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Orignal Article

Fatigue following radiation therapy in nasopharyngeal cancer survivors: A dosimetric analysis incorporating patient report and observer rating

MD Anderson Head Neck Cancer Symptom Working Group Contributing authors Mona Kamal [a,e], David I. Rosenthal [a], Aakash Batra [a], Stefania Volpe [a,f], Baher Elgohari [a], Ryan P. Goepfert [b], Adam S. Garden [a], Jack Phan [a], Salman Eraj [a], Amy Dursteler [a], Bowman Williams [a], Joshua Smith [a], Jeremy Aymard [a], Joel Berends [a], Aubrey White [a], Amit Jethanandani [a,g], Carlos E. Cardenas [c], Steven J. Frank [a], William H. Morrison [a], Erich M. Sturgis [b], Charles S. Cleeland [d], Tito R. Mendoza [d], Abdallah S.R. Mohamed [a,h,i], Clifton D. Fuller [a,i], G. Brandon Gunn [a,*]

[a] *Department of Radiation Oncology;* [e] *Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt;* [f] *University of Milan, Department of Oncology and Hemato-Oncology, Milano, Italy;* [b] *Department of Head and Neck Surgery;* [g] *The University of Tennessee Health Science Center, College of Medicine, Memphis, USA;* [c] *Department of Radiation Physics;* [d] *Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, USA;* [h] *Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, University of Alexandria, Alexandria, Egypt;* [i] *MD Anderson Cancer Center/UTHealth Graduate School of Biomedical Sciences, Houston, USA*

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ABSTRACT

Purpose: To explore for fatigue-related regions and the radiotherapy (RT) dose-fatigue relationship in nasopharyngeal cancer (NPC) survivors.
Methods: Eighty disease-free NPC survivors completed the MD Anderson Symptom Inventory-Head and Neck module (MDASI-HN) after RT. Fatigue was evaluated by the MDASI-HN fatigue item (MDASI-HN-F) and Common Terminology Criteria for Adverse Events v3.0 (CTC-AE), between 6 and 36 months after RT to determine the presence of chronic fatigue. Skull base MRIs and planning CT/RT dose were retrievable for 56 patients. Dosimetric data were extracted for 10 MRI-defined potential fatigue at-risk structures (FARS): brainstem (BS), pituitary gland (PG), hypothalamus (HT), basal ganglia, internal capsule, pineal gland, sub-thalamic nuclei, thalamus, substantia nigra, and hippocampus (HC). Recursive partitioning analysis (RPA) was used to identify dose-volume effects associated with chronic fatigue.
Results: 56 pts formed the cohort. Thirty patients (54%) reported any fatigue per MDASI-HN-F. Thirty-three pts (59%) had any fatigue by CTC-AE. The maximum point doses (Dmax) for PG, BS, HC, and HT were numerically higher in patients with fatigue. Dmax and Dmean of the PG were significantly higher in patients with chronic fatigue, $p \leq 0.01$. A dose-volume threshold of PG V52 Gy $\geq$16% (LogWorth 2.4, AUC 0.7) was identified on RPA, and potential sensitivity to the PG doses was observed in younger patients (<53 years-old).
Conclusion: A dose-fatigue relationship was identified for the pituitary gland, both patient-reported and observer ratings. We recommend limiting the Dmax of PG to <54 Gy and V52 Gy to <16%, particularly in young NPC patients, during plan optimization when achievable.
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Radiation therapy (RT) is a mainstay in the management of nasopharyngeal carcinoma (NPC), commonly in combination with chemotherapy [1]. Given that the RT target volume for these patients is at the base of the skull (and often intracranial), intimate with numerous critical central nervous system (CNS) structures, clinicians must balance goals of maximizing disease control while minimizing treatment-related toxicity [2]. The use of intensity-modulated RT (IMRT) in the treatment of NPC has allowed for enhanced delivery of therapeutic doses and improved quality of life (QOL) [3–5]. Although this allows for relative dose sparing of nearby critical organs such as the brainstem and neuro-optic apparatus, the effects of "beam path toxicity" with the use of multiple oblique IMRT fields on non-defined normal tissue is of potential concern [6–9]. One observed toxicity after NPC chemoradiation is

* Corresponding author at: Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
E-mail address: gbgunn@mdanderson.org (G.B. Gunn).

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increased patient fatigue, which has been attributed to the proximity of CNS structures to the RT targets and associated integral dose [7,10].

Multiple factors are likely to contribute to fatigue following RT, but the exact pathophysiology of has not been elucidated [11,12]. The risk of hypopituitarism, which could be manifest as fatigue, could increase from 3–7% to 30–60% with RT dose of 50–60 Gy, respectively [13], and the recommended dose to the pituitary gland varies between 45 Gy in cases of pituitary adenoma treatment [14,15] and 50–60 Gy in NPC and other skull base tumors [16,17]. While various candidate organs at risk for the development of RT-driven fatigue in head and neck cancer (HNC) patients have also been proposed, there is no consensus as to what structures should be prioritized for sparing and to what degree. Likewise, while investigators have demonstrated a dose–response relationship for some fatigue-related structures, the definition of clinically applicable constraints has not been reached [10,18,19]. Therefore, we performed this study in a patient group at particularly high risk for development of fatigue after RT and for whom MRI is routinely obtained, which allows for accurate delineation of specific CNS structures and substructures in order to identify clinically applicable constraints to be used in RT plan optimization. Since fatigue could be underestimated by physician assessment alone [20], we utilized dual assessment methods for fatigue after RT: the MD Anderson Symptom Inventory – Head and Neck module (MDASI-HN) and observer rating (clinician documentation) to evaluate both patient-reported and observer/clinician-rated assessments.

As part of a broader effort of our MD Anderson Head and Neck Symptom Working Group to profile patient-reported outcomes after RT for HNC survivors and to advance current clinical practice by developing and integrating predictive models for RT-attributable and potentially modifiable toxicities and symptoms, the specific aims of our study were to:

1. Correlate patient reported- and observed-rated chronic fatigue following definitive RT in a cohort of NPC survivors;
2. Identify candidate MRI-defined, fatigue-related regions of interest (ROIs);
3. Evaluate and quantify the potential dose-fatigue relationship;
4. Propose practical dose constraints to mitigate chronic fatigue;
5. Generate testable hypotheses and future investigation.

Materials and methods

Study population

Following approval from our Institutional Review Board (IRB), adults (≥18 years old) previously treated for HNC without evidence of active disease and who completed initial therapy more than 6 months previously were eligible for a prospective longitudinal symptom assessment study. Study-specific informed consent was provided by all participants, who then as part of the study either self-completed the MDASI-HN via pencil/paper or via telephone interview, conducted by study personnel using a study-specific IRB approved script with the MDASI-HN delivered verbatim. The questionnaire data analyzed in this study were cross-sectional in nature. The MDASI-HN assessment was available for 80 NPC survivors who were treated between 2001 and 2013. The planning CT/RT doses were non-retrievable for 21 patients, leaving 59 patients. Of those 59 patients, 56 patients who were treated between 2006 and 2013 had brain MRIs. Patient demographics, tumor and treatment characteristics were extracted from their medical records. Data regarding body mass index, hemoglobin (HGB) level, marital status, thyroid functions and thyroid replacement therapy were retrieved. Presence of anemia was coded for any reported anemia by clinicians or for an HGB level <12 and <13.5 for women and men, respectively. Hypothyroidism was defined by a TSH ≥ the upper lab reference range within a year from the fatigue assessment. Participants considered for this analysis were those previously treated with curative-intent RT at our center for NPC and for whom RT plans and MRI images were available. Patients who underwent re-irradiation were excluded and only one patient had a recurrence after surgical intervention. All patients completed the MDASI-HN, however, we considered only the fatigue item of the MDASI-HN (MDASI-HN-F). We evaluated fatigue scores between 6 and 36 months after RT to determine presence or absence of chronic fatigue. All patients had been assessed by their treating physicians, including assessment for any fatigue, at regular intervals as a part of standard routine clinical follow-up. At each visit, fatigue was assessed during the clinical interview and nursing assessment. Based on patient responses, the fatigue was recorded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTC-AE) v3.0 scale. The CTC-AE rated fatigue grades, within ±3 months from the corresponding MDASI-HN, were retrieved from the electronic nursing record (MOSAIQ, Elekta Medical Systems, Mountain Valley, CA).

Study instruments and fatigue assessment

MD Anderson Symptom Inventory-Head and Neck module (MDASI-HN):

The MDASI-HN is a validated, brief, patient-reported, disease-site specific, multi-symptom assessment tool. It contains 13 "core symptom items" (symptoms common to all cancer types), 9 additional symptom items specific to the MDASI-HN, and 6 items concerning how these symptoms interfere with activities of daily living. The 22 symptom items are rated on a 0–10 ordinal scale from "not present" to "as bad as you can imagine", indicating the presence and severity of the symptom in the past 24 h [21,22]. For the current analysis, we analyzed only the fatigue single-item question, where patients rate their fatigue during the last 24 h as "Your fatigue (tiredness) at its WORST".

Common Terminology Criteria for Adverse Events

CTC-AE is an instrument derived from the National Cancer Institute Common Toxicity Criteria. It is a collection of descriptive clinical expressions for use in adverse event and toxicity reporting. For this study, observer-rated fatigue was recorded as per CTC-AE v3.0 as follows:

Grade 1: mild fatigue over baseline;

Grade 2: moderate or causing difficulty performing some activities of daily living;

Grade 3: severe fatigue interfering with activities of daily living;

Grade 4: disabling.

Radiation therapy plan data and ROIs

Archived DICOM-RT plans were restored and dosimetric data were retrieved. Delivered RT doses were re-calculated, using Pinnacle 14 software (Phillips Medical Systems, Andover, MA). Subsequently, computed tomography (CT) DICOM files and associated RT structures for the selected regions of interest (ROI) files were exported. Planning CT DICOM files were exported into a commercial deformable registration/segmentation software (Velocity AI 3.0.1, Velocity Medical Solutions, Atlanta, GA, 2004–2013) [23]. Deformable image registration was used in order to overlay simulation CT images and correspondent pre-RT magnetic resonance images (MRIs); axial T2-weighted sequences were used for registration and subsequent ROI delineation. Based on previously

published data on putative fatigue at-risk structures (FARS) [10,19], the following 10 intracranial ROIs were manually segmented: brainstem, pituitary gland, hypothalamus, basal ganglia, internal capsule, pineal gland, sub-thalamic nuclei, thalamus, substantia nigra, and hippocampus. See Fig. 1 for a representative 3-D projection of the segmented ROIs on CT-MRI registration coronal image. These ROIs were manually segmented by a trained medical student AB and a radiation oncologist (BE) and reviewed by two radiation oncologists (ASR and MK) for accuracy; discrepancies were addressed through the consultation of the aforementioned atlas and peer review (GBG). Dose-volume histograms (DVHs) were reconstructed per bins of 1 Gy (range: 1–75) and were extracted for the aforementioned structures. In addition, the maximum point dose (Dmax) and mean dose (Dmean) were captured.

Statistical analysis

Analyses were performed using the JMP v12Pro (SAS Institute, Cary, NC) and MATLAB R2014 (MathWorks, Natick, MA). The correlation between MDASI-HN-F ratings and CTC-AE grades was determined by Spearman coefficient. By using both MDASI-HN-F (item score >0) and CTCAE fatigue (grade >0), patients were dichotomized into binary categorical groups (yes/no) according to the presence of any fatigue. The association between the presence of fatigue according to MDASI-HN-F (and selected patient and tumor variables, including age, sex, body mass index, presence of anemia, marital status, thyroid function status, T-category (T1/2 versus T3/4), N-category (N0/1 versus N2/3), and systemic therapy were investigated through univariate analysis. All variables that achieved significance ($p < 0.05$) in the univariate analysis were then included in the multivariate regression.

Wilcoxon rank-sum test was used to compare the maximum (Dmax) and mean doses (Dmean) across patients with and without fatigue. Linear regression analysis was done to determine the relation between Dmax and Dmean of ROIs and fatigue, assessed by both MDASI-HN-F and CTC-AE, as continuous variables, with a calculation of resultant receiver operator characteristic curves (ROC) area-under-the-curve (AUC). Bivariate plots of cumulative group DVHs were used to display the cumulative DVHs across the two groups based on the presence of late fatigue by MDASI-HN-F.

Recursive partitioning analysis (RPA), also known as classification and regression trees, with 20% verification "holdback" and a minimum split size of 10% per split/partition was used to identify candidate ROI dose-volume parameters [24]. DVH data in 1 Gy bins for the 10 potential FARS were evaluated using RPA to allow identification and simultaneous dose-threshold selection of all FARS, using "any fatigue" (i.e., MDASI-HN-F $\geq$1) as a discriminant. Next, dose-volume thresholds within "best" candidate parameters for each ROI using receiver operating curve (ROC) and K-fold cross-validation were identified. Effect sizes, and LogWorth values (wherein Log Worth represents $-$log10 [p-value], such that $p = 0.01$ is equivalent to a LogWorth of 2.0, $p = 0.001$ is denoted by LogWorth of 3.0, etc.) were utilized [8,25].

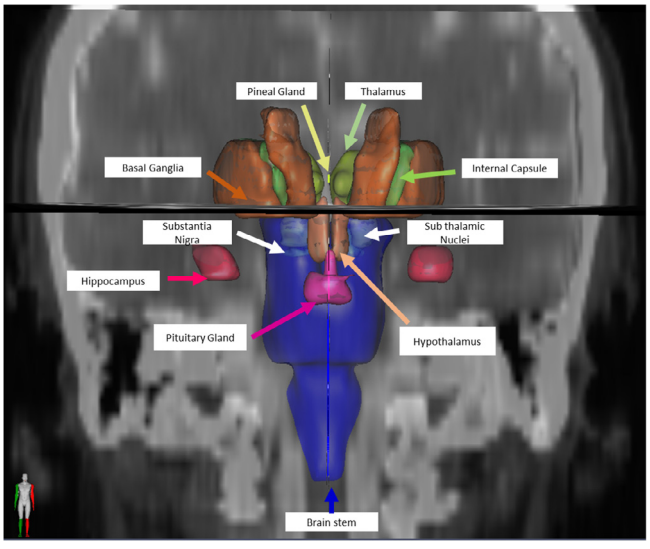

Fig. 1. 3-D projection on coronal view of CT-MRI registration of the 10 potential fatigue at-risk structures.

Results

Participants

Fifty-six patients who had been treated at our center for NPC from 2005 to2013 were eligible for analysis. The majority were male (66%); the median age was 52 years, and 75% were married. Fifty-five percent presented with advanced T stages, i.e., T3/4. In 17 patients, a hypothyroid status had occurred within a year of the fatigue assessment. Of those 17 patients, 12 (70%) reported fatigue ($p = 0.09$), and 14 (82%) were on thyroid replacement therapy at the time of fatigue assessment. Data for the presence or absence of anemia around the time of fatigue assessment (i.e., within 6 months) were available for 38 (68%) patients; of which 14 had anemia and 7 had both anemia and fatigue ($p = 0.4$). Ninety-three percent had received IMRT, and the median RT dose was 70 Gy (range, 57–70). Twenty-nine percent, 11%, 54% and 7% had received CCRT, IC, IC-CCRT and RT, respectively. Patient demographics, disease and previous treatment characteristics are shown in Table 1.

Fatigue assessments

The median time from the end of RT to MDASI-HN completion was 17 months (range, 6–36); 48% and 23% completed the MDASI-HN during the 2nd and 3rd years after RT, respectively. Thirty patients (54%) reported any level of fatigue (i.e., MDASI-HN-F score >0). Of those 30 patients, 14 (47%) reported moderate-to-severe ratings (i.e., score $\geq$5). The mean (±SD) MDASI-HN-F score was 2.5 (±2.9). Thirty-three patients (59%) had any level of fatigue by CTC-AE. Of those 33 patients, 19 (57%) exhibited moderate-to-severe grades (i.e., grade 2–3). We observed a strong linear relationship between the MDASI-HN-F scores and CTC-AE fatigue grades ($\rho = 0.89$, $p < 0.01$). The patients who reported fatigue were predominantly men (73%), with a median age of 53 years; most were married (80%) and most were presented with advanced T stage (60%). Patients who reported fatigue had a smaller BMI (1.87; 95% CI 1.76–2) than that of patients without fatigue (1.91; 95% CI 1.8–2), $p = 0.6$.

On univariate analysis, there was no association between the tested clinical factors and presence of fatigue by MDASI-HN-F. Twenty-three percent, 13%, 57% and 7% of the patients who reported fatigue received CCRT, IC, IC + CCRT and RT alone, respectively ($p = 0.7$). The dosimetric and volume characteristics for the 10 FARS are shown in Supplementary Table 1.

Dosimetric correlate and thresholds

Dmax values by the presence of fatigue for the 10 potential FARS by MDASI-HN-F and CTC-AE are shown in Table 2. The Dmax values for brainstem, hippocampus, hypothalamus, and pituitary gland were numerically lower (by both MDASI-HN-F and CTC-AE assessment) in patients without fatigue, and differences in the Dmax for the pituitary gland between those with and without

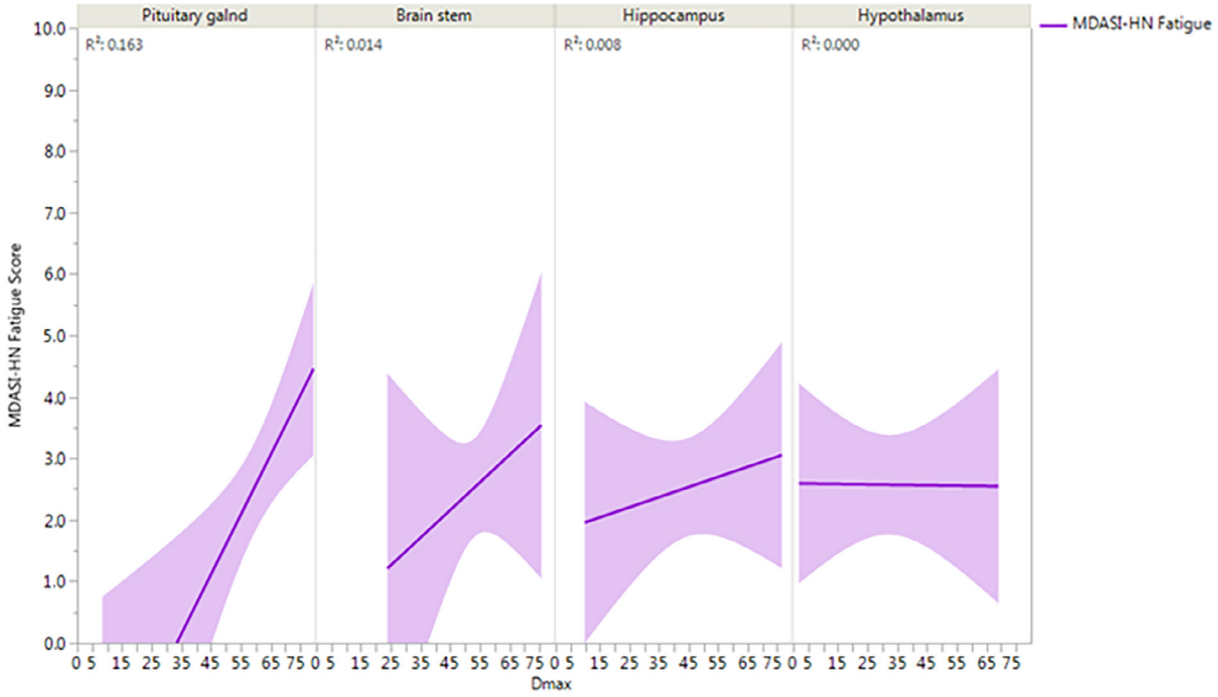

Fig. 2. Fatigue rating by MDASI-HN-F plotted against Dmax for select* Fatigue at risk structures. *The four selected ROIs are those structures with numerical difference in the Dmax. Abbreviations: MDASI-HN-F, Fatigue item of MD Anderson Symptom Inventory-Head and Neck module; ROIs, regions of interest.

Table 1
Patient, disease and treatment characteristics.

Characteristic	*N* (%)
Sex	
Male	38 (68)
Female	18 (32)
Age, years	
Median (Range)	52 (20–78)
Race	
White	41 (73)
Black	3 (5)
Hispanic	7 (13)
Other	5 (9)
Smoking history	
Current smoker	12 (21)
Former smoker	17 (30)
Never smoker	27 (47)
T-category	
1	12 (21)
2	13 (23)
3	12 (21)
4	19 (34)
N-category	
0	15 (27)
1	14 (25)
2	20 (36)
3	7 (13)
Treatment modality	
Induction chemotherapy → CCRT	30 (54)
CCRT	16 (29)
Induction → RT	6 (11)
RT alone	4 (7)

Abbreviations: RT = radiation therapy; CCRT; concurrent chemotherapy and radiation therapy.

fatigue were statistically significant by both MDASI-HN-F and CTC-AE assessment (Table 2). See Fig. 2 for MDASI-HN-F rating versus Dmax for selected FARS. After adjusting for clinical factors, this difference remained significant for MDASI-HN-F assessment ($p < 0.01$). Boxplots of Dmax for the four FARS with a numerical difference by the Dmax and presence of fatigue by both MDASI-HN-F and CTC-AE are shown in Supplementary Fig. 1.

Dmean values by the presence of fatigue for the 10 potential FARS by MDASI-HN-F and CTC-AE are shown in Supplementary Table 2. For only pituitary gland, the Dmean was numerically lower (by both MDASI-HN-F and CTC-AE assessment) in patients without fatigue, and this difference was statistically significant by both MDASI-HN-F ($p = 0.02$) and CTC-AE assessment ($p = 0.01$).

Results from logistic regression analysis with ROC comparison in order to assess the probability of fatigue association are shown for all 10 tested FARS for Dmax in Supplementary Table 3 and for Dmean in Supplementary Table 4. The resultant areas under the curves (AUCs) showed that dose to the pituitary gland had the strongest correlation with fatigue by both MDASI-HN-F (AUC = 0.74 for Dmax and 0.68 for Dmean) and CTC-AE (AUC = 0.68 for Dmax and 0.62 for Dmean). A notable lower discriminant utility was observed for the doses to the hippocampus (e.g. Dmax: AUC = 0.60 for MDASI-HN-F and 0.57 for CTC-AE) and brainstem (e.g. Dmax: AUC = 0.56 for MDASI-HN-F and 0.52 for CTC-AE). Results from logistic regression analysis for the pituitary gland, brainstem, hippocampus, and hypothalamus are displayed in Supplementary Fig. 2.

DHVs for each ROI by the presence of fatigue by MDASI-HN-F are shown in Fig. 3. Variability in overall curve shape and regions of DVH separation differ for the FARS. The magnitude of curve separation was largest for the pituitary gland, with separation evident in the 20–55 Gy range for those with versus those without fatigue.

Regarding fatigue severity, the Dmax values for four selected FARS are shown by MDASI-HN-F severity ratings (none/mild [score 0–4] versus moderate/severe [score 5–10]) in Table 3A and by CTC-AE severity grouping (grade 0/1 versus grade 2/3) in Table 3B. Results from RPA decision tree analysis of ROI-specific dose-volume thresholds with the presence of fatigue, with training and validation ROC/AUC optimization, identified a pituitary gland dose-volume threshold of V52 Gy $\geq$16% (LogWorth 2.4; AUC 0.7)

Table 2
Dmax by presence of fatigue for each potential fatigue-related ROI by MDASI-HN-F and CTC-AE assessment.

		Fatigue by MDASI-HN			Fatigue by CTC-AE		
ROIs	Fatigue	Mean values of Dmax	±SE	*P* value	Mean values of Dmax for	±SE	*P* value
Basal ganglia	No	20	3.18	0.7998	19	3.32	0.83780
Basal ganglia	Yes	19	2.91		18	2.82	
Brainstem	No	52	1.49	0.4698	52	1.59	0.75800
Brainstem	Yes	54	1.38		54	1.33	
Hippocampus	No	42	3.00	0.1753	42	3.21	0.36404
Hippocampus	Yes	47	2.79		46	2.68	
Hypothalamus	No	31	3.53	0.8525	32	3.68	0.89142
Hypothalamus	Yes	33	3.22		33	3.12	
Internal capsule	No	15	2.73	0.7353	15	2.85	0.78485
Internal capsule	Yes	15	2.49		15	2.41	
Pineal gland	No	10	1.37	0.9328	10	1.45	0.89142
Pineal gland	Yes	10	1.29		10	1.23	
Pituitary gland	No	54	2.16	0.0019	54	2.37	0.02351
Pituitary gland	Yes	64	2.01		63	1.98	
Sub-thalamic nucleus	No	24	2.62	0.6858	23	2.79	0.86451
Sub-thalamic nucleus	Yes	23	2.48		23	2.36	
Substantia nigra	No	29	2.67	0.7874	29	2.84	0.79799
Substantia nigra	Yes	28	2.53		28	2.40	
Thalamus	No	15	1.98	0.6542	15	2.07	0.60276
Thalamus	Yes	13	1.81		13	1.75	

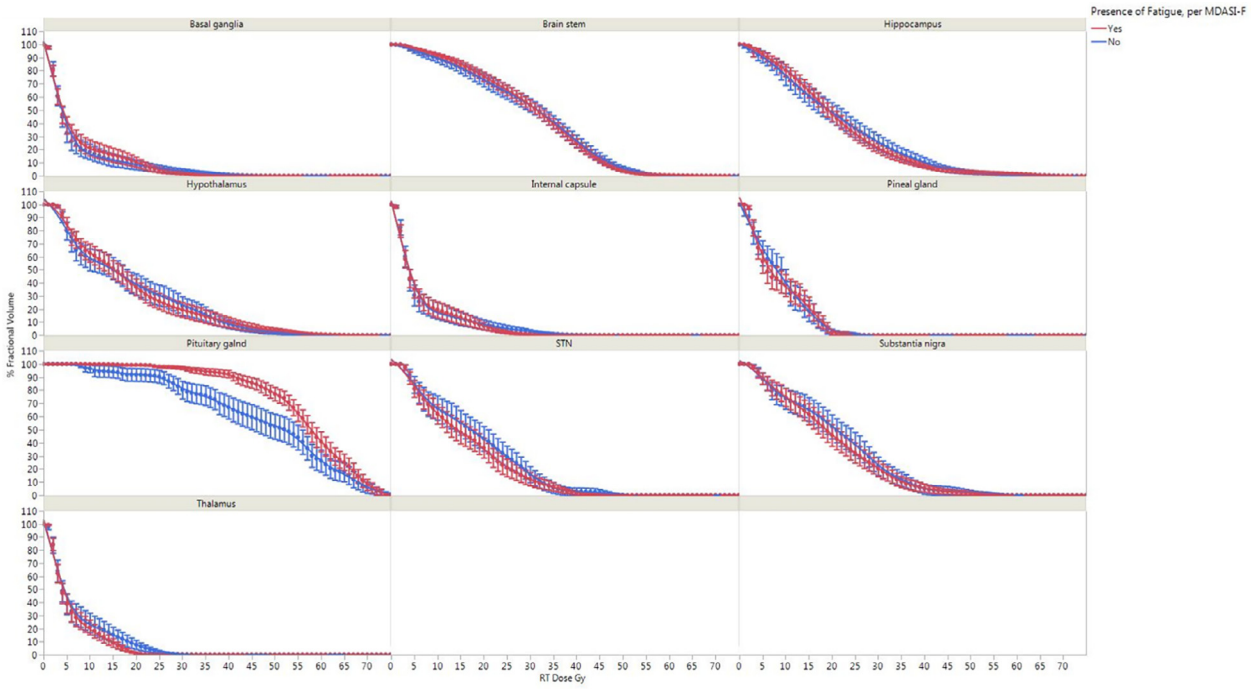

Fig. 3. Cumulative dose volume histograms with standard error bars for each potential fatigue at-risk structures by presence of fatigue by MDASI-HN-F. Abbreviations: MDASI-HN-F, Fatigue item of MD Anderson Symptom Inventory-Head and Neck module.

as the most discriminative threshold. The group of patients who received higher doses to the pituitary gland and reported fatigue ($N = 29$) was characterized by being younger (mean age of 53 years) in comparison to those who received similar doses to the pituitary gland and did not report fatigue ($N = 14$) (mean age of 56 years). However, 7% of both groups received RT alone and 62% vs. 64% presented with advanced T stages among patients who reported fatigue vs. those who did not.

Discussion

The present study is part of our larger effort focused on the development of effective strategies to prevent and/or reduce symptoms and treatment-related toxicities in HNC patients. Our previous efforts and others' demonstrated that incidental radiation of the non-target CNS normal tissues could increase the incidence and burden of acute fatigue [10], cognitive impairment [26] and nausea/vomiting [6,8]. In the current study, we analyzed the relationship between patient-reported and observer-assessed chronic fatigue (presence and severity) and the delivered RT doses to ten potential FARS in NPC patients treated with RT (±chemotherapy).

We identified a linear association between the MDASI-HN-F single-item scores and the CTC-AE severity grades. The Dmax values of four FARS (pituitary gland, brainstem, hippocampus, and hypothalamus) trended consistently and uniformly lower in patients without fatigue, with statistical significance for the pituitary gland, even after controlling for clinical variables.

Table 3
Dmax (A) and Dmean (B) for select* potential fatigue-related ROIs by MDASI-HN-F severity grouping.

ROIs	MDASI-fatigue	Number	Mean values of Dmax	±SE	Lower 95%	Upper 95%	*P* value
A							
Brainstem	None/Mild	42	53	1.18	50.39	55.10	0.26
Brainstem	Moderate/Severe	14	54	2.04	50.03	58.21	
Hippocampus	None/Mild	42	45	2.39	39.93	49.52	0.09
Hippocampus	Moderate/Severe	14	44	4.14	35.36	51.98	
Pituitary gland	None/Mild	42	58	1.81	53.99	61.23	0.01
Pituitary gland	Moderate/Severe	14	65	3.13	59.09	71.63	
Hypothalamus	None/Mild	42	30	0.2	32.5	34	0.3
Hypothalamus	Moderate/Severe	14	33	0.7	27	30	
ROIs	CTCAE-fatigue	Number	Mean values of Dmax	±SE	Lower 95%	Upper 95%	*P* value
B							
Brainstem	None/Mild	37	52	1.21	49.96	54.88	0.56
Brainstem	Moderate/Severe	19	54	1.84	50.52	58.26	
Hippocampus	None/Mild	37	43	2.35	38.48	48.01	0.49
Hippocampus	Moderate/Severe	19	47	4.00	38.42	55.24	
Pituitary gland	None/Mild	37	57	2.19	52.44	61.33	0.01
Pituitary gland	Moderate/Severe	19	65	1.57	61.42	68.03	
Hypothalamus	None/Mild	37	33	0.3	32.5	34	0.4
Hypothalamus	Moderate/Severe	19	33	0.4	30	32	

* The four selected ROIs are those with numerical difference in the Dmax.

Consistently, across our data we found fairly comparable dosimetric results whether considering MDASI-HN-F or CTC-AE. For each parameter tested and method (Dmax, Dmean, logistic regression, fatigue severity grouping), the dose to the pituitary gland showed the strongest correlation and was the only positive isolated variable in term of statistical significance. Given the relatively uniform technique and routine IMRT optimization methods applied during planning, this cohort had relative dose homogeneity to the brainstem and other FARS more superior (and posterior) to the target volumes, which could explain the lack of statistical difference of the Dmax for brainstem, hippocampus, and hypothalamus in this study.

Of note, the steepness of the Dmax/MDASI-HN-F relationship for the pituitary gland highlights that small increases in the Dmax for non-target FARS could affect long-term fatigue. The dose-fatigue score relationships for the brainstem and hippocampus relationships were comparatively flat and with larger spread but could also be considered for dose reduction in fatigue-sparing IMRT or proton therapy strategies. There was no statistical association between either Dmax or Dmean and fatigue for the other 6 FARS considered in our analysis. It is notable that overall Dmax and Dmean to these structures were in the low-dose range (Dmax <20 Gy and Dmean <10 Gy), so we cannot rule out that higher doses to these structures would not have clinical impact. Moreover, given the lack of dose differential for many of these FARS, the potential clinical benefit of eliminating the unnecessary integral dose to CNS structures, such as that achievable using proton therapy, will require additional study.

In the PARSPORT trial, there was no dosimetric association across the pituitary gland, pineal gland, hypothalamus, hippocampus and basal ganglia, as these structures received low doses (i.e., Dmean and Dmax were <10 Gy) [19]. In our study, and in contrast to the PARSPORT study (in which the majority of cases were oropharyngeal tumors), given the proximity of the pituitary gland to the target volumes for patients with NPC, particularly for those with T3/4 disease where the superior aspect of the target volume typically includes the sphenoid sinus and often the cavernous sinus, the doses to the pituitary gland were substantially higher and we were able to identify a consistent dose-fatigue relationship.

Our study expands the existing literature on fatigue and NPC, as previous studies have focused on acute, rather than chronic fatigue. Additionally, concerning the CNS ROIs within the intermediate-dose region, Powell et al. [10] showed that in an NPC cohort predominantly treated by IMRT, the Dmean for the pituitary gland was associated with RT-associated fatigue during and shortly after treatment. Moreover, Gulliford and Ferris demonstrated that dose parameters of the brainstem had a statistically significant association with acute fatigue [18,19]. While it could be argued that acute fatigue may represent a possible surrogate for chronic fatigue, no study has addressed this question so far. Therefore, our study is the first to correlate dosimetric data from MRI-segmented ROIs to late, patient-reported and clinician-rated fatigue in NPC survivors.

Other reports of irradiation of brain tumors have focused on minimizing doses to the hippocampus especially in the setting of pediatric oncology. There is a growing trend to utilize hippocampal sparing techniques to preserve the neurocognitive function [27,28], based on the hypothesis that radiotherapy-induced damage to neuronal progenitor cells in the subgranular zone of the hippocampi may increase the risk of cognitive impairment [29,30]. However, clear dose limits have yet to be identified, and the general conclusion of these previous studies is to keep the dose to the bilateral hippocampus as low as possible without jeopardizing target coverage [31–33]. Applying this philosophy, in order to potentially mitigate fatigue, we recommend that the pituitary gland be routinely contoured and constrained to Dmax <54 Gy during plan optimization when achievable without compromising target volume coverage. While our findings are disease-site and mostly RT technique-specific and should be considered hypothesis generating, given the numerical trends and relative strength of associations by logistic regression, it may be practical to implement constraints for the brainstem, hippocampus, and hypothalamus in the low- and intermediate-dose range as well. Prospective validation of these planning strategies is needed to further define the ROI specific dose-fatigue relationship.

Recently, efforts have focused on the elucidation of the biological mechanisms underlying fatigue, which could be hypothalamic-pituitary dysfunction [34] or increased pro-inflammatory cytokine production (such as hippocampal TNF-α and IL-1) [35,36]. It has been demonstrated that the prevalence of hypopituitarism is higher in the pediatric age group [37,38] and patients with NPC [39,40] after radiotherapy. Xiao et al. [41] correlated inflammation as measured according to serum interleukin-6 and C-reactive protein levels with fatigue in HNC patients before and after IMRT.

Future studies incorporating hormonal and inflammatory biomarkers to fully characterize the dose-fatigue relationship and RT-driven mechanism would be ideal. These studies need to also consider circadian rhythms of adrenocortical axis hormone baseline levels and baseline and other medical contributing factors.

Based on our data and data from others' previous experience, postulating that irradiation induces disruption of neural connections between FARS seems legitimate. A recent report by Ratnasingam and colleagues [42] on a small cohort of NPC patients given three-dimensional conformal RT seems to support this hypothesis. Specifically, the authors reported a prevalence rate of up to 82% for hypothalamic/pituitary dysfunction and a significant correlation between the diagnosis of endocrinopathies and the follow-up time after RT and the use of concomitant chemotherapy and RT. The complexity of the mechanisms involved in fatigue and contribution of other factors such as chemotherapy, comorbidities, and psychological disorders calls for both further investigations and multidisciplinary clinical assessment of NPC patients.

From a practical standpoint, manual segmentation of the pituitary gland on planning images is straightforward, and constraints are simple to implement into plan optimization and evaluation. Our results point to Dmax for the pituitary gland of <54 Gy and V52 Gy <16% as potential target constraints for clinical implementation to reduce the chronic fatigue after RT, particularly in the treatment of young patients, who showed more potential sensitivity to higher RT dose to the pituitary gland; however, physicians should ensure that target volume coverage is not compromised. Future study is needed to uncover the potential relationship between the hormonal-pathophysiological mechanisms, and the patient- and treatment-related variables for those with problematic levels of fatigue.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.12.023.

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