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ORIGINAL ARTICLE

Factors associated with weight loss during radiotherapy in patients with stage I or II head and neck cancer

Alice Nourissat · Isabelle Bairati · André Fortin · Michel Gélinas · Abdenour Nabid · François Brochet · Bernard Têtu · François Meyer

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Abstract
Background The purpose of the study was to identify factors associated with weight loss during radiotherapy (RT) in patients with stage I or II head and neck (HN) cancer.
Methods This study was conducted as part of a phase III chemoprevention trial. A total of 540 patients were randomized. The patients were weighed before and after RT. Patients' characteristics, dietary intake, health-related quality of life (HRQOL), tumor characteristic, treatment characteristics, and acute adverse effects of RT were evaluated at baseline and during RT. Factors independently associated with weight loss during RT were identified using the multiple linear regression ($P \leq 0.05$).
Results The mean weight loss during RT was 2.2 kg (standard deviation, 3.4). In bivariate analyses, the occurrence of adverse effects of RT and most of the HRQOL dimensions evaluated during RT were correlated with weight loss. In the multivariate analysis, eight factors were associated with a greater weight loss: all HN cancer sites other than the glottic larynx ($P<0.001$), TNM stage II disease ($P=0.01$), higher pre-RT body weight ($P<0.001$), dysphagia before RT ($P<0.005$), higher mucosa adverse effect of RT ($P=0.03$), lower dietary energy intake during RT ($P<0.001$), lower score of the digestive dimension on the Head and Neck Radiotherapy Questionnaire ($P<0.001$) and a higher score of the constipation symptom on the EORTC QLQ-C30 during RT ($P=0.02$).
Conclusions The results underline the importance of maintaining energy intake in early stage HN cancer patients during RT and the importance of preventing and treating adverse effects.

Keywords Weight loss · Radiotherapy · Head and neck cancer · Nutrition · Early stage, adverse effects

A. Nourissat (✉)
Department of Public Health, Saint-Etienne University Hospital,
Cancer Institute of Loire,
108 bis avenue Albert Raimond,
42270 Saint Priest en Jarez, France
e-mail: alice.nourissat@icloire.fr

I. Bairati · F. Meyer
Clinical Epidemiology Unit,
Laval University Cancer Research Center,
Quebec City, Quebec, Canada

A. Fortin
Department of Radio-oncology, Quebec University Hospital,
Quebec City, QC, Canada

M. Gélinas
Department of Radio-oncology, Montreal University Hospital,
Montreal, QC, Canada

A. Nabid
Department of Radio-oncology, Sherbrooke University Hospital,
Sherbrooke, QC, Canada

F. Brochet
Department of Radio-oncology, Sagamie Hospital,
Saguenay, QC, Canada

B. Têtu
Department of Pathology, Quebec University Hospital,
Laval University,
Quebec City, QC, Canada

Weight loss before, during, and after cancer treatment is frequent in patients with head and neck (HN) cancer. At the time of initial treatment, more than 50% of the HN cancer patients have already lost weight [1]. All treatment modalities, including surgery, chemotherapy, radiotherapy (RT) alone, or in combination may result in adverse effects that could affect nutritional status. RT in HN cancer patients can induce oral side effects like mucositis, dysgeusia, xerostomia, and change in viscosity of saliva, which could be in relation with weight loss [2]. About 30% of HN cancer patients treated by RT have digestive adverse effects, such

as nausea and vomiting, which could also be responsible of weight loss [3].

In patients with advanced HN cancer, weight loss could influence the morbidity by, for example, reducing quality of life and treatment tolerance [4–7]. Several studies suggest that global health status, diet, and quality of life could influence the ability of cancer patients to maintain adequate nutritional intake during their cancer treatments [7–11]. The modalities of nutritional support in HN cancer patients are still debated with regard to dietary counseling, nutritional supplements, drug intervention, and enteral feeding methods [12, 13]. Enteral nutrition via tube feeding is not routinely indicated in all HN cancer patients during RT, especially in the early stage [12, 14].

The nutritional status of early stage HN cancer patients has not been much explored because these patients have, theoretically, a good prognosis and low expected morbidity from RT. We previously reported that critical weight loss (of more than 5% during RT) occurred in approximately 25% of the cases in early stage HN cancer patients [15]. To manage nutritional support, it would be useful to have a better knowledge of the factors associated with weight loss in this group of cancer patients. In a previous publication, we identified baseline predictors of weight loss during RT [15]. Site and classification of malignant tumor (TNM) stage of the tumor, pre-RT body weight, dysphagia, and performance status before RT explained only 23% of the variance in weight loss during RT. With the goal to better explained weight loss, we evaluated whether diet, occurrence of RT adverse effects and quality of life during RT could contribute to better understand the phenomena of weight loss during RT.

Materials and methods

Study population

This study was carried out as part of a phase III multicenter, double-blind, placebo-controlled chemoprevention trial involving 540 patients treated by RT for stage I or II HN cancer [16]. The main objective of the trial was to evaluate the efficacy of α-tocopherol and β-carotene supplementation in reducing the incidence of second primary cancers. The institutional review board at each participating center approved the protocol. All patients gave written informed consent prior to randomization.

Eligible patients were aged 18 years and over, had received a first diagnosis of stage I or II squamous cell carcinoma of the head and neck area (tongue, gums or mouth, oropharynx, hypopharynx, and larynx), and were scheduled to be treated by RT between October 1, 1994 and June 6, 2000 in one of five radiotherapy centers in the province of Quebec, Canada. Patients with any of the following criteria were ineligible: a Karnofsky Performance Score (KPS) of less than 60 [17]; multiple primary HN cancers or previous cancer; severe cardiovascular disease; inadequate renal, hepatic, or hematological function; anticoagulant therapy; pregnancy; or average daily supplement intake of β-carotene or vitamin E above 6.0 mg or 50 IU, respectively.

Data collection

The study nurses weighed the patients at the baseline visit and at the end of RT. They administered several validated questionnaires before RT and at the end of RT.

At the baseline visit before the beginning of RT, a structured general questionnaire was administrated to evaluate the patients' characteristics, including their demographic and socioeconomic data, KPS, medical history, history of alcohol consumption, and smoking habits. The Charlson Index, a comorbidity score, was calculated based on the medical history [18]. At the end of RT, the same questionnaires were administered in order to evaluate the patient's characteristics during RT.

A semiquantitative, 84-item food frequency questionnaire (FFQ), previously validated in a population of 73 patients with HN cancer [19, 20], was administered at the beginning and at the end of RT. The FFQ assessed the dietary intakes respectively over the year preceding randomization for the first questionnaire and during RT for the second. Average daily nutrient intakes (e.g., total energy intake, protein, lipids, carbohydrates, alcohol, vitamin D, and omega-3 fatty acids) were calculated using the 2007 Canadian food composition table [21]. Nutrients intake from supplements were also evaluated.

Health-related quality of life was evaluated at baseline and at the end of RT using two validated instruments. The Quality of Life Questionnaire-C30 (QLQ-C30), developed and validated by the European Organization for Research and Treatment of Cancer (EORTC) is a 30-item questionnaire [22]. This instrument was designed to generate five functional scales, global health status (scored 0 to 100, with 100 for perfect functioning) and several symptom scores (scored 0 to 100, with 0 for no symptoms). Quality of life was also assessed by an HN cancer-specific quality of life questionnaire (HNRQ) developed and validated by Browman et al. [23]. This 22-item instrument includes six domain-specific scores and a global score using a scale of 1 to 7, where 7 is no symptoms. These two instruments were used to assess quality of life during the week preceding randomization and during the week preceding the end of RT.

The radiation oncologists provided detailed information on the primary tumor: site, dimensions, and the clinical

TNM stage. They assessed before the beginning and during RT the presence of acute adverse effects in six organ tissues (mucosa, salivary glands, pharynx and esophagus, larynx, skin, and ear) according to the Radiotherapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria [24].

Outcomes

We defined weight loss during RT (in kilograms) as the difference between the weight at baseline minus the weight at the end of RT. We kept weight loss as a continuous variable since it corresponded to our objective. In addition, the original continuous variable is more informative than a dichotomous variable. Furthermore, the distribution of weight loss was normal thus allowing us to perform a linear regression analysis.

Statistical analysis

Bivariate analyses were performed to examine all the associations between weight loss and selected factors occurring during RT. Dietary energy, alcohol, and nutrient intakes were categorized into quartiles. To separate the effect of dietary nutrients from those of total energy intake, we adopted the residual method proposed by W. Willett and used energy adjusted nutrients [25]. Acute adverse effects collected during RT, according to the RTOG Acute Radiation Morbidity Scoring Criteria, were coded as ordinal variables (grade 0 to 4). Acute adverse effects in the pharynx and esophagus during RT were not considered in the analyses because weight loss is part of criteria for grade 3 adverse effects. There were 15 patients with grade 3 pharyngeal or esophageal adverse effects. Student's *t* tests and analyses of variance were performed for comparisons involving categorical variables. Continuous variables (acute adverse effects and quality of life variables) were correlated with weight loss using Pearson correlations. Tests for trend were performed for dietary variables by entering an ordinal quartile-based variable in a linear regression model as a variable.

All the variables occurring during RT associated with weight loss in the bivariate analyses ($P \leq 0.15$) were considered for inclusion in an expended multivariate linear regression model which already included the baseline predictors [15]. In this baseline model, independent baseline predictors were the site of the tumor, the stage, the body weight before RT, the presence of dysphagia before RT, and the KPS before RT. Firstly, we tested whether some exposures occurring during RT such as smoking, vitamin and nutritional supplementation could affect weight loss. Secondly, the associations with total dose of RT and adverse effects of RT were evaluated by adding one variable per step to the model, starting with the most significant association in the bivariate analyses. When *p* values were similar, the criteria of the strongest association were selected. Thirdly, the same procedure was done for dietary and quality of life variables. For quality of life, we first introduced in the model the HNRQ scores, followed by the QLQ-C30 functional scales and the symptom scales. We only considered the QLC-C30 symptom scales independent from the HNRQ scores already retained in the model. If some baseline factors from our predictive model were no longer significantly associated with weight loss, they were removed from the model. At each step, we verified the lack of multicollinearity between the variables. The regression diagnostic methods used on the final model showed the appropriateness of the regression assumptions. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). All statistical tests were two-sided ($\alpha = 0.05$).

Results

Of the 540 HN cancer patients, 535 had body weight measurements both at baseline and at the end of RT. The patients' characteristics at baseline and during RT are presented in Table 1. The mean age was 62.4 years (standard deviation [SD], 9.8) and 79% of the participants were males. The primary tumor site and the stage were the glottic larynx (64.9%) and stage I (61.5%). Mean weight loss during RT was 2.2 kg (SD, 3.4). Only 29 patients (5.6%) had taken nutritional supplements before RT and 275 (51.4%) during RT. Fourteen patients had a feeding tube (2.6%). The mean total dose of RT was 62 Gy (SD, 7.3).

Table 2 presents the mean weight loss according to categories of selected important variables. The trial intervention was not associated with weight loss. The mean weight loss was 2.23 kg (SD, 3.08) in the supplementation arm of the trial and 2.16 kg (SD, 3.66) in the placebo arm ($P = 0.80$). Total dose of RT ($r = 0.19$; $P = 0.001$) was positively associated with weight loss. Patients who received a total dose≥64.2 Gy (median) had a higher weight loss than the others (2.6 kg versus 1.6 kg; $P = 0.0004$). Patients with nutritional supplements during RT had a higher weight loss than those without (3.2 kg versus 1.2 kg; $P < 0.001$). Patients who received nutritional supplements were more frequently patients with stage II disease (66% among stage II versus 43% among stage I ($P < 0.001$)) and with HN cancer sites other than glottis (70% among other HN cancer sites versus 42% for glottic cancer ($P < 0.001$)). There was no association between weight loss and smoking status during RT, mean of weight loss was 2.2 kg in the two groups ($P = 0.93$). The correlations between

Table 1 Description of the study population (N=535)

Characteristic	Value	
Age, mean, (SD), years	62.4	(9.8)
Gender, Male, N_0 (%)	422	(78.9)
Weight at baseline, mean, (SD), kg	73.5	(14.4)
Living alone, N_0 (%)	116	(21.7)
White collar worker, N_0 (%)	142	(26.5)
Smoking, *n* (%)		
At baseline	130	(25.7)
During RT	164	(30.7)
Alcohol intake, mean, (SD), g/day		
At baseline	13.0	(21.6)
During RT	2.2	(8.4)
Oral nutritional supplement use, N_0 (%)		
At baseline	29	(5.6)
During RT	275	(51.4)
Karnofsky performance score, mean (SD)		
At baseline	96.5	(7.2)
During RT	91.9	(10.9)
Baseline Charlson comorbidity index, mean (SD)	0.6	(1.0)
Baseline dysphagia, N_0 (%)	56	(10.5)
Primary tumor site, N_0 (%)		
Glottic larynx	347	(64.9)
Supraglottic larynx	100	(18.7)
Other[a]	88	(16.4)
TNM clinical stage, stage I, N_0 (%)	329	(61.5)
Major surgery before RT, N_0 (%)	32	(6.0)
Total dose of RT, mean (SD), Gy	61.6	(7.3)

[a] Oral cavity (n=63), oropharynx (n=17), hypopharynx (n=8)

weight loss and adverse effects of RT are presented in Table 3. During RT, severe adverse effects (grades 3 and 4) affected predominantly the oral mucosa (12.2%) and the laryngeal site (11.2%). Weight loss during RT was positively associated with the severity of adverse effects of RT on salivary glands, mucosa, and skin (P<0.0001).

Most of the quality of life dimensions were significantly correlated with weight loss during RT (Table 4). The strongest correlation coefficients in absolute value with weight loss were the HNRQ digestive domain, the HNRQ oral stomatitis domain, and the HNRQ global quality of life. During RT, the score of HNRQ digestive domain was lower than the score at baseline (6.1 versus 6.7; P<0.001), showing the presence of more digestive symptoms during treatment. The QLQ-C30 instrument also reported strong correlation coefficients with digestive symptoms such as appetite loss, constipation, nausea, and vomiting. The mean of the constipation score was higher during RT than the score at baseline (31.8 versus 11.7; P<0.001). Dietary energy intake was lower in patients with constipation. The correlation between energy intake and score of constipation symptom was statistically significant (r=−0.12, P=0.01).

There was an inverse linear trend between energy intake from diet and weight loss (P>0.001). For example, patients with dietary energy intake of less than 1,200 kcal (first quartile) had a mean of weight loss of 4.0 kg (SD, 4.2), while those in the fourth quartile (more than 2,085 kcal) had a mean of weight loss of 1.3 kg (SD, 3.0) (Table 5). Alcohol intake during RT was positively associated with weight loss (P=0.004). None of other selected nutritional variables from diet was significantly associated with weight loss during RT.

In the multivariate analysis, eight factors were independently associated with a greater weight loss during RT (Table 6) : supraglottic larynx (β=1.21, P=0.0007) and all sites other than larynx (β=1.44, P<0.0001), TNM stage II disease (β=0.68, P=0.01), pre-RT body weight (β=0.06, P<0.0001), pre-RT dysphagia and/or odynophagia (β=1.17, P=0.005), more severe mucosa adverse effect of RT (β=0.35, P=0.03), lower dietary energy intake during RT (β=−0.46, P<0.0001), lower score of the digestive dimension on the HNRQ (β=−0.78, P<0.0001) during RT, and a higher score of the constipation symptom on the EORTC QLQ-C30 during RT (β=0.008, P<0.02). The model explained 36% of the variance in weight loss during RT.

Discussion

In this study, several clinical factors were explored to identify factors that could explained weight loss during RT. Multivariate analyses showed that eight factors were associated with the occurrence of weight loss during RT in early stage HN cancer : the site of the tumor, the stage of the disease, the weight at the beginning of RT, the presence of dysphagia and/or odynophagia at baseline, the total energy intake during RT, the occurrence of mucositis during RT, the presence of constipation, and other digestive symptoms during RT.

When factors occurring during RT were taken into account, all baseline predictors remained significantly associated with weight loss, except KPS at baseline [15]. KPS of at least 60, which was the study eligibility criteria, reflects both the patients' ability to have a normal activity and the presence of cancer symptoms. In our data, KPS was no longer an independent predictor when we took into account the occurrence of oral symptom during RT, such as pain associated with mucositis. HN cancer site and stage are the factors which are consistently reported associated with weight loss in the literature [10, 26, 27]. Treatment modalities, such as total dose of RT, are mainly tailored according to the site and stage of the tumor. This explains why dosage of RT was not an independent factor in our

Table 2 Mean weight loss according to selected characteristics at baseline and during radiation therapy

Variables	Mean of weight loss in kg (SD)	*P* value
Primary tumor site		
Glottic larynx (*n*=347)	1.3 (2.8)	<0.0001
Supraglottic larynx (*n*=100)	3.7 (3.8)	
Other* (*n*=88)	4.0 (3.8)	
TNM clinical stage		
Stage 1 (*n*=329)	1.5 (2.8)	<0.0001
Stage 2 (*n*=206)	3.4 (3.9)	
Weight at baseline[a]		
< 73.5 kg (n=269)	1.7 (2.8)	0.0002
≥ 73.5 kg (n=266)	2.7 (3.8)	
Alcohol intake during RT[a]		
<2.03 g/day (*n*=402)	2.1 (3.1)	0.22
≥2.03 g/day (*n*=133)	2.6 (4.1)	
Smoking during RT		
Yes (*n*=164)	2.2 (3.5)	0.93
No (*n*=370)	2.2 (3.4)	
Total energy intake[a]		
<1.649 kcal/J (*n*=280)	2.9 (3.6)	<0.0001
≥1.649 kcal/J (*n*=255)	1.4 (2.9)	
Total dose of RT[a]		
<64.2 Gy (*n*=217)	1.6 (3.1)	0.0004
≥64.2 Gy (*n*=318)	2.6 (3.5)	
Trial group		
Intervention (*n*=272)	2.23 (3.7)	0.80
Placebo (*n*=263)	2.16 (3.1)	
Oral nutritional supplement use during RT		
No (*n*=259)	1.2 (2.8)	<0.0001
Yes (*n*=275)	3.2 (3.6)	
Feeding tube		
No (*n*=521)	2.1 (3.3)	<0.0001
Yes (*n*=14)	6.7 (3.4)	
Dysphagie and/or odynophagie at baseline		
Yes (*n*=56)	1.9 (3.1)	<0.0001
No (*n*=479)	4.8 (4.4)	
Digestive symptoms[b]		
<6.5 (*n*=289)	1.3 (2.9)	<0.0001
≥6.5 (*n*=246)	3.3 (3.6)	
Constipation[c]		
<31.8 (*n*=241)	1.3 (3.0)	<0.0001
≥31.8 (*n*=294)	2.9 (3.5)	
Acute adverse effects/organ tissue[d]		
Larynx		
Grade 0, 1, 2 (*n*=474)	2.2 (3.3)	0.52
Grade 3, 4 (*n*=60)	2.5 (3.9)	
Pharynx and esophagus[e]		
Grade 0, 1, 2 (*n*=519)	2.0 (3.2)	0.0002
Grade 3, 4 (*n*=16)	8.0 (5.0)	
Mucosa		
Grade 0, 1, 2 (*n*=469)	1.9 (3.2)	<0.0001
Grade 3, 4 (*n*=65)	4.4 (4.2)	

[a] Variables were categorized according to the median

[b] HNRQ: scores range from 1 to 7 (7 is for perfect quality of life or no symptom); cutoff at the median, 6.5

[c] QLQ-C30: scores range from 0 to 100 (0 is no symptom); cutoff at the median, 31.8

[d] Acute adverse effects during RT coded according to the RTOG Acute Radiation Morbidity Scoring Criteria

[e] Sixteen patients had grade 3 or 4 adverse effects during RT which include weight loss as one of the criteria

study. The presence of dysphagia before treatment, reflecting both the obstruction by the tumor and difficulties of swallowing, remained an independent predictor of weight loss. A stronger association should have been anticipated with a measure of dysphagia during RT. However, this adverse side effect could not be taken into account because weight loss is one of the criteria for grade 3 dysphagia.

Four factors during RT, in addition to baseline factors, explained weight loss: dietary energy intake during RT, presence of constipation and other digestive symptoms during RT, and occurrence of adverse effects on the oral mucosa. Symptoms described by the patient on the HNRQ digestive domain were strongly associated with weight loss. The HNRQ digestive domain investigated three symptoms: nausea and vomiting, appetite loss and digestive embarrassment. In addition, we found an independent association with constipation during RT assessed by the EORTC QLQ-C30 questionnaire. At the beginning of RT, 28% of HN cancer patient reported having constipation [1]. In the current study, constipation, as well as digestive symptoms, worsened during RT. One of the reasons may be the low food intake of these patients. Radiation-induced nausea and/or vomiting is also a common problem in cancer patients [28, 29]. It may occur with RT alone or in combination with surgery or chemotherapy although the side effects of nausea and vomiting are usually less severe and less frequent with RT than with chemotherapy. The pathogenesis is not clearly understood when nausea and/or vomiting occur with RT alone.

In the first observational study by the Italian Group for Antiemetic Research in Radiotherapy (IGAAR) which included patients receiving radiation therapy alone, without concomitant chemotherapy, 40.4% of the patients with head and neck irradiation experienced nausea and/or vomiting during RT [30]. In the second observational study by the

Table 3 Distribution (%) of HN cancer patients according to the severity of acute adverse effects and correlations between weight loss and acute adverse effects during RT coded according to the RTOG Acute Radiation Morbidity Scoring Criteria

Organ Tissue	Grade					Correlation	
	0	1	2	3	4	r	*P*
Larynx	34.6	12.4	41.8	11.2	0.0	0.03	0.51
Pharynx and esophagus[a]	13.6	36.3	47.1	2.8	0.2	–	–
Mucosa	9.4	25.5	53.0	12.0	0.2	0.28	<0.0001
Salivary glands	46.5	33.6	19.8	0.0	0.0	0.28	<0.0001
Ear	93.5	6.0	0.4	0.2	0.0	0.13	0.003
Skin	8.0	71.8	18.7	1.3	0.2	0.22	<0.0001

r Pearson's correlation coefficient

[a] Correlation not estimated because16 patients had grade 3 or 4 adverse effects during RT which include weight loss as one of the criteria

Table 4 Associations between weight loss and quality of life during the week before the end of RT

Quality of life dimensions			Correlation	
	Mean	SD	*r*	*P*
QLQ-C30 Functioning scales[a]				
Physical	84.6	21.0	−0.15	0.0004
Role	80.4	30.7	−0.09	0.04
Emotional	76.5	23.0	−0.12	0.006
Cognitive	87.2	19.6	−0.05	0.24
Social	82.1	26.1	−0.15	0.0006
Global quality of life	62.7	23.5	−0.21	<0.0001
QLQ-C30 symptom scales and/or items[b]				
Appetite loss	34.4	37.6	0.42	<0.0001
Pain	37.5	28.3	0.16	0.0001
Fatigue	34.3	27.8	0.20	<0.0001
Nausea and vomiting	14.6	22.5	0.27	<0.0001
Dyspnea	19.5	25.7	0.07	0.09
Sleep disturbance	33.2	35.1	0.04	0.30
Constipation	31.8	34.9	0.28	<0.0001
Diarrhea	5.1	15.3	0.12	0.007
Financial impact	14.9	25.9	0.08	0.07
HNRQ domains[c]				
Global	5.2	1.1	−0.34	<0.0001
Oral stomatitis	5.0	1.5	−0.38	<0.0001
Skin	5.4	1.5	−0.16	0.0002
Throat	3.7	1.6	−0.16	0.0002
Digestion	6.1	1.2	−0.39	<0.0001
Energy	5.1	1.7	−0.14	0.002
Psychosocial	5.5	1.5	−0.20	<0.0001

[a] Scores range from 0 to 100 (100 is for perfect quality of life or perfect functioning)

[b] Scores range from 0 to 100 (0 is no symptom)

[c] Scores range from 1 to 7 (7 is for perfect quality of life or no symptom)

IGAAR which included patients receiving different modalities of RT with or without concurrent chemotherapy, an incidence of 30.5% for nausea and/or vomiting in head and neck radiation was observed [29]. In the updated 2009 MASCC/ESMO guideline for antiemetics in radiotherapy, HN cancer patients treated by RT with or without concurrent or recent chemotherapy have changed risk group. They were in the minimal risk group (<30%) of emesis and they are now considered at low emetogenic risk (30–60%) [3–31]. To prevent or to treat weight loss, the use of antiemetic drugs during RT alone or with chemotherapy can be useful [3, 30–36]. In addition, in order to achieve an optimal treatment strategy to prevent nausea and/or vomiting, Feyer et al. have proposed an individual emetogenic risk score [31]. This index, useful to identify patients at high risk of developing nausea and/or vomiting, include age, gender, alcohol consumption, previous experience of nausea and vomiting, and anxiety [3].

Vomiting and nausea have also an impact on quality of life, anxiety and depression, and seems to be not always sufficiently treated in clinical practice [37].

Oral mucositis was a factor independently associated with weight loss in our multivariate model. A systematic literature review reported that 97% of HN cancer patients receiving conventional RT experienced oral mucositis (34% with grade 3 or 4) [38]. Managing oral complications can enhance patient's nutritional status by decreasing the difficulties in eating and by enhancing the effectiveness of cancer therapy [39]. Strategies to prevent and to limit the extent of oral mucositis include both preventive and therapeutic oral care regimen [40, 41]. In HN cancer patients undergoing RT, amifostine and hydrolytic enzymes appear promising for both preventing and reducing the severity of mucositis [42].

Our study showed an inverse association between weight loss and total dietary energy intake during RT, while adjustment was done for oral mucositis and digestive symptoms. In our study, we were not able to evaluate the

Table 5 Associations between weight loss and diet during RT

Dietary variables[a]	Means of weight loss (kg) by quartiles of dietary variables				β (SE)	*P* value for trend
	Q_1	Q_2	Q_3	Q_4		
Total energy intake	4.0	1.9	1.6	1.3	−0.82 (0.13)	<0.001
Protein	1.5	2.6	2.3	2.3	0.22 (0.13)	0.10
Carbohydrate	1.9	2.6	2.6	1.6	−0.09 (0.13)	0.50
Fat	1.9	1.6	3.1	2.1	0.23 (0.13)	0.08
Alcohol	1.6	1.9	2.7	2.6	0.34 (0.13)	0.004
Vitamin A	1.7	2.7	2.5	1.9	0.03 (0.13)	0.83
α-Tocopherol	2.1	2.5	2.5	1.7	−0.15 (0.13)	0.25
β-Carotene	1.8	2.5	2.9	1.6	−0.01 (0.13)	0.92
Total saturated fatty acids	1.5	2.5	2.7	2.0	0.19 (0.13)	0.14
N-3 fatty acids						
DHA	1.9	2.3	2.1	2.5	0.16 (0.13)	0.21
EPA	2.2	2.5	1.9	2.2	−0.03 (0.13)	0.83
ALA	2.0	2.5	2.4	1.9	−0.06 (0.13)	0.65

β indicates parameter estimate, *SE* standard error, *DHA* dihydroxyacetone, *EPA* eicosapentaenoic acid, *ALA* alpha-linolenic acid

[a] Nutrients are adjusted for total energy according to the residual method

effect of total energy intake provided by both the diet and the nutritional interventions because patients with higher levels of weight loss received nutritional supplements for that very reason. This also hampered the evaluation of the effect of other nutrients, such as omega 3, provided by supplements. In a recent literature review considering ten randomized controlled trials, Garg concluded that nutritional status in HN cancer patients receiving RT appeared to be maintained or improved with dietary counseling, megestrol acetate, and prophylactic enteral tube feeding [13]. For nutritional supplements, the data are more conflicting and further research will be necessary to know their real impact on weight loss. A systematic review reported the results of clinical trials evaluating the advantage of using of n-3 fatty acids in patients with cancer [43]. Oral supplements with n-3 fatty acids benefit patients with advanced cancer and weight loss, and are indicated in tumors of the upper digestive tract and pancreas. Increased weight and appetite were observed. One promising avenue would be to explore whether n-3 fatty acids would improve nutritional status during radiation therapy in HN cancer patients.

Conclusion

The importance of weight loss in advanced HN cancer patients undergoing RT has long been recognized. However,

Table 6 Multiple linear regression showing all factors independently associated with weight loss during RT

Factors	Multiple linear regression			
	β	SE	*P* value	Partial R^2
Site				
Supraglottic laryngeal cancer versus glottic cancer	1.21	0.35	0.0007	0.05
Hypopharynx, oropharynx, oral cavity versus glottic cancer	1.45	0.38	0.0001	0.08
TNM stage, II versus I	0.68	0.27	0.01	0.02
Weight at baseline (continuous)	0.06	0.01	<0.0001	0.07
Dysphagia and/or odynophagia at baseline[a] (dichotomous)	1.17	0.41	0.005	0.02
Mucosa adverse effect of RT[a] (ordinal)	0.35	0.16	0.03	0.02
Total energy intake during RT (ordinal)	−0.46	0.11	<0.0001	0.04
HNRQ digestive domain during RT[b] (ordinal)	−0.78	0.11	<0.0001	0.08
EORTC QLQ-C30 constipation during RT[c] (ordinal)	0.008	0.004	0.02	0.01
Adjusted R^2	0.36			

β indicates parameter estimate, *SE* standard error

[a] Assess using the first version of the RTOG Acute Radiation Morbidity Scoring Criteria; scale, 0 to 4 (0 is no symptom)

[b] From HNRQ; scale of 1 to 7 (7 is for no symptom)

[c] From QLQ-C30; scores range from 0 to 100 (0 is no symptom)

in early HN cancer stages, this phenomenon is less described and consequently the nutritional management is not well defined. Dietary energy intake during RT and adverse effects of RT contributed to better explain weight loss during RT. These results underline the importance of maintaining energy intake in early stage HN cancer patients during RT using several modalities of interventions. Further phase III clinical trials are needed to better define preventive and supportive strategies in patients with early HN cancer.

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Conflicts of interest All of the authors declare that they participated in designing and carrying out this study and in the data analysis. They have read and agreed on the contents of the enclosed manuscript. They declare that they have no potential conflicts of interest that could influence their professional judgment.

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