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Scientific Article

Fatigue in Patients With Head and Neck Cancer Treated With Radiation Therapy: A Prospective Study of Patient-Reported Outcomes and Their Association With Radiation Dose to the Cerebellum

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Abstract

Purpose: Although fatigue is a known side effect in patients with head and neck cancer (HNC) receiving radiation therapy, knowledge regarding long-term fatigue and dose-response relationships to organs at risk is scarce. The aim of this prospective study was to analyze patient-reported fatigue in patients with HNC receiving radiation therapy and to explore any possible association with organ-at-risk doses.

Methods and Materials: Patients with HNC referred for curative radiation therapy were eligible for inclusion in the study. To assess patient-reported fatigue, quality of life questionnaires (European Organization for Research and Treatment of Cancer QLQ-C30 and QLQ-FA12) were distributed before treatment and 1, 3, 6, 12, 24, and 60 months after the start of treatment. Mean dose (D_{mean}) and near maximum dose (D2%) of the cerebellum and brain stem were evaluated in relation to baseline-adjusted fatigue scores at 3 months.

Results: One hundred twenty-six patients treated with intensity modulated radiation therapy between 2008 and 2010 were available for final analysis. Female sex and age <60 years were associated with higher fatigue at baseline, whereas patients also treated with

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chemotherapy had reduced physical and emotional fatigue at 6 months. Physical fatigue (QLQ-FA12 scale) increased from baseline up to 3 months (29 vs 59; $P < .0001$) but showed no difference compared with baseline from 1 to 5 years. Emotional fatigue was significantly lower at 5 years compared with baseline (14 vs 28; $P < .0001$). Patients with cerebellum $D_{mean} > 3.5$ Gy had higher mean physical fatigue scores at 3 months (38 vs 27; $P = .036$).

Conclusions: Although there is a significant increase in fatigue scores for patients with HNC up to 1 year after radiation therapy, this study showed a return to baseline levels at 5 years. A possible association was found between physical fatigue and a higher mean dose to the cerebellum.

Introduction

Fatigue, during and after radiation therapy, is one of the side effects causing substantial distress in patients with cancer, greatly affecting health-related quality of life (HRQOL).[1,2] Specifically in patients with head and neck cancer (HNC), fatigue has been described as an acute complication to radiation therapy and has also been reported in a few studies to have a strong association with overall quality of life.[3,4] Apart from being an acute side effect of treatment, there is growing evidence of persisting fatigue in long-term survivors of cancer from other cancer types than HNC.[5,6] With a growing population of long-term survivors after treatment for HNC, studies of the incidence and patterns of lasting fatigue in this patient group are warranted.

The mechanisms of radiation-induced fatigue are not well understood and organs at risk (OARs) that should be spared at treatment planning are yet to be determined.[7] With the introduction of intensity modulated radiation therapy (IMRT), doses to OARs such as the parotid glands have been substantially reduced, leading to improved salivation and decreased dryness of the oral mucous membranes.[8] However, as shown in the parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT) trial, levels of fatigue were higher in patients treated with IMRT, possibly due to relatively higher doses to the posterior cerebral fossa and cerebellum.[9] Further studies support that brain stem and pituitary gland doses contribute to fatigue levels, suggesting that by reducing the absorbed dose to these OARs during treatment planning, fatigue symptoms may be mitigated.[10,11] Patient-reported outcome fatigue measures have been used rarely in previous studies, and their addition is likely to increase the understanding of radiation-induced fatigue.[12] As several different brain structures are likely involved in the development of fatigue symptoms, a multidimensional tool covering both the physical and cognitive effects of fatigue would be most useful in a clinical setting.[13,14] The European Organization of Research and Treatment of Cancer (EORTC) QLQ-FA12 fatigue questionnaire comprises physical as well as emotional and cognitive subscales enabling more granular scoring.[15] The aim of this study was to prospectively investigate longitudinal patterns of fatigue in long-term survivors of HNC treated with definitive radiation therapy and to investigate the association with radiation doses to OARs, specifically the brain stem and cerebellum.

Methods and Materials

Study design

All patients with newly diagnosed HNC, discussed at our regional tumor board, and referred for curative radiation therapy with IMRT between 2008 and 2010 were consecutively invited to participate in this prospective study. HRQOL questionnaires (EORTC QLQ-30 to measure general HRQOL for patients with cancer and EORTC FA12 for measurement of fatigue) were distributed to the patients at baseline and 1, 3, 6, 12, 24, and 60 months after start of treatment. The questionnaires were sent out by mail to patients at each predefined time point and nonresponders were reminded once. The Regional Ethics Committee in Gothenburg, Sweden granted study approval (Dnr: 076-08).

Treatment

Radiation therapy was delivered in doses ranging from 64 to 72 Gy to full-dose target volumes and 40 to 52 Gy to elective target volumes. For most patients, accelerated fractionation schedules were used either with 1.7 Gy per fraction given 10 times a week or 1.9 to 2 Gy per fraction given 6 to 8 times a week.[16-18] Patients with nasopharyngeal cancer were treated with conventional fractionation, but with a 2.2-Gy concomitant boost to the gross tumor volume. All patients were treated with IMRT using 6-MV photons and sliding-window IMRT technique. Sequential boost, when given, was either delivered with IMRT or 3-dimensional conformal radiation therapy. Treatment plans were generated in Eclipse TPS (Varian Medical Systems, Palo Alto, CA) and final absorbed doses were calculated using the pencil beam convolution algorithm (versions 8.1.18-8.9.08) with modified Batho

heterogeneity correction. Dose prescriptions to the volumes of interest were as of International Commission on Radiation Units and Measurements report 83, with a maximum dose to the spinal cord <46 Gy and a parotid gland mean dose <25 Gy being prioritized during treatment planning.[19,20] Doses to other OARs (including mandible, larynx, oral and oropharyngeal cavity, and submandibular glands) were kept as low as possible. Induction (cisplatin and fluoruracil) or concomitant (weekly cisplatin) chemotherapy was added to the radiation therapy for patients with stage III and IV disease. Patients with oral cancers stage III and IV were treated with a combination of surgery followed by postoperative radiation therapy, unless considered medically inoperable. Radical modified neck dissections were performed in node-positive patients with oral cavity tumors and in patients with an unknown primary tumor, whereas node-negative patients with oral cancers underwent diagnostic neck dissections. Locoregional salvage surgery was offered to patients with residual disease after radiation therapy.

Fatigue assessment

Fatigue data were assessed with the EORTC QLQ-C30 (version 3.0) and QLQ-FA12 questionnaires. The QLQ-C30 covers general symptoms common for all patients with cancer but for the purpose of this study, only the fatigue and global quality of life scales were used.[21] In the QLQ-FA12 questionnaire, the 12 questions were grouped into 3 domains (ie, physical, cognitive, and emotional fatigue), except for 2 single items on "interference of fatigue with daily activities" and "lack of understanding of tiredness by people close to the subject."[22,23] The scores were transformed to scales ranging from 0 to 100 (higher score corresponding to greater degree of fatigue) using the procedure described in the EORTC scoring manual.[24] The psychometric properties of QLQ-FA12 have been validated according to EORTC guidelines in 11 European countries with corresponding translations, including Swedish.[22]

Organ-at-risk volumes and doses

Delineation of the brain stem and cerebellum was performed according to EORTC/Radiation Therapy Oncology Group guidelines by an experienced radiation oncologist (EA) using original pretreatment planning computed tomography scans.[25] Absorbed doses was converted to equivalent dose at 2 Gy per fraction using the scripting application programming interface of the Eclipse TPS version 16.1 (Varian Medical Systems), to account for differences in fractionation schedules before extraction of dose-volume histogram metrics for each patient. Corrections for incomplete repair between fractions were done using the adjusted version of the Linear-quadratic formula with an $\alpha/\beta = 3$ Gy. We used individually determined H_m values with an assumed repair half-time of 5 hours for brain tissue and the actual time interval between fractions as recorded in the oncology information system. Fractionation-corrected near-maximum absorbed dose (D2%) and fractionation-corrected mean absorbed dose (D_{mean}) were chosen to study potential dose-response effects.

Statistical analysis

The association between fatigue scores and sex, age (>60 years vs <60 years), Karnofsky Performance Score (KPS; KPS = 90-100 vs KPS <90), and chemotherapy (yes vs no) was assessed in univariate analysis. To estimate the effect of baseline fatigue levels, patients were split into no fatigue (score <10) versus fatigue (score >10) assuming a difference in score of 10 points as clinically relevant.[26] Changes from baseline fatigue levels were compared for all scales. For comparison over time, the Wilcoxon signed-rank test was used for continuous variables and sign test was used for categorical variables. To categorize doses to OARs, the median in the patient cohort for each dose variable (D2% and D_{mean} for brain stem and cerebellum) was chosen as the cutoff value for high versus low dose. To adjust for baseline fatigue scores, the difference in score between the time point where fatigue levels peaked after start of treatment (3 months) and baseline values were used in the dose-fatigue analyses.

The Fisher nonparametric permutation test was used to compare continuous variables between groups. A significance level of 95% was considered throughout. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics

The patient characteristics at inclusion are shown in Table 1. In total, 186 patients with a new diagnosis of head and neck cancer planned for full-dose radiation therapy were asked to participate in the study. One hundred fifty-six patients accepted inclusion and 135 were planned using IMRT technique. For various reasons, 9 patients did not receive radiation therapy, leaving 126 patients for evaluation. The average age at inclusion was 59.9 years and 77% of patients were men. Oropharynx was the predominant site (63%) of disease and a majority (86%) of patients received a diagnosis of advanced stage disease (III-IV). Ninety-one patients (72%) were treated with chemotherapy and 20 patients (16 %) underwent surgery. The median follow-up time was 63 months

Table 1 Patient characteristics at inclusion

Characteristic	Patients included (N = 126)
Sex	
Female	29 (23.0%)
Male	97 (77.0%)
Mean age (range; SD), y	59.9 (26-82;10.2)
Karnofsky Performance Score	
<90	13 (10.4%)
90-100	113 (89.6%)
Tumor site	
Oral	16 (12.7%)
Oropharynx	80 (63.5%)
Hypopharynx	9 (7.1%)
Nasopharynx	11 (8.7%)
Unknown primary	10 (7.9%)
Stage	
I	3 (2.4%)
II	15 (11.9%)
III	19 (15.1%)
IV	89 (70.6%)
Chemotherapy	91 (72.2%)
Primary surgery + neck dissection	10 (7.9%)
Neck dissection only	10 (7.9%)
1-y survival	119 (94.4%)
2-y survival	109 (86.5%)
5-y survival	95 (75.4%)

Abbreviation: SD = standard deviation.
Data are presented as n (%) unless otherwise indicated.

(range, 3-120 months) and the 5-year survival rate was 75%. Survival data were available for all patients at 5-year follow-up. None of the surviving patients at 5 years had received additional cancer treatment after the primary treatment.

Fatigue over time for all patients

Fatigue and global quality of life scores according to the EORTC QLQ-C30 and physical, emotional, and cognitive fatigue from the QLQ-FA12 at all time points are presented in Table 2. Seventy-three of 95 patients (77%) alive responded at 5 years. There were no differences in baseline patient characteristics between responders and nonresponders. From the QLQ-FA12, physical fatigue increased significantly from baseline up to 6 months after treatment, peaking at 3 months. From 1 year and up to 5 years, physical fatigue returned to slightly lower scores

Table 2 EORTC QLQ-FA12 scores for all patients at all time points

	Baseline	1 m		3 m		6 m		12 m		24 m		60 m	
	Mean score (SD) (n = 126)	Mean score (SD) (n = 85)	Change from baseline *P* value	Mean score (SD) (n = 96)	Change from baseline *P* value	Mean score (SD) (n = 94)	Change from baseline *P* value	Mean score (SD) (n = 95)	Change from baseline *P* value	Mean score (SD) (n = 84)	Change from baseline *P* value	Mean score (SD) (n = 73)	Change from baseline *P* value
QLQ-FA12													
Physical fatigue	29 (24.1)	53 (26.9)	**<.0001**	59 (23.8)	**<.0001**	38 (25.5)	**.0003**	22 (18.8)	.21	23 (19.3)	.97	23 (23.6)	.26
Emotional fatigue	28 (27.5)	27 (27.8)	.90	34 (24.6)	**.0078**	22 (26.7)	.45	9 (14.3)	**.0008**	14 (23.3)	**.013**	14 (14.1)	**<.0001**
Cognitive fatigue	16 (24.3)	14 (20.6)	.64	19 (21.6)	**.028**	11 (18.3)	.51	7 (17.0)	.17	6 (15.4)	**.0015**	10 (19.3)	.52
QLQ-C30													
Fatigue	27 (23.4)	56 (28.1)	**<.0001**	61 (23.9)	**<.0001**	40 (24.1)	**<.0001**	26 (21.4)	.45	24 (31.9)	.47	23 (23.5)	1.00
Global QOL	63 (22.5)	49 (21.8)	**<.0001**	45 (18.2)	**<.0001**	59 (20.1)	**.016**	68 (21.6)	.81	74 (21.5)	**.022**	73 (21.9)	**.0060**

Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; m = months after start of treatment; QOL = quality of life; SD = standard deviation.
Higher values denote more symptoms for fatigue scales but better functioning for global quality of life. Values in boldface indicate significant change from baseline scores.

than baseline, although the difference was nonsignificant. Emotional fatigue also increased significantly from baseline to 3 months after treatment, but from 1 up to 5 years the score was significantly reduced compared with baseline. Cognitive fatigue was likewise significantly increased at the 3-month follow-up, before returning to near baseline values from 6 months and onwards. Fatigue in the QLQ-C30 followed a similar pattern as physical fatigue from the QLQ-FA12, with a significant increase up to 6 months after treatment before returning to baseline values. Global quality of life was reduced up to 6 months after start of treatment (45-59 vs 63; $P = .016$), but was significantly improved compared with baseline at 2 (74 vs 63; $P = .022$) and 5 years (73 vs 63; $P = .006$) after treatment. The results from the QLQ-FA12 scores over time are visualized in Fig. 1.

Fatigue in subgroups over time

The QLQ-FA12 scores in patient subgroups over time are shown in Table 3. Female sex and younger age were predictive for significantly higher scores in the emotional and cognitive scales at baseline. Additionally, physical fatigue was significantly higher in younger patients and patients with poorer performance status (KPS <90) at treatment start. Patients who received chemotherapy showed no significant differences in fatigue compared with radiation therapy–only patients at baseline.

Physical and emotional fatigue scores were significantly higher during treatment (1 month after start of treatment) in women compared with men, but showed no difference at the other time points. There were no differences between age groups in any of the scales at any timepoint after treatment start. Patients with a KPS lower than 90 had a higher cognitive fatigue score at 5 years; however, it should be noted that only 4 patients in this group responded at that time point. Physical and emotional fatigue were significantly increased at 6 months in patients who had not received chemotherapy, but remained nonsignificant for all other time points. Mean values for patients scoring <10 compared with >10 at baseline was 2.7 versus 36.8 for physical fatigue, 0 versus 36.6 for emotional fatigue and 0 versus 39.5 for cognitive fatigue. There were no differences in patient characteristics for these 3 groups compared with all patients. Change in fatigue in patients with no baseline fatigue were significantly higher at all time points and in all scales compared with patients with fatigue at baseline.

Fatigue in relation to cerebellum and brain stem dose

The increase of mean fatigue scores from baseline to 3 months after treatment is shown in Table 4 for high and low OAR doses, respectively. The QLQ-FA12 physical fatigue mean score increase was significantly higher for the group of patients with a cerebellar D_{mean} of >3.5 Gy

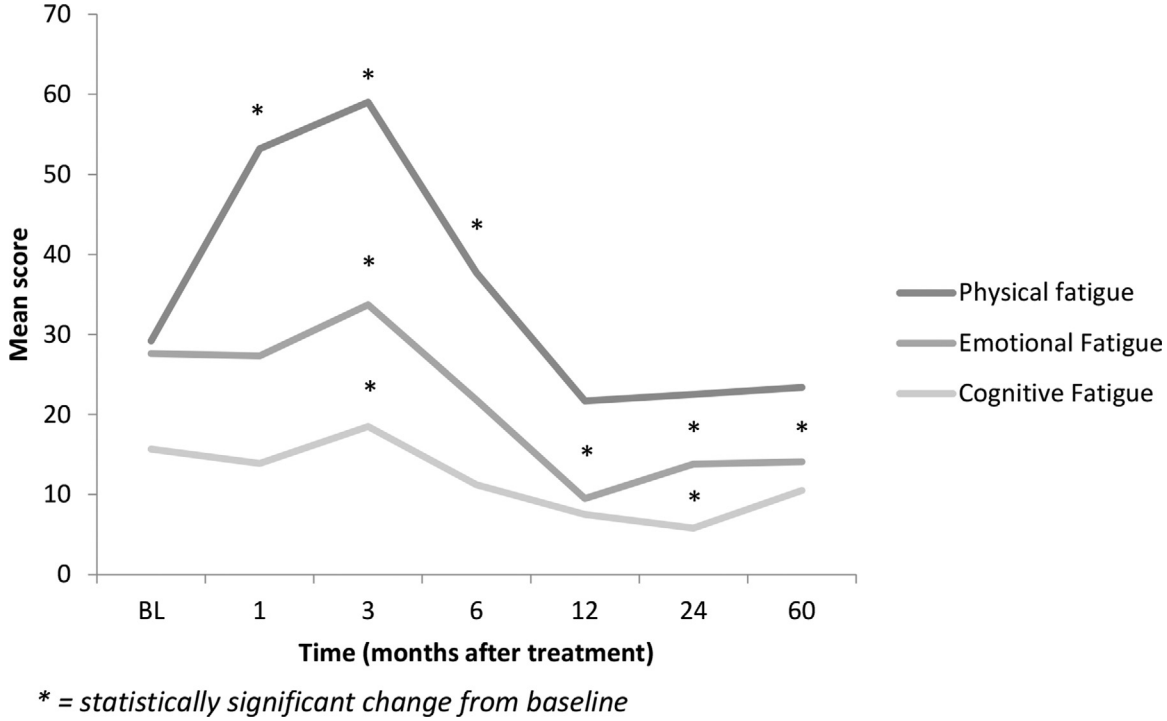

Figure 1 Mean fatigue scores according to the European Organization for Research and Treatment of Cancer QLQ-FA12 questionnaires for patients with head and neck cancer at baseline and 1 to 60 months after treatment.

Table 3 Comparison of EORTC QLQ-FA12 scores at all time-points for selected subgroups

Gender																					
	Baseline			***1 m***			***3 m***			***6 m***			***12 m***			***24 m***			***60 m***		
	F (*n*=29)	**M (*n*=97)**	***P***	**F (*n*=23)**	**M (*n*=62)**	***P***	**F (*n*=19)**	**M (*n*=77)**	***P***	**F (*n*=21)**	**M (*n*=73)**	***P***	**F (*n*=18)**	**M (*n*=77)**	***P***	**F (*n*=17)**	**M (*n*=67)**	***P***	**F (*n*=18)**	**M (*n*=55)**	***P***
Physical Fatigue	33	28	*.33*	62	50	***.036***	59	59	*.73*	40	37	*.97*	22	18	*.67*	25	22	*.58*	27	22	*.63*
Emotional fatigue	38	24	***.018***	40	22	***.041***	33	34	*.67*	27	21	*.97*	4	10	*.25*	11	14	*.67*	23	11	*.18*
Cognitive Fatigue	26	13	***.009***	22	11	*.10*	20	18	*.60*	17	10	*.27*	6	8	*.87*	6	6	*.31*	17	8	*.46*
Age																					
	Baseline			***1 m***			***3 m***			***6 m***			***12 m***			***24 m***			***60 m***		
	≤60 (*n*=50)	**>60 (*n*=76)**	***P***	**≤60 (*n*=38)**	**>60 (*n*=47)**	***P***	**≤60 (*n*=37)**	**>60 (*n*=59)**	***P***	**≤60 (*n*=32)**	**>60 (*n*=62)**	***P***	**≤60 (*n*=37)**	**>60 (*n*=58)**	***P***	**≤60 (*n*=33)**	**>60 (*n*=51)**	***P***	**≤60 (*n*=30)**	**>60 (*n*=43)**	***P***
Physical Fatigue	35	25	***.021***	54	52	*.76*	60	59	*.92*	35	39	*.63*	22	22	*.98*	22	23	*.89*	26	21	*.46*
Emotional fatigue	36	22	***.0006***	26	28	*.78*	35	33	*1.00*	22	22	*.87*	10	9	*.88*	13	15	*.59*	18	11	*.41*
Cognitive Fatigue	22	11	***.009***	17	11	*.09*	19	18	*.73*	12	10	*.45*	8	7	*.80*	6	6	*.46*	16	7	*.16*
Karnofsky Performance Score																					
	Baseline			***1 m***			***3 m***			***6 m***			***12 m***			***24 m***			***60 m***		
	≥90 (*n*=113)	**<90 (*n*=13)**	***P***	**≥90 (*n*=80)**	**<90 (*n*=5)**	***P***	**≥90 (*n*=88)**	**<90 (*n*=8)**	***P***	**≥90 (*n*=85)**	**<90 (*n*=8)**	***P***	**≥90 (*n*=88)**	**<90 (*n*=7)**	***P***	**≥90 (*n*=78)**	**<90 (*n*=5)**	***P***	**≥90 (*n*=69)**	**<90 (*n*=4)**	***P***
Physical Fatigue	27	48	***.011***	53	64	*.37*	59	60	*.95*	37	50	*.22*	21	33	*.25*	22	33	*.52*	23	28	*.42*
Emotional fatigue	27	38	*.07*	26	47	*.09*	33	37	*.86*	21	28	*.18*	9	11	*.36*	13	11	*.55*	13	31	*.08*
Cognitive Fatigue	15	22	*.19*	13	23	*.34*	18	21	*.77*	11	14	*.50*	8	0	*.48*	6	0	*.68*	9	38	***.023***
Chemotherapy																					
	Baseline			***1 m***			***3 m***			***6 m***			***12 m***			***24 m***			***60 m***		
	No (*n*=35)	**Yes (*n*=91)**	***P***	**No (*n*=20)**	**Yes (*n*=65)**	***P***	**No (*n*=26)**	**Yes (*n*=70)**	***P***	**No (*n*=26)**	**Yes (*n*=68)**	***P***	**No (*n*=24)**	**Yes (*n*=71)**	***P***	**No (*n*=22)**	**Yes (*n*=62)**	***P***	**No (*n*=21)**	**Yes (*n*=52)**	***P***
Physical Fatigue	33	27	*.38*	53	53	*.99*	57	60	*.82*	48	34	***.015***	27	21	*.35*	26	22	*.61*	25	23	*1.00*
Emotional fatigue	32	26	*.54*	25	28	*.26*	34	34	*.78*	32	18	***.014***	11	9	*.94*	19	13	*.42*	19	12	*.35*
Cognitive Fatigue	22	13	*.15*	13	14	*.76*	16	19	*.62*	13	11	*.39*	4	8	*.44*	10	11	*.77*	0	2	*.74*
Change in Fatigue level from Baseline if Non-fatigue (<10) or fatigue present (>10) at baseline																					
	1 m			***3 m***			***6 m***			***12 m***			***24 m***			***60 m***					
	Non-fatigue (*n*=35)	**Fatigue present (*n*=91)**	***P***	**<10 (*n*=35)**	**>10 (*n*=91)**	***P***	**<10 (*n*=35)**	**>10 (*n*=91)**	***P***	**<10 (*n*=35)**	**>10 (*n*=91)**	***P***	**<10 (*n*=35)**	**>10 (*n*=91)**	***P***	**<10 (*n*=35)**	**>10 (*n*=91)**	***P***			
Physical Fatigue	44	21	***.0014***	48	27	***.0005***	26	6	***.005***	9	-9	***.006***	13	-6	***.0056***	8	-7	***.0024***			
Emotional fatigue	19	-1	***.009***	29	3	***.0002***	12	-8	***.0038***	4	-24	***.0006***	4	-18	***.025***	2	-16	***.02***			
Cognitive Fatigue	7	-8	***.001***	13	-7	***.0002***	4	-12	***<.0001***	3	-17	***.0014***	1	-20	***<.0001***	10	-20	***<.0001***			

Higher values denote more symptoms; Fisher's nonparametric permutation test was used to compare continuous variables between groups; Bold values represent 95% significance difference between groups; Abbreviations: m=months after start of treatment; F=Female; M=Male; ≤60=up to 60 years of age at inclusion; >60=more than 60 years of age at inclusion; ≥90=KPS of 90-100; KPS of <90; No= no chemotherapy given; Yes=chemotherapy given

Table 4 Mean for difference between 3 months after start of treatment and baseline fatigue scores between patients above or below median dose to organs at risk

			EORTC FA-12						EORTC QLQ-30	
		n	Mean Δscore Physical fatigue (SD)	P	Mean Δscore Emotional fatigue (SD)	P	Mean Δscore Cognitive fatigue (SD)	P	Mean Δscore Fatigue (SD)	P
Brainstem D2 (Gy)	> 30	45	32 (23.8)	.81	11 (28.3)	.42	6 (22.8)	.91	34 (27.9)	.51
	< 30	46	33 (26.7)		6 (30.9)		5 (24.3)		37 (25.5)	
Brainstem DMean (Gy)	> 4.3	45	32 (23.8)	.73	8 (28.9)	.89	4 (20.8)	.63	31 (25.5)	.079
	< 4.3	46	33 (26.6)		9 (30.7)		7 (26.0)		41 (27.0)	
Cerebellum D2 (Gy)	> 17.5	45	36 (25.2)	.18	11 (29.7)	.43	7 (23.5)	.55	38 (26.5)	.33
	< 17.5	46	29 (24.9)		6 (29.6)		4 (23.6)		33 (26.7)	
Cerebellum DMean (Gy)	> 3.5	45	38 (25.6)	**.036**	11 (30.3)	.43	7 (23.7)	.79	40 (26.8)	.10
	< 3.5	46	27 (23.7)		6 (29.0)		5 (23.5)		31 (25.9)	

Bold values represent 95% significance difference between groups. Abbreviations: SD=Standard Deviation; Gy=Gray; D2=near-maximum absorbed dose; DMean=mean absorbed dose

compared with those with a D_{mean} <3.5 Gy (38 vs 27; $P = .036$). There were no statistically significant differences in mean scores for any other fatigue domain in neither the groups of patients separated into high vs low cerebellum D2% nor in the groups separated into high versus low brain stem D_{mean} or D2%. Nor were there any statistically significant differences in the QLQ-C30 fatigue scores between any of the investigated dose groups.

Discussion

In this study, we demonstrate an acute-phase increase in fatigue levels reported by patients with HNC up to 6 months after treatment with radiation therapy. However, we observe a return to baseline levels or slightly below during long-term follow-up (from 1 year up to 5 years after diagnosis). At baseline, female sex and younger age (<60 years) is associated with higher levels of fatigue, but these differences do not persist longitudinally. In the acute phase, 3 months start after treatment, cerebellum D_{mean} correlates with increased EORTC QLQ-FA12 physical fatigue levels, suggesting a dose-response relationship. Although fatigue is recognized as a significant side effect in HNC, there are few studies on the long-term effect of full-dose radiation therapy in these patients. Levels of fatigue in survivors of HNC have been described in several studies, but lack of baseline data makes them difficult to interpret.[27,28] Jellema et al[29] prospectively studied the effect of radiation-induced xerostomia on HRQOL and found significantly higher patient-reported fatigue levels 24 months posttreatment in patients with xerostomia (according to the Radiation Therapy Oncology Group scale). In the present study, we instead show that all 3 fatigue scales return to baseline already 1 year after treatment and remain there up to 5 years posttreatment. We have previously reported that long-term patient-reported xerostomia is significant in these patients, but with no clear effect on fatigue levels.[30] As the patients in the study by Jellema et al were treated with conventional radiation therapy, the effect on fatigue is not entirely comparable to patients treated with parotid-sparing IMRT. For comparison with survivors of cancer with other cancer diagnoses, there is a recent study from Schmidt et al[31] in which they have assessed fatigue levels approximately 2 years after diagnosis with the EORTC QLQ-FA12 questionnaire. They analyzed 2,244 patients with 15 different cancer diagnoses (no patients with HNC included) and the mean values for all 3 dimensions (physical, emotional, and cognitive) are higher for all diagnoses compared with the scores in this present study. It is our belief that the findings in the present study indicate that fatigue, although present, is not a dominating symptom among HNC long-term survivors.

The finding that female patients scored higher than male patients at baseline is not necessarily related to the

cancer diagnosis. In a study on normative HRQOL from the Swedish population, women score generally a bit worse than men.[32] Furthermore, Hinz et al[33] showed in a study using QLQ-FA12 in a German general population cohort that women report higher scores than men in all 3 fatigues scales. Although no explanation is proposed by the authors, they conclude that sex should be accounted for when analyzing scores. There were no observed sex differences in the present study after treatment completion. The addition of chemotherapy to radiation therapy is known to increase posttreatment fatigue in patients with HNC.[34] We could not find any significant difference in fatigue levels between patients receiving chemotherapy or not from baseline and up to 3 months after treatment. Surprisingly, there was a significant difference at 6 months favoring the chemotherapy group. Although there is no clearcut explanation, there are differences between the 2 groups regarding subsites and surgery. The level of fatigue at baseline seems to be of importance for how severely patients are experiencing fatigue posttreatment, where patients with close to no fatigue have greater increase of fatigue score at all time points. This could possibly be attributed to the response shift model described by Sprangers et al,[35] where patients who experience fatigue already at baseline don't experience the treatment-induced symptoms as severe as nonfatigued patients.

Few previous studies report the potential effects of radiation doses to structures in the central nervous system (CNS) on fatigue. The PARSPORT study was successful in showing the benefit of parotid-sparing IMRT, but one surprising finding was the increase of acute fatigue in the IMRT group.[36] In a retrospective analysis, published by the same group, they found significantly higher doses in several CNS structures in patients treated with IMRT compared with conventional radiation therapy.[9] Patients who experienced fatigue, measured as grade 2 or higher in the Common Toxicity Criteria Adverse Events version 3.0, received significantly higher doses to the brain stem, cerebellum, and posterior fossa, suggesting a potential dose-response relationship. Another prospective analysis on 40 patients with nasopharyngeal cancer, showed a significant difference in mean cerebellum dose of 3 Gy (35 Gy vs 32 Gy), comparing patients with high (grade $\geq$2) versus low-grade fatigue posttreatment.[11] High-grade fatigue during treatment correlated with higher doses to the pituitary gland and basal ganglia, leading the authors to propose that the disruption of pathways between basal ganglia and higher cortical centers and hormonal imbalances may be possible causes of radiation-related fatigue. In contrast to the present study, no patient-reported data were available in any of these studies, and the correlation between clinician and patient-reported outcomes is known to be weak, especially regarding symptoms that are not easily evaluated by clinical examination, such as fatigue.[12,14]

In a study by the MD Anderson Head and Neck Cancer Symptom Working Group composed of 56 patients with nasopharyngeal cancer treated with curative chemoradiation therapy, fatigue was correlated to doses to 10 potential risk structures, including the pituitary gland, brain stem and basal ganglia.[37] Using patient-reported as well as observer assessment of fatigue, the investigators found a dose-fatigue relationship for the pituitary gland alone. However, the mean brain stem maximum dose reported was approximately 53 Gy and therefore considerably higher than in our present study with a mean brain stem D2% of approximately 28 Gy (data not shown). If the effect on fatigue, as our data suggest, is already present at low dose levels to the relevant OARs, this effect might be concealed if virtually all patients have been exposed to high OAR doses. The median doses to the cerebellum and brain stem in our present study seem to correspond well with the doses reported in a study by Ferris et al[10] containing 124 patients with HNC evaluated with the Multidimensional Fatigues Inventory (MFI-20), before and shortly after radiation therapy. The investigators found a significant association between maximum dose to the brain stem and medulla and MFI-20 scores, where a 1-Gy increase in dose resulted in an increase of total MFI-20 score of 0.30 and 0.25 at the sixth week of treatment and 1 month posttreatment, respectively. Furthermore, this association was found to mainly affect the physical dimension of fatigue. Even if our results show an association with the cerebellum rather than the brain stem and D_{mean} rather than D2% as possible targets for clinically useful dose constraints, these findings, combined with the PARSPORT trial follow-up studies, strengthen the notion of a probable relation between fatigue and doses to the cerebellum, brain stem, and/or posterior fossa.

A limitation of the results is that we do not know the quality of life for the 22 of 95 patients alive at 5 years who did not respond to the questionnaires. One reason for not responding could have been a reduced general condition, which could have influenced our reported scores negatively. The use of different fractionation schedules in the cohort is another limitation that somewhat complicates interpretation of the results. There are data suggesting that central nervous system structures have longer recovery times between fractions, leading to more damage with accelerated fractionation.[38,39] Even with our recalculation of the absorbed dose into equivalent dose at 2 Gy per fraction, there are uncertainties, which could have affected our results. As not all simulation computed tomography in our patient cohort included the whole brain, we were restricted to the cerebellum and brain stem as possible OARs. Analyzing whole-brain dose in relation to fatigue should be of interest in future studies. Finally, we lack comprehensive data in our study on possible other factors affecting fatigue, such as thyroid function, anemia, and cytopenia.

Conclusion

Fatigue levels are most pronounced up to 1 year after radical radiation therapy but return to baseline levels at 5 years. A possible association with >3.5-Gy mean cerebellum dose and fatigue was found just after treatment. This association generates hypotheses for in silico studies and potentially also for future randomized clinical trials in patients with HNC receiving radical radiation therapy applying relevant dose constraints for OARs including the cerebellum.

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