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CLINICAL INVESTIGATION | Head and Neck

FATIGUE DURING HEAD-AND-NECK RADIOTHERAPY: PROSPECTIVE STUDY ON 117 CONSECUTIVE PATIENTS

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Purpose: Fatigue is an underevaluated cancer-related and treatment-related symptom. We analyzed fatigue in head and neck cancer patients undergoing radiotherapy (RT).

Methods and Materials: A total of 117 patients were enrolled (mean age, 58 years). Radiation therapy (median dose, 66 Gy) was given with either exclusive or postoperative intent in 52 and 65 patients, respectively. Chemotherapy (CT) was added before and/or during RT in 61 patients. The patients completed a 20-item questionnaire (Multidimensional Fatigue Inventory [MFI-20]) before, during (weekly), and after RT. The impact of patient-, tumor-, and treatment-related factors on fatigue was evaluated with unifactorial and multifactorial tests.

Results: Fatigue level increased during RT reaching a maximum at Week 6 and then slowly decreased. In multivariate stepwise regression analysis age (inversely related, $p < 0.05$), psychologic disorders ($p < 0.005$), and previous head-and-neck surgery (inversely related, $p < 0.005$) were correlated with higher pre-RT fatigue level. Pre-RT fatigue score ($p < 0.0001$), induction and/or concomitant CT ($p = 0.035$), need of cortisone during RT ($p = 0.005$), and thyroid disorders ($p = 0.032$) were correlated with higher during-RT fatigue level. Pre-RT fatigue score ($p < 0.0001$), induction and/or concomitant CT ($p < 0.001$), and need of cortisone during RT ($p < 0.005$) were correlated with higher post-RT fatigue level. No impact of gender, performance status, comorbidities other than psychologic and thyroid, tumor stage/site, RT intent, dose, volume, duration, or toxicity was observed.

Conclusion: Fatigue affects all patients undergoing RT for head-and-neck cancer, reaches maximum score at the 6th week of RT, and slowly decreases thereafter. Age, thyroid dysfunction, psychologic disorders, pre-RT fatigue score, CT, and cortisone use are correlated with RT-related fatigue levels.

Fatigue, Radiotherapy, Asthenia, MFI-20, Head and neck cancer.

INTRODUCTION

Fatigue is a common and poorly understood symptom reported by cancer patients (1). Despite its high prevalence and serious adverse effects on the quality of life, it is underestimated by medical and nursing staff (2). Both presence of tumor and cancer treatment may induce fatigue. Fatigue can have great implications on therapeutic decisions to interrupt the therapy or to decrease the dose. In many analyses, patients believed that fatigue adversely affected the quality of life more than pain, sexual dysfunction, or other symptoms (1, 3). Severity of fatigue is related to diagnosis and is worst in patients with lung, alimentary, and head and neck carcinoma (4). However, specific studies on RT-related fatigue in head and neck cancer

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Table 1. Patient, tumor, and treatment characteristics and acute radiotherapy toxicity

Characteristic	No. of patients
Number of patients	117
Age (y), mean ± SD (range)	58.4±12.4 (19–84)
Gender:	
Male	93 (79.5%)
Female	24 (20.5%)
KPS	
100	78 (66.7%)
90	32 (27.4%)
80	6 (5.1%)
Unknown	1 (0.9%)
Tumor histology:	
Squamous cell carcinoma	89 (76%)
Undifferentiated carcinoma	16 (13.5%)
Salivary tumors	8 (7%)
Melanoma	2 (1.5%)
Lymphoma	1 (1%)
Osteosarcoma	1 (1%)
Tumor stage	
Initial*	19 (16%)
Locally advanced†	98 (84%)
Tumor site	
Oral cavity	29 (25%)
Pharynx	50 (42.5%)
Larynx	24 (20.5%)
Other sites	14 (12.0%)
Comorbidities (presence of):	64 (54.7%)
Cardiovascular diseases	46 (39.3%)
Diabetes mellitus	10 (8.6%)
Respiratory diseases	8 (6.8%)
Thyroid dysfunction	7 (6.0%)
Neurologic disorders	6 (5.1%)
Psychologic disorders	9 (7.7%)
Liver diseases	11 (9.4%)
Renal diseases	4 (3.4%)
Previous malignancy	6 (5.1%)
Hemoglobin level	
Unknown	13 (11.1%)
Severe anemia‡	5 (4.3%)
Mild anemia§	34 (29.1%)
Normal hemoglobin‖	65 (55.6%)
Intent of RT	
Exclusive RT	52 (44.4%)
Postoperative RT	65 (55.6%)
Chemotherapy	61 (52%)
Induction CT	4 (3.5%)
Concomitant CT	17 (14.5%)
Induction + concomitant CT	40 (34%)
Any previous surgery for head and neck malignancy	69 (59%)
Acute RT toxicity ¶	
Mucositis	
G0	3 (2.6%)
G1	
G2	
G3	42 (36.2%)
G4	1 (0.9%)
Dysphagia	
G0	13 (11.1%)
G1	
G2	47 (40.2%)
G3	19 (16.2%)
G4	0
Skin toxicity	
G1	35 (29.9%)
G2	59 (50.4%)
G3	22 (18.8%)
G4	1 (0.8%)
Weight loss	
<5%	72 (62%)
>5%	45 (38%)
Cortisone administration during RT	80 (68%)
RT interruption due to acute toxicity**	11 (9%)

Abbreviations: CT = chemotherapy; KPS = Karnofsky performance status; RT – radiotherapy; SD = standard deviation.

* T1–T2N0.

† T3-4 and/or N positive tumors.

‡ Hemoglobin (Hb) <11 g/dl.

§ Hb for female 11 g/dl < Hb < 11.9 g/dl; for male 11 g/dl < Hb < 12.9 g/dl.

‖ Hb for female ≥12 g/dl and for male ≥ 13 g/dl (51).

¶ According to the criteria of the Radiation Therapy Oncology Group (RTOG) (8).

** Median duration of interruption: 1 day (range, 1–10 days).

patients are lacking (1). There are some reports on the quality of life, but not directly on the fatigue related to RT (5–7). The aims of our study were to analyze prospectively fatigue level and its evolution during treatment in a series of consecutive patients undergoing RT for head and neck cancer and to evaluate the impact of patient-, tumor-, and treatment-related variables.

METHODS AND MATERIALS

Study patients

A total of 125 consecutive patients undergoing RT for head-and-neck tumor between January and December 2005 at the Division of Radiotherapy of the European Institute of Oncology in Milan, Italy, were prospectively included in the study. Five patients who underwent head-and-neck RT in that period were excluded from the study because of low compliance (for reasons such as advanced age or illiteracy). Three patients, initially included in the study, were excluded from the analysis because of the low number of filled-out questionnaires (<4). Thus the final study population consisted of 117 patients (Table 1). All patients gave written informed consent to undergo RT and verbal consent to participate in the study.

Treatment

A total of 52 patients (44.4%) were treated with exclusive RT, whereas 65 patients (55.6%) received postoperative RT (Table 1). In 2 cases re-irradiation was performed. The RT was given by 6-MV photons from a linear accelerator using 2 Gy fractions, in five fractions per week. The total dose varied from 36 to 70 Gy (median, 66 Gy). In all patients three-dimensional conformal RT was performed with one of the following techniques: (*1*) two opposite, equally weighted parallel lateral or oblique fields and one anterior field (82 patients, 70%); (*2*) two lateral fields (without

middle- and lower-neck RT) (6 patients, 5%); (*3*) two small laryngeal fields (10 patients, 8.5%); (*4*) two oblique wedged upper fields with or without ipsilateral neck irradiation (19 patients, 16.5%). These techniques were classified as large-volume (items 1 and 2 above), and small-volume techniques (items 3 and 4). The RT was delivered on an out-patient basis and ranged in duration from 32 to 71 days (median, 49 days).

All patients were given guidelines about oral hygiene and alimentation. During RT patients were seen by the radiation oncologist at least once a week. Treatment toxicity (according to the Radiation Therapy Oncology Group [RTOG] criteria) and weight loss were recorded (8). Blood tests (including blood count, liver, renal, and thyroid function tests) were performed before RT, at the 4th week of treatment and 10 days after the treatment completion.

Chemotherapy was added to RT in 61 patients (52%). Induction chemotherapy included three cycles of cisplatin (100 mg/m^2 intravenous, Day 1) and 5-fluorouracil (1,000 mg/m^2/day, continuous intravenous infusion, Days 1–5) and concomitant chemotherapy included weekly carboplatin (area under the curve, 1.5) or cisplatin (100 mg/m^2) given every 3 weeks.

Instruments and methods

All patients were asked to fill out a 20-item questionnaire (Multidimensional Fatigue Inventory [MFI-20]) (9) before treatment start (pre-RT), every week of the RT (during-RT), and 10 and 40 days after the treatment completion (post-RT). The MFI-20 was translated into Italian and then evaluated independently by 2 of the investigators. The original MFI-20 was modified to have the same direction of response for all items, with response 0 corresponding to the lowest and 5 to the highest level of fatigue). Twenty responses were summed giving the value ranging from 0 (minimum) to 80 (maximum) for each measurement. Each patient was considered evaluable for analysis if at least four forms were filled out.

Statistics

Patient characteristics were summarized as frequencies and percentages for categorical variables as and means ± standard deviations (SD) for continuous variables. Time course of fatigue was reported in terms of means ± standard errors.

Strategies for replacing missing values because of unfilled questionnaire

As expected, a remarkable number of missing scores were observed. These missing values were replaced, when necessary, with the closest valid score. If occurred before RT, the missing fatigue score was replaced by the first valid one reported during RT (first observation carried backward). Because of this replacement, mean fatigue level at baseline could result greater then that calculated from the original values and the RT effect could be slightly underestimated. In case of missing scores at both post-treatment visits, replacement was done using the last (valid) score during RT (last observation carried forward [LOCF]).

Statistical analysis

The mean effect of RT was evaluated calculating the difference between the mean MFI-20 fatigue score over the entire RT period, and the baseline score. A paired *t* test was applied to quantify the statistical significance of this difference. The trend of the fatigue score over time was evaluated through three time-points: baseline pre-RT, maximum during-RT, and average post-RT scores. To check for associations among fatigue level predictors, Spearman's correlation coefficient was used. To explore the associations among each predictor of pre-RT, during-RT, or post-RT fatigue level and response variable(s), univariate analysis of variance models were used.

The predictor variables included were: age, sex, Karnofsky performance status, concomitant disorders (cardiovascular diseases, diabetes mellitus, respiratory disorders, neurologic diseases, psychologic disorders, liver diseases, thyroid dysfunction including mainly clinical or sublinical hypothyroidism, renal disorders, previous malignancy), tumor stage (initial vs. locally advanced), tumor site, intent of RT (exclusive vs. postoperative), previous head-and-neck surgery for malignancy, RT total dose, RT volume (large vs. small), RT duration, RT toxicity (mucositis, dysphagia, weight loss), administration of cortisone, induction chemotherapy, concomitant chemotherapy, and hemoglobin level. The statistical models regarding during- and post-RT fatigue predictors included also the pre-RT fatigue score as covariate, to estimate its impact and to adjust for intrasubject correlation.

The model regarding post-RT fatigue prediction has been produced on the entire set of 117 patients. To estimate the replacement effect with LOCF, the analysis has also been repeated on the subset of patients with at least one valid fatigue score reported after RT. Values of $p < 0.05$ were considered statistically significant; those between 0.05 and 0.1 were also included in the multivariate model.

For each dependent variable a final multivariate stepwise regression model (using $p = 0.1$ as entry and stay threshold levels), including the most important and statistically significant variables revealed during univariate analysis, was used. The global goodness of fit of each model, that is the amount of variance explained by the model in comparison with the total variance, as well as the partial variance explained by each variable, were evaluated by the R^2 statistic.

RESULTS

Time course of fatigue

All 117 patients who were considered evaluable for analysis filled out at least one MFI-20 questionnaire during RT. There were 102 (82.7%) and 72 (61.5%) patients with available pre-RT and post-RT fatigue data, respectively. The mean number of filled-out forms per patient was 8.3 ± 1.8 (range, 4–11).

After applying the first observation carried backward and the LOCF approaches for missing data, statistical analyses were carried on the whole sample of 117 patients. Fatigue level increased from 25.8 ± 1.7 (baseline) to 33.7 ± 1.8 as average during-RT (impairment of 7.8 points, $p < 0.0001$, Table 2). Furthermore the maximum level of fatigue during RT was 44 ± 2.0. During the whole RT period fatigue was lowest at Week 1 (27.2 ± 1.8) and highest at Week 6 (36.1 ± 2.2), showing a gradual increase in fatigue over the period of RT (Fig. 1). Only when RT was completed did fatigue begin to decrease; on average the post-RT fatigue level was 37.2 ± 2.0 (Table 2). In comparison to the average post-RT calculated on the subset of 72 patients with at least one post-RT visit (32.8 ± 2.6), the fatigue score after replacement turned out to be slightly overestimated (Table 2). The statistical analysis, designed to reveal the

Table 2. Fatigue scores over treatment time (original values and summary data after replacements)

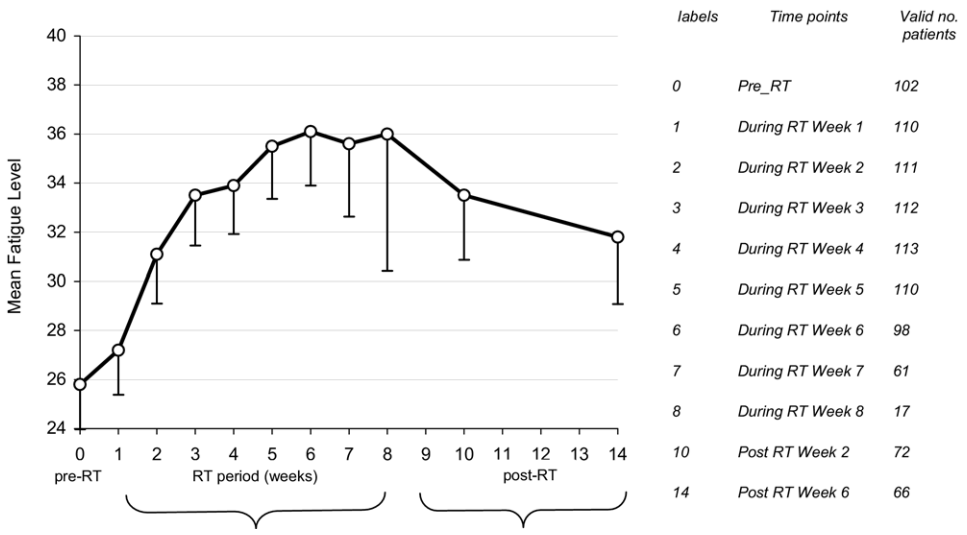
		Before RT			During RT										After RT			
	Over all time points	Original data		After FOCB replacement	Original data										Original data			After LOCF replacement
					Week								Average over time	Maximum	Week		Average over time	
N	117	102	(*) 72	(A) 117	1st 110	2nd 111	3rd 112	4th 113	5th 110	6th 98	7th 61	8th 17	(B) 117	(C) 117	2nd 72	6th 66	72	(D) 117
Mean	33.1	25.8	23.3	25.8	27.2	31.1	33.5	33.9	35.5	36.1	35.6	36.0	33.7	44.0	33.5	31.8	32.8	37.2
SD	18.5	18.5	17.5	18.3	19.1	21.1	21.7	21.0	22.5	21.8	23.2	23.0	19.2	21.7	22.6	22.1	21.8	22.0
SE	1.7	1.8	2.1	1.7	1.8	2.0	2.1	2.0	2.1	2.2	3.0	5.6	1.8	2.0	2.7	2.7	2.6	2.0
Median	33.7	23.0	20.4	22.0	24.3	29.0	34.0	34.0	35.3	37.5	35.0	40.0	35.0	46.0	36.0	32.5	33.2	37.0
Min-max	0–77.3	0–76.0	0–64.0	0–76.0	0–69.0	0–80.0	0–80.0	0–78.0	0–80.0	0–80.0	0–80.0	0–80.0	0–77.3	0–80.0	0–80.0	0–80.0	0–77.0	0–80.0

Abbreviations: CI = confidence interval; FOCB = first observation carried backward; LOCF = last observation carried forward; *N* = number of available measurements (out of 117 patients); RT = radiotherapy; SD = standard deviation; SE = standard error.

* Subset of 72 patients with original fatigue data after RT.

RT effect: *t* test on (B) – (A) difference: $p < 0.0001$; estimate of the fatigue worsening attributable to RT: 7.8 (95% CI, 5.2–10.5)

Fatigue trend over time: repeated-measures analysis of variance on (A) vs. (C) vs. (D): p (linear trend) < 0.0001; p (quadratic trend) < 0.0001



labels	Time points	Valid no. patients
0	Pre_RT	102
1	During RT Week 1	110
2	During RT Week 2	111
3	During RT Week 3	112
4	During RT Week 4	113
5	During RT Week 5	110
6	During RT Week 6	98
7	During RT Week 7	61
8	During RT Week 8	17
10	Post RT Week 2	72
14	Post RT Week 6	66

Fig. 1. Fatigue evolution during radiotherapy (RT) for head and neck tumor. Fatigue scores assessed before, during, and after RT with use of the Multidimensional Fatigue Inventory (MFI-20) questionnaire are shown. Data are mean ± standard deviation.

existence of any kind of trend, provided a statistically significant result (repeated-measures analysis of variance, $p < 0.0001$).

Analysis of predictors for on-treatment fatigue level

For each variable, Table 3 contains baseline (pre-RT) fatigue score, the mean impairment caused by RT, the maximum impairment caused by RT (means ± SD), and the relevant univariate test. The variables significantly associated, at univariate analysis, with the mean during-RT fatigue impairment included the following: induction and/or concomitant chemotherapy, thyroid disorders, severe anemia, RT duration, RT-related toxicity (mucositis, dysphagia, weight loss), and need of cortisone during RT.

In a multivariate stepwise regression analysis, the association was confirmed for the following: pre-RT fatigue ($p < 0.0001$), induction and/or concomitant chemotherapy ($p = 0.035$), need of cortisone ($p = 0.005$), and thyroid disorders ($p = 0.032$). This model fitted the observed data quite well, explaining nearly 59% of the variance in during-RT fatigue score. As expected, more than 80% of this variance (49% of 59%) was attributable to pre-RT fatigue score.

Similar results were provided using maximum during-RT fatigue level instead of during-RT average (Table 3).

Analysis of predictors for post-treatment fatigue level

For each variable, Table 4 shows pre-RT fatigue score, post-RT vs. pre-RT score difference (means ± SD), and relevant univariate tests on the entire sample ($N = 117$ after LOCF replacement) and original data ($N = 72$).

In 117 patients, the impairment caused by RT, evaluated approximately 4 weeks after RT (estimated period computed as average of 10-day and 40-day post-RT evaluations), was quantified as 11.3 points ($p < 0.0001$).

The variables statistically associated in the univariate analysis to impairment of post-RT fatigue levels in comparison to pre-RT were age, induction and/or concomitant chemotherapy, RT-related toxicity (mucositis, dysphagia, weight loss), and need of cortisone during RT (Table 4).

In a multivariate stepwise regression analysis the association was confirmed for pre-RT fatigue ($p < 0.0001$), induction and/or concomitant chemotherapy ($p < 0.001$), and need of cortisone ($p < 0.005$). The goodness of fit of the model was lower than for the "during-RT" evaluation ($R^2 = 0.402$ vs. 0.59). However, the weight of pre-RT score on the total variance lowered to 68% (26.7% of 40%) from 80%. Similar results were provided by the analysis of the original data ($n = 72$) (Table 4).

Analysis of predictors for pre-RT fatigue level

From the foregoing analyses it was clear that pre-RT fatigue was the most important predictor of the degree of fatigue after treatment. Therefore the factors contributing to pre-treatment fatigue were investigated with a similar regression analysis (Table 5). Pretreatment fatigue was used as response variable. The predictors correlated in the univariate analysis with pre-RT higher fatigue level fatigue included RT intent, previous head-and-neck surgery, psychologic disorders, and induction CT. Previous surgery (inversely related, $p < 0.005$), psychologic disorders ($p < 0.005$), and age (inversely related, $p < 0.05$) were significantly correlated with pre-RT fatigue in multivariate analysis (Table 5).

DISCUSSION

To our knowledge this is the largest study published to date that presents detailed information regarding the severity, correlates, and course of fatigue during RT for head and

Table 3. Univariate and multivariate analysis of potential predictors of the during-treatment fatigue ($N = 117$)

		Before RT	During RT					
		After FOCB replacement	Average over time			Maximum value over time		
Variable	N	Mean ± SD	Impairment caused by RT (vs. baseline)	p Values		Impairment due to RT (vs. baseline)	p Values	
				Univar*	Multivar†		Univar*	Multivar†
Overall	117	25.8 ± 18.3	7.8 ± 14.3	<0.0001		18.1 ± 17.8	<0.0001	
Pre-RT fatigue								
Below median	57	10.6 ± 7.2	10.8 ± 13.1	0.027	<0.0001	21.7 ± 19.5	0.032	<0.0001
Above median	60	40.3 ± 13.1	5.0 ± 14.0			14.7 ± 15.4		
Age (y)								
≤50	28	31.2 ± 20.1	4.5 ± 18.1			13.0 ± 18.0		
51-60	34	23.6 ± 17.5	10.0 ± 12.3	0.14‡	–	20.7 ± 19.1	0.21‡	0.077§
61-70	39	22.0 ± 16.3	10.1 ± 14.2			20.6 ± 18.1		
>70	16	30.5 ± 19.8	3.7 ± 9.6			15.7 ± 12.7		
Induction CT								
No	73	22.7 ± 17.4	5.8 ± 15.1	0.0022	–	15.7 ± 17.5	0.0049	–
Yes	44	31.1 ± 18.8	11.2 ± 12.5			22.3 ± 17.8		
Thyroid disorder								
No	109	26.0 ± 18.4	7.0 ± 14.2	0.04	0.032	17.4 ± 18.0	0.13	
Yes	7	20.2 ± 14.6	19.3 ± 13.8			29.3 ± 13.8		
Basal hemoglobin								
Unknown	13	24.8 ± 20.0	10.9 ± 16.8	–		21.5 ± 24.8	–	
Severe anemia‖	5	32.4 ± 15.6	14.2 ± 13.7			24.2 ± 19.7		
Mild anemia¶	34	26.9 ± 20.0	10.9 ± 13.9	0.025	–	21.0 ± 17.8	0.1	
Normal hemoglobin**	65	25.0 ± 17.5	5.1 ± 13.8			15.4 ± 16.0		
Concomitant CT								
No	60	23.0 ± 17.7	6.3 ± 15.5	0.061	–	15.6 ± 17.9	0.03	
Yes	57	28.8 ± 18.6	9.4 ± 12.9			20.8 ± 17.5		
Chemotherapy								
No	56	21.8 ± 17.3	6.3 ± 16.0			15.4 ± 18.3		
Induction CT	4	39.8 ± 16.4	6.2 ± 7.1	0.023	0.035	18.3 ± 14.0	0.04	0.028
Concomitant CT	17	25.6 ± 17.8	4.0 ± 11.7			16.5 ± 15.2		
Concomitant+Induction CT	40	30.2 ± 19.0	11.8 ± 12.8			22.7 ± 18.2		
RT total dose (Gy)								
≤60	29	23.6 ± 16.3	6.4 ± 13.2			18.4 ± 17.7		
61-69	44	23.1 ± 18.2	6.7 ± 15.9	0.085§	–	16.8 ± 19.3	0.44§	
≥70	44	30.1 ± 19.3	9.9 ± 13.5			19.3 ± 16.6		
RT duration (days)								
<45	22	26.3 ± 19.8	-0.2 ± 18.8			9.1 ± 22.5		
45-49	39	23.3 ± 15.9	11.0 ± 11.5	0.05§	0.07	21.3 ± 14.6	0.07§	
50-54	38	26.9 ± 19.3	9.0 ± 14.5			19.7 ± 19.4		
≥55	18	28.6 ± 19.9	8.5 ± 10.0			19.0 ± 10.8		
RT-induced mucositis								
0-2 RTOG grade	74	25.4 ± 17.4	5.9 ± 15.1	0.03	–	15.8 ± 17.9	0.04	
3-4 RTOG grade	43	26.6 ± 19.9	11.3 ± 12.2			22.2 ± 17.1		
RT-induced dysphagia								
0-2 RTOG grade	98	23.8 ± 17.8	7.1 ± 15.2	0.02	–	17.6 ± 18.9	0.1	
3-4 RTOG grade	19	36.5 ± 17.8	11.7 ± 7.7			21.0 ± 10.8		
RT-induced weight loss								
<5%	72	24.8 ± 17.1	5.5 ± 14.5	<0.01	–	14.5 ± 16.4	0.002	0.088
≥5%	45	27.5 ± 20.1	11.6 ± 13.4			23.9 ± 18.8		
Cortisone administration								
No	37	23.6 ± 18.7	3.2 ± 15.6	<0.01	0.005	11.7 ± 17.0	0.002	0.027
Yes	80	26.9 ± 18.1	10.0 ± 13.3			21.1 ± 17.5		

Abbreviations: CT = chemotherapy; FOCB = first observation carried backward; multivar = multivariate; N = number of patients in each subgroup; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; SD = standard deviation; univar = univariate.

* Comparing the differences adjusted by pre-RT score using analysis of variance.

† Multivariate stepwise regression analysis.

‡ Test for quadratic trend.

§ Test for linear trend.

‖ Hemoglobin (Hb) < 11 g/dl.

¶ Hb for women, 11 g/dl < Hb ≤ 11.9 g/dl; for men, 11 g/dl < Hb <12.9 g/dl.

** Hb for women, ≥12 g/dl; for men ≥13 g/dl (51).

Table 4. Univariate and multivariate analysis of potential predictors of the post-treatment fatigue

	After replacement (N = 117)					Original data (N = 72)				
		Before RT (FOCB)	After RT (LOCF)	p Values			Before RT	After RT	p Values	
Variable	N	Mean±SD	Impairment due to RT (vs. baseline)	Univar*	Multivar†	N	Mean±SD	Impairment due to RT (vs. baseline)	Univar*	Multivar†
Overall	117	25.8 ± 18.3	11.3 ± 19.8	<0.0001		72	23.3 ± 17.5	9.4 ± 16.8	<0.0001	
Pre-RT fatigue										
Below median	57	10.6 ± 7.2	16.4 ± 20.0	0.007	<0.0001	57	9.4 ± 7.0	12.8 ± 18.6	0.067	0.0063
Above median	60	40.3 ± 13.1	6.5 ± 18.4			60	38.9 ± 11.6	5.6 ± 13.8		
Age (y)										
≤50	28	31.2 ± 20.1	4.4 ± 20.8			15	28.3 ± 18.5	6.4 ± 11.3		
51-60	34	23.6 ± 17.5	15.7 ± 19.1			19	20.8 ± 17.5	14.0 ± 19.1		
61-70	39	22.0 ± 16.3	15.0 ± 19.2	0.03‡	0.07§	27	20.5 ± 16.9	10.6 ± 18.1	0.13‡	–
>70	16	30.5 ± 19.8	5.3 ± 17.4			11	28.0 ± 17.8	3.0 ± 14.8		
Induction CT										
No	73	22.7 ± 17.4	8.2 ± 20.0	<0.001	–	49	19.8 ± 16.1	6.0 ± 15.7	<0.001	–
Yes	44	31.1 ± 18.8	16.6 ± 18.5			23	30.9 ± 18.3	16.8 ± 16.9		
Concomitant CT										
No	60	23.0 ± 17.7	7.5 ± 19.6	0.003	–	42	19.6 ± 14.9	6.7 ± 16.0	0.03	–
Yes	57	28.8 ± 18.6	15.3 ± 19.3			30	28.6 ± 19.7	13.2 ± 17.4		
Chemotherapy										
No	56	21.8 ± 17.3	7.8 ± 20.2			40	19.1 ± 15.1	6.6 ± 16.4		
Induction	4	39.8 ± 16.4	3.8 ± 8.9	0.005	<0.001	2	29.6 ± 2.0	9.1 ± 3.7	0.009	0.0014
Concomitant	17	25.6 ± 17.8	9.4 ± 19.7			9	22.9 ± 20.7	3.0 ± 13.0		
Concomitant+Induction	40	30.2 ± 19.0	17.8 ± 18.8			21	31.0 ± 19.2	17.5 ± 17.5		
RT duration (days)										
<45	22	26.3 ± 19.8	2.9 ± 24.8			12	22.0 ± 16.1	4.8 ± 15.2		
45–49	39	23.3 ± 15.9	13.7 ± 16.3	0.08§	–	27	19.8 ± 13.6	10.6 ± 13.3	0.42§	–
50–54	38	26.9 ± 19.3	13.5 ± 22.1			25	27.4 ± 21.4	10.6 ± 22.3		
≥55	18	28.6 ± 19.9	12.0 ± 11.6			8	24.5 ± 18.3	8.9 ± 9.5		
RT-induced mucositis										
0–2 RTOG grade	74	25.4 ± 17.4	8.3 ± 19.1	0.01	–	49	22.4 ± 16.1	7.3 ± 15.8	0.08	–
3-4 RTOG grade	43	26.6 ± 19.9	16.6 ± 20.1			23	25.4 ± 20.4	14.0 ± 18.3		
RT-induced dysphagia										
0-2 RTOG grade	98	23.8 ± 17.8	10.2 ± 20.8	0.01	–	62	21.5 ± 17.0	8.4 ± 17.4	0.08	–
3-4 RTOG grade	19	36.5 ± 17.8	17.0 ± 12.4			10	34.5 ± 17.3	15.5 ± 10.9		
RT-induced weight loss										
<5%	72	24.8 ± 17.1	7.7 ± 18.5	0.003	–	48	21.7 ± 16.0	7.5 ± 15.5	<0.1	–
≥5%	45	27.5 ± 20.1	17.2 ± 20.5			24	26.7 ± 20.1	13.3 ± 18.8		
Cortisone administration										
No	37	23.6 ± 18.7	4.3 ± 17.9	<0.0001	<0.005	25	17.6 ± 14.6	5.6 ± 13.2	0.06	–
Yes	80	26.9 ± 18.1	14.6 ± 19.9			47	26.4 ± 18.3	11.5 ± 18.2		

Abbreviations: CT = chemotherapy; FOCB = first observation carried backward; LOCF = last observation carried backward; multivar = multivariate; N = number of patients in each subgroup; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; SD = standard deviation; univar = univariate.

* Comparing the differences adjusted by pre-RT score using analysis of variance.

† Multivariate stepwise regression analysis.

‡ Test for quadratic trend.

§ Test for linear trend.

neck cancer. We have shown that fatigue affects all patients undergoing RT for head and neck tumor, reaches maximum score at the Week 6 of RT, and slowly decreases thereafter. Such evolution of fatigue was reported also for the other tumor sites (10, 11–13) and confirms the adaptation of the organism to a continuing stress (11). Age, thyroid dysfunction, psychologic disorders, pre-RT fatigue score, chemotherapy, and cortisone use are correlated with RT-related fatigue levels. The comparison of our results on head-and-neck cancer patients with other reports is not straightforward, as the majority of series include numerous tumor sites (varying in such factors as prognosis and comorbidities) and cancer treatments (4, 14–15).

Fatigue is thought to be a nonspecific, multidimensional

Table 5. Univariate and multivariate analysis of potential predictors for pretreatment fatigue

Variable	$N = 102$	Mean ± SD	Univariate p value	Multivariate p value
Age (y)				
≤50	24	31.2 ± 19.8		
51–60	29	25.2 ± 18.3		
61–70	37	22.1 ± 16.7	0.14*	<0.05†
>70	12	27.9 ± 20.4		
Intent of RT				
Exclusive	43	31.2 ± 20.1	0.01	–
Postoperative	59	21.9 ± 16.2		
Induction CT				
No	66	21.8 ± 17.4	0.0025	–
Yes	36	33.2 ± 18.3		
Previous head-and-neck surgery				
No	39	33.0 ± 20.0	0.0017	<0.0005
Yes	63	21.4 ± 16.0		
Respiratory disease				
No	94	25.0 ± 18.1	0.15	<0.1
Yes	8	34.8 ± 21.0		
Psychologic disorder				
No	95	24.4 ± 18.1	0.004	<0.005
Yes	7	45.1 ± 11.7		
Previous malignancy				
No	96	25.0 ± 18.0	0.09	–
Yes	6	38.3 ± 22.3		

Abbreviations: CT = chemotherapy; N = number of patients; SD = standard deviation; RT = radiotherapy.

* Test for quadratic trend.

† Test for linear trend.

concept that involves subjective feeling of tiredness, weakness, and/or lack of energy. Distinct dimensions of fatigue, *e.g.,* sensory, emotional, and cognitive, have to be measured (3). In the last decade modern instruments have been designed to measure fatigue (3, 9, 16, 17). For our prospective study we have chosen the MFI-20 questionnaire. The MFI-20 was developed as a self-report instrument by the Dutch authors (9) and covers the following dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Several studies confirmed the internal consistency and construct validity of the scale (14). At present, MFI-20 has been frequently used in oncology research (10, 15, 18) and in research on chronic conditions (19–21). We calculated the total score (a sum of the score of the individual items) to obtain the global judgment on the fatigue. Such an MFI-20 calculation has been demonstrated to be useful and justified from a statistical perspective (22).

In our study we decided to evaluate only acute and subacute fatigue levels. The evaluation of the impact of some patient-related factors was limited because of the high number of missing data (for example, post-RT hemoglobin level). Further evaluation of chronic fatigue and the impact of the biologic factors in the fatigue etiology would definitely be interesting. However, because of the specificity of the head and neck cancer population (low compliance confirmed also in our study by the high number of missing forms), such analysis requires better patient motivation means.

Contrary to other studies, in our analysis fatigue only slightly decreased at Week 6 after RT, and post-RT fatigue score was significantly higher than the pre-RT one (10). This can be partially explained by the long recovery of highly invalidating RT-related toxicity typical for head-and-neck irradiation (mucositis, dysphagia, weight loss etc.).

An important question addressed in our study involved the patient-, tumor-, and treatment-related factors correlated with pre-RT, during-RT, and post-RT fatigue levels. In our study younger age, psychologic disorder, and absence of previous surgery for head-and-neck malignancy were correlated with higher baseline fatigue score. Patient-related characteristics such as age, gender, and social factors (education level, marital status, socioeconomic status) were found in some studies to correlate with therapy-related fatigue (15, 23–27) but were not relevant in other studies (4, 10). These contradictory data on RT-related fatigue could be explained by impact of numerous variables such as various tumor sites, methods of assessment, and retrospective nature of the majority of the studies. Thus, multifactorial analyses of large homogeneous patient series with use of widely accepted instruments might help to elucidate these issues.

The association between fatigue and psychologic factors has already been reported (10, 12, 15, 28–30). Fatigue was

also found to correlate with symptom distress, mood disturbance, and alterations in usual functional activities (9, 12).

Lower levels of fatigue in the patients who underwent the surgery and/or chemotherapy have been already observed when compared to the previously untreated patients (31). This phenomenon, confirmed in our series, is called a "response shift" and results from changes in internal standards that occur in cancer patients undergoing cancer therapy (32). Another explanation of higher fatigue in the patients treated with primary RT for head and neck cancer (no previous surgery) could be the presence of active malignancy; however, this has to be further explored (the tumor stage was not correlated with fatigue level).

Higher during-RT and post-RT fatigue levels were correlated with higher pre-RT fatigue score, thyroid disorder, induction and/or concomitant chemotherapy, and need of cortisone during RT (administrated usually for Grade 2 or 3 mucositis and/or dysphagia). As in numerous studies (10, 13, 27), pre-treatment fatigue was more powerful than any other indicator in predicting during- and post-RT fatigue. Contrary to the findings of Smets *et al.* (10), in our study no correlation between psychologic factors and during- and post-RT fatigue was found. Addition of chemotherapy to irradiation significantly increased both acute and chronic treatment-related fatigue in several studies (25, 28, 33, 34). In head and neck cancer survivors treated with RT (conventional or hypofractionated) with or without surgery, social function, emotional function, and fatigue were significantly influenced by type of surgery but not by RT regimen (35). The lack of correlation between the fatigue levels and the RT parameters (dose, volume, duration) as well tumor-related factors (stage, site) was reported in our series. Indeed, the correlation between fatigue and treatment-related factors is not yet clear, and conflicting data have been published. An increase in fatigue with increase of RT fields and dose was observed (36–40), although it was not confirmed by other groups (4, 15). We observed higher fatigue levels in the patients who needed cortisone, suggesting the role of RT-induced toxicity, although no impact of toxicity was found in the multivariate analysis. These issues as well as the significance of concurrent medications need to be explored further (4).

In our analysis only thyroid disorders were correlated with the during-RT fatigue. It has been already reported that thyroid dysfunction can lead to higher fatigue levels (41), and the cancer treatment by itself may induce thyroid disorders (42).

Multiple physical etiologies of RT-induced fatigue reported in the literature include anemia, change in weight, serum interleukins, reverse triiodothyronine, decline in neuromuscular efficiency, and pulse change with orthostatic stress, myelosupression, concomitant symptoms (infections, dehydratation, malnutrition, mucositis), concurrent use of analgesics (1, 10, 16, 13). Low pre-RT hemoglobin level was associated with high lever of RT-induced fatigue in some studies (40), whereas in the others it was not (18, 29). Wratten *et al.* (13) found higher baseline fatigue in patients with high baseline neutrophil and red blood cell counts.

The aim of our study was the evaluation of the fatigue and its correlates. We did not address the management of this symptom. Because fatigue is one of the most common acute and long-term RT side effects, it is well known that many patients continue to seek information (1). Therapeutic strategies for RT-induced fatigue have not yet been well-defined; however several randomized studies have been recently published (43–48). Physical exercise, psychotherapy, and relaxation have been demonstrated effective. Moreover, pharmacologic treatment of concomitant disturbances (anemia, pain, insomnia, depression, dehydratation, infection, malnutrition, hormonal insufficiency) and other RT side effects should be considered (1). Correction of anemia before or during the RT can be useful if fatigue is accompanied by low hemoglobin levels (49, 50). Adjuvant therapies with antidepressants, tranquilizers, and analgesic agents have been also proposed (30, 31). Fatigue should definitely be considered as both a cancer- and treatment-related symptom, and a more active approach to addressing this should be encouraged. Further methodologically correct studies are warranted to define better the causes, prevention, assessment, and management of this symptom.

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APPENDIX 1

MULTIDIMENSIONAL FATIGUE INVENTORY
*** MFI-20 ***

by E. Smets et al. (9)
with kind permission of Dr. E. Smets
modified (see "Methods and Materials" section in text for explanation)

Instructions:
By means of the following statements we would like to get an idea of how you have been feeling lately. There is, for example, the statement:

"I FEEL RELAXED"

If you think that this is entirely true, that indeed you have been feeling relaxed lately, please, place an X in the extreme left box; like this:

Yes, that is true	x					No, that is not true

The more you disagree with the statement, the more you can place an X in the direction of "No, that is not true". Please, do not miss out a statement; place one X next to each statement.

1.	I feel fit.	Yes, that is true					No, that is not true
2.	Physically I feel able to do a lot.	Yes, that is true					No, that is not true
3.	I feel very active.	Yes, that is true					No, that is not true
4.	I feel like doing all sorts of nice things.	Yes, that is true					No, that is not true
5.	I do not feel tired.	Yes, that is true					No, that is not true
6.	I think I do a lot in a day.	Yes, that is true					No, that is not true

7. When I am doing something, I can keep my thoughts on it.	Yes, that is true						No, that is not true
8. Physically I can take on a lot.	Yes, that is true						No, that is not true
9. I do not dread having to do things.	Yes, that is true						No, that is not true
10. I do a lot in a day.	Yes, that is true						No, that is not true
11. I can concentrate well.	Yes, that is true						No, that is not true
12. I am rested.	Yes, that is true						No, that is not true
13. It takes little effort to concentrate on things.	Yes, that is true						No, that is not true
14. Physically I feel I am in a good condition.	Yes, that is true						No, that is not true
15. I have a lot of plans.	Yes, that is true						No, that is not true
16. I hardly get tired.	Yes, that is true						No, that is not true
17. I get done a lot.	Yes, that is true						No, that is not true
18. I feel like doing something.	Yes, that is true						No, that is not true
19. My thoughts hardly wander.	Yes, that is true						No, that is not true

20. Physically I feel I am in an excellent condition.	Yes, that is true					No, that is not true

Thank you very much for your cooperation.