48 to 12.70)	0.497 (−10.82 to 5.28)	0.708 (−9.60 to 6.54)
2) Medulla D2	0.091 (−0.04 to 0.54)	0.178 (−0.08 to 0.42)	0.107 (−0.04 to 0.45)
Intact vs. post-op	0.009 (2.26–15.41)	0.095 (−0.090 to 10.96)	0.031 (0.60–12.52)
Chemotherapy	0.748 (−8.76 to 12.14)	0.498 (−10.76 to 5.27)	0.713 (−9.53 to 6.54)
3) Brainstem Dmax	0.085 (−0.04 to 0.54)	0.195 (−0.08 to 0.40)	0.147 (−0.06 to 0.42)
Intact vs. post-op	0.009 (2.26–15.40)	0.090 (−0.81 to 11.03)	0.028 (0.75–12.66)
Chemotherapy	0.690 (−8.47 to 12.75)	0.487 (−10.83 to 5.19)	0.679 (−9.72 to 6.36)
4) Brainstem D2	0.213 (−0.11 to 0.48)	0.223 (−0.09 to 0.39)	0.191 (−0.08 to 0.40)
Intact vs. post-op	0.007 (2.64–15.82)	0.080 (−0.65 to 11.15)	0.026 (0.84–12.76)
Chemotherapy	0.897 (−9.76 to 11.11)	0.471 (−10.93 to 5.09)	0.642 (−9.92 to 6.14)
<u>General fatigue</u>			
1) Medulla Dmax	0.101 (−0.01 to 0.12)	0.592 (−0.04 to 0.07)	0.145 (−0.01 to 0.09)
Intact vs. post-op	< 0.001 (1.22–4.18)	0.264 (−0.57 to 2.08)	0.009 (0.44–3.06)
Chemotherapy	0.678 (−1.92 to 2.94)	0.671 (−2.20 to 1.42)	0.937 (−1.85 to 1.71)
2) Medulla D2	0.052 (0.0–0.13)	0.582 (−0.04 to 0.07)	0.104 (−0.01 to 0.10)
Intact vs. post-op	< 0.001 (1.20–4.14)	0.265 (−0.58 to 2.08)	0.010 (0.42–3.04)
Chemotherapy	0.637 (−1.81 to 2.95)	0.668 (−2.20 to 1.42)	0.956 (−1.82 to 1.72)
3) Brainstem Dmax	0.103 (−0.01 to 0.12)	0.565 (−0.04 to 0.07)	0.157 (−0.02 to 0.09)
Intact vs. post-op	< 0.001 (1.23–4.19)	0.263 (−0.57 to 2.08)	0.009 (0.46–3.08)
Chemotherapy	0.678 (−1.92 to 2.94)	0.670 (−2.20 to 1.42)	0.910 (−1.88 to 1.68)
4) Brainstem D2	0.144 (−0.02 to 0.12)	0.592 (−0.04 to 0.07)	0.193 (−0.02 to 0.09)
Intact vs. post-op	< 0.001 (1.29–4.24)	0.253 (−0.55 to 2.09)	0.008 (0.47–3.09)
Chemotherapy	0.802 (−2.08 to 2.68)	0.662 (−2.21 to 1.41)	0.876 (−1.92 to 1.63)
<u>Physical fatigue</u>			
1) Medulla Dmax	0.054 (0.0–0.15)	0.049 (0.0–0.13)	0.115 (−0.01 to 0.11)
Intact vs. post-op	0.125 (−0.39 to 3.13)	0.063 (−0.08 to 3.11)	0.014 (0.38–3.32)
Chemotherapy	0.949 (−2.66 to 2.84)	0.672 (−2.56 to 1.66)	0.886 (−2.07 to 1.79)
2) Medulla D2	0.086 (−0.01 to 0.14)	0.043 (0.0–0.13)	0.065 (0.0–0.11)
Intact vs. post-op	0.118 (−0.36 to 3.17)	0.066 (−0.10 to 3.09)	0.016 (0.34–3.27)
Chemotherapy	0.925 (−2.84 to 2.61)	0.663 (−2.56 to 1.64)	0.924 (−2.01 to 1.83)
3) Brainstem Dmax	0.057 (0.0–0.15)	0.047 (0.0–0.13)	0.131 (−0.01 to 0.10)
Intact vs. post-op	0.122 (−0.38 to 3.14)	0.060 (−0.07 to 3.11)	0.013 (0.40–3.34)
Chemotherapy	0.951 (−2.67 to 2.84)	0.651 (−2.58 to 1.62)	0.854 (−2.11 to 1.75)
4) Brainstem D2	0.159 (−0.02 to 0.13)	0.040 (0.0–0.13)	0.100 (−0.01 to 0.10)
Intact vs. post-op	0.095 (−0.27 to 3.26)	0.054 (−0.02 to 3.14)	0.013 (0.40–3.33)
Chemotherapy	0.822 (−3.03 to 2.41)	0.651 (−2.57 to 1.61)	0.865 (−2.08 to 1.75)

MFI-20 component and time point	6th week of RT	1-month post-RT	Combined [†]
<u>Reduced activity</u>			
1) Medulla Dmax	0.235 (−0.03 to 0.12)	0.222 (−0.02 to 0.10)	0.218 (−0.02 to 0.10)
Intact vs. post-op	0.096 (−0.27 to 3.29)	0.163 (−0.44 to 2.57)	0.224 (−0.60 to 2.55)
Chemotherapy	0.684 (−2.36 to 3.57)	0.212 (−3.33 to 0.75)	0.154 (−3.73 to 0.59)
2) Medulla D2	0.256 (−0.03 to 0.12)	0.146 (−0.02 to 0.11)	0.175 (−0.02 to 0.11)
Intact vs. post-op	0.093 (−0.26 to 3.30)	0.175 (−0.47 to 2.54)	0.232 (−0.62 to 2.53)
Chemotherapy	0.729 (−2.42 to 3.44)	0.222 (−3.28 to 0.77)	0.155 (−3.71 to 0.60)
3) Brainstem Dmax	0.219 (−0.03 to 0.12)	0.189 (−0.02 to 0.10)	0.224 (−0.02 to 0.10)
Intact vs. post-op	0.095 (−0.27 to 3.29)	0.162 (−0.43 to 2.57)	0.218 (−0.59 to 2.56)
Chemotherapy	0.671 (−2.33 to 3.60)	0.209 (−3.32 to 0.73)	0.146 (−3.75 to 0.56)
4) Brainstem D2	0.667 (−0.06 to 0.09)	0.129 (−0.01 to 0.11)	0.287 (−0.03 to 0.10)
Intact vs. post-op	0.072 (−0.15 to 3.42)	0.155 (−0.41 to 2.57)	0.203 (−0.56 to 2.59)
Chemotherapy	0.897 (−2.74 to 3.12)	0.218 (−3.28 to 0.76)	0.136 (−3.79 to 0.52)

Abbreviations: MFI-20 = Multidimensional Fatigue Inventory-20; Dmax = maximum point dose to the structure; D2 = dose received to 2% of structure volume; Dmean = mean dose.

* Multivariable linear regression *p*-value (95% confidence interval); controlled for pre-radiation scores. Bolded values are significant.

[†] Association tested between dosimetry variable and highest value of either 6th week of RT or 1-month post-RT score.

[‡] Definitive radiation, as opposed to post-operative radiation, was associated with higher fatigue.