Differences in quality of life in obese and normal weight head and neck cancer patients undergoing radiation therapy

Helen Egestad
Carsten Nieder

UiT The Artic University of Norway
Tromsø, Norway

Abstract

Purpose: The aim of this study was to evaluate health-related quality of life (HRQOL) in patients with different body mass index (BMI, <25 vs ≥ 25) undergoing radiation treatment for head and neck cancer.

Methods: HRQOL was examined by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EORTC QLQ-H&N35, in the beginning and in the end of radiation treatment in 60 patients treated at University Hospital in Northern Norway. Information about nutritional status with weight loss, hemoglobin level (Hb), serum albumin and a study- specific questionnaire also was filled out in the beginning and in the end of treatment. The patients` general condition, skin and mucous membranes (CTCAE v.3.0) (grades 1 to 5 with unique clinical descriptions) were documented four times during radiation treatment. Changes in HRQOL were calculated and compared by paired sample T-test. Multiple regression analyses were used to examine correlations between baseline BMI and changes in HRQOL, CTCAE v.3.0 toxicity, nutritional status and information that radiotherapists provided to patients.

Results: Patients with BMI ≥ 25 had less mucosal changes after two weeks of radiation treatment than patients with BMI < 25 (p= 0.010). Differences regarding feeding tube use (p= 0.037) and intake of nutritional supplements before radiation treatment (p= 0.001) were also seen. Patients with overweight had more dyspnea (p= 0.033) before treatment and more problems with dry mouth (p= 0.042) after treatment. During treatment patients with BMI ≥25 had more problems with opening mouth (p= 0.034) than patients with BMI <25 and more changes in sexuality (p= 0.019). Patients with BMI ≥ 25 received less information about food and drink (p=0.011) in the radiation treatment period than normal weight patients.

Conclusions: BMI influences HRQOL and toxicity. Additional longitudinal studies should examine whether or not overweight patients persistently experience more problems with dry mouth and opening their mouth. Regardless of BMI, all patients should be informed about nutritional recommendations during treatment.

Keywords Head and neck cancer- Radiotherapy- BMI- Quality of life

Introduction

Patients with head and neck cancer are at high risk for malnutrition due to dysphagia from the tumor itself and treatment toxicity. It is estimated that 25-57% of cancer patients with tumors in the oral cavity or pharynx already have an impaired nutrition status at the time of diagnosis and before beginning treatment [1,2] .

Radiotherapy (RT) often results in mucositis, xerostomia, dysphagia, hoarseness, nausea and vomiting [3]. Approximately 30% of patients experience weight loss and associated morbidity during treatment [4].

It is a reliable indicator of malnutrition if patients lose more than 5% of their usual body weight (BW) in 1 month, or 2% in 1 week [4]. Poor nutrition diminishes the ability of the immune system to function effectively [5] and increases the risk of infections, hospitalization, and treatment interruption, potentially resulting in poor treatment outcomes [6]. Studies found that maintaining adequate nutrition before and during treatment can

decrease weight loss, help to avoid dehydration, and lead to better tolerance without treatment interruptions [4,7].

Previous studies have shown that quality of life in head and neck cancer patients is lower at diagnosis compared with the general population, and becomes worse during and immediately after treatment [8,9]. Women score lower than men at diagnosis and immediately after treatment [10,11] and patients > 65 years of age score lower in quality of life studies than those under 65 [11]. In addition, tumor size, smoking, alcohol abuse, depression, social network, personality and marital status can affect the quality of life of head and neck cancer patients [12-17].

However, few studies have focused on the effect of body mass index (BMI) on treatment outcomes [18]. The World Health Organization (WHO) defines overweight as body mass index (BMI) 25-29.9 kg/m^2 and obesity as BMI ≥30. Obesity is characterized by a number of side effects; among others obesity reduces quality of life and physical activity [19].

There are several reasons why quality of life studies in head and neck cancer patients are important. Better understanding of therapeutic healing aspects will help staff to be able to inform patients and thus prepare them for any function changes and symptoms during RT. Better understanding of different health aspects is also essential for preventing and mitigating functional impairment and symptoms. Although much research has been done regarding quality of life, function and symptoms, there are still areas that are less well explored. It is for example unclear how overweight and obesity can affect the quality of life of patients undergoing RT. Therefore, we conducted a secondary analysis of a prospective study to evaluate whether BMI was associated with quality of life during RT in head and neck cancer patients. The prospective single-arm study was designed to follow head and neck cancer patients during their radiation treatment period with the purpose to document how the patients experienced the radiotherapy period in terms of information needs, side effects and quality of life. There are four earlier publications regarding primary aspects of this study [20-23].

Methods

Study design and patient sample

The study was conducted at the University Hospital in Northern Norway, in the time period from May 2009 to November 2012. All ambulatory adult patients (18 years or older) with an untreated primary head and neck cancer, referred to the oncology center for radiotherapy, were potentially eligible to participate in the study. Exclusion criteria were patients who were unable to answer the health-related quality of life (HRQOL) questionnaires as a result of mental disturbance, or unable to fill in the questionnaire for other reasons, e.g., poor general condition, or if they were unable to speak and understand Norwegian. Totally 87 potentially eligible patients were originally identified. Eligible patients received a letter explaining the purpose and the methods of the study and the level of commitment required to participate. A research assistant met the patients during treatment planning or initiation to seek consent and administer the questionnaire. Eighty-two patients met the criteria and were invited to attend the study. Three patients refused participation and one relative of a patient declined. Eleven patients did not return the written consent. Sixty-seven were included, providing an attendance rate of 82.7%. Sixty patients had available BMI data. The study was approved by the Regional Committee for

Medical Research Ethics (P REK NORD 200900504-3KST017/400), and the Norwegian Social Science Data Services (21831).

Data collection

Socio demographic and tumor-related patient characteristics were recorded at inclusion, i.e. sex, age, tumor location according to ICD-10, TNM stage (T=tumor size, N=node, M= metastasis) and planned treatment. In addition, a study-specific questionnaire about which information the health care workers had given the patients was filled out twice by the research radiation therapist, before the patients started treatment and after they completed treatment. The patients responded to what information they had received about nutrition and which food and drinks they should avoid during the radiation treatment period. Information regarding dietary counselling was not structured before or under radiation treatment; the doctors, nurses and radiation therapists gave individual dietary advice. The patients were provided with verbal nutrition information from the radiation therapists during the treatment. They were not encouraged to use media or websites to gain further information. The nutrition information questionnaire consisted of open questions where the patients should answer the radiation therapist. Patients were also asked about current use of nutritional supplements such as powders or liquids providing extra calories, and if they wanted to talk to a nutritionist. In addition, nutritional status with weight loss, hemoglobin level (Hb) and serum albumin was filled out in the beginning (0Gy), after 2 weeks (20Gy), after 4 weeks (40Gy) and after 6 weeks (60Gy) by the research radiation therapist. The patients` general condition, skin and mucous membranes (CTCAE v.3.0) (mucositis clinical, grades 1 to 5 with unique clinical descriptions) were documented by the research radiation therapist four times during radiation treatment, in the beginning (0Gy), after 2 weeks (20Gy), after 4 weeks (40Gy) and after 6 weeks (60Gy).

HRQOL questionnaires

Data were collected at two time points: at baseline which was the first radiation treatment week (T1), and during the last week after 60 Gy (T4). At T1 and T4, the patients filled in the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [24] and EORTC QLQ-H&N35 [25]. The EORTC QLQ-C30 questionnaire is a generic questionnaire to all cancers. The questionnaire is a patient-based measurement designed for self-administration which assesses multiple dimensions of HRQOL and responses of this 30-item questionnaire are categorized into five functional domains (physical, role, emotional, cognitive, and social) scored on a four-point scale, one global HRQOL domain (scored on a seven-point scale), three symptom domains (fatigue, nausea/vomiting, pain) and six single items (scored on a four-point scale). Each score is transformed into 0-100 point scale. Both EORTC instruments were scored according to recommendations in the EORTC QLQ-C30 scoring manual [8]. In the five functional scales and the global HRQOL scale, a high score represents a high level of functioning or global HRQOL. In the symptom scales and single items, a higher score implies a high level of symptoms or problems. EORTC QLQ-H&N35 is a questionnaire specifically developed for head and neck cancer patients consisting of 35 items on health-related HRQOL. It includes seven scales (pain, swallowing, senses, speech, social eating, social contact and sexuality) and 11 single items (problems with teeth, problems opening the mouth, dry mouth, sticky salvia, cough, feeling ill, pain killers, nutritional supplements, feeding tube, weight loss and weight gain). Items 1-30 are scored on a four-point scale (1; not at all, 2; a little, 3; quite a bit, 4; very much). Items 31-35 have a yes (2) or no (1) response format. Given that all the scales assess symptoms, higher scores correspond to lower quality of life.

Clinical treatment

Radiotherapy was administered to the primary tumor and the regional neck lymphatics (dependent on N stage) by conventional fractionation, i.e. dose of 2 Gy, 1 fraction per day, 5 days per week. The total radiation doses were 60-70 Gy. RT was delivered using megavoltage equipment (6MV linear accelerator) over a period of six to seven weeks. In all patients, thermoplastic mask immobilization and planning computed tomography scans were used, and all patients were treated with three-dimensional conformal (n=48) or intensity-modulated radiotherapy (n=12). None of the patients had distant metastases. The patients received standardized oral care kits before radiotherapy, which contained soft toothbrush, flourished toothpaste without soap, artificial salvia spray and lozenges, fluoride mouthwash, saltwater and dexpanthenol lotion. Further counseling was individualized.

Statistical analysis

In the present study, the primary outcome of interest was to examine correlations between obesity and quality of life during RT. Secondary outcomes were differences in information that obese patients received compared to normal weight patients regarding nutrition. Sixty patients with available BMI data were included. Changes in HRQOL were calculated and compared by paired sample T-test. Multiple regression analyses were used to examine correlations between baseline BMI and changes in HRQOL, CTCAE v.3.0 toxicity, nutritional status and information that radiotherapists provided to patients. To obtain the latter parameter, patients' answers were converted to a three-tiered score, which was compared between groups by Pearson Chi-Square test. Baseline frequency data were compared by Fisher exact probability test. The significance level was set at $p = 0.05$ using the statistical software SPSS 19.0 for Windows.

Results

Mean age of all 60 patients was 60 years. Seventy-seven percent were males (Table 1). Twenty-five percent were never smokers. Mean BMI was 25.7 (<25 in 26 patients, 43%). There were 9 obese (BMI > 30) patients, and 1 underweight (BMI < 18.5) patient. The differences in baseline parameters included in Table 1 (for example chemotherapy utilization, baseline weight loss or gender) between overweight and normal weight patients were not statistically significant. There was no statistically significant difference in baseline Hb and serum albumin between overweight and normal weight patients either (Table 2). As also shown in Table 2, BMI decreased slightly during radiotherapy, both in overweight and normal weight patients. Numerical decreases in Hb and albumin were also found. The magnitude of these changes was similar in both groups.

Table 3 shows that quality of life (EORTC QLQ-C30) was largely comparable at baseline, except for dyspnea which was significantly worse in overweight patients. Differences between baseline and end of treatment were similar in both groups. Table 4 shows the results of the QLQ-H&N35 questionnaire. At baseline, overweight patients had lower rates of feeding tube use ($p = 0.037$) and intake of nutritional supplements ($p = 0.001$). At end of treatment, overweight patients had significantly more problems with dry mouth ($p = 0.042$). During treatment patients with BMI ≥ 25 had more problems with opening mouth ($p = 0.034$) than patients with BMI < 25 and more changes in sexuality ($p = 0.019$). The persistent differences in feeding tube use lie below the border of statistical significance.

Table 5 shows that patients with BMI ≥ 25 had less mucosal changes after two weeks of radiation treatment than patients with BMI < 25 (p= 0.010), and comparable trends were seen at later time points. However, this difference was not statistically significant at later time points when the higher cumulative radiation doses generally caused more severe side effects. Course of skin changes and performance status was not clearly related to BMI. Patients with BMI ≥ 25 received less information about food and drinks that they should avoid in the radiation treatment period than normal weight patients (p= 0.011), although general nutrition information was comparable between the groups (Table 6).

Table 1 Pretreatment body mass index and other baseline parameters

Patient characteristics	**All n(%) 60(100)**	**BMI <25 n(%) 26(43.3)**	**BMI ≥25 n(%) 34(56.7)**	**P-value**
Age,				
Mean (min, max)	60.0 (21-84)	59.2 (35-73)	60.6 (21-84)	0.669
Gender				0.241
Male n (%)	46(76.7)	18(69.2)	28(82.4)	
Female n(%)	14(23.3)	8(30.8)	6(17.6)	
Tumor location				0.952
Oral cavity n(%)	16(26.7)	6(23.1)	10(29.4)	
Pharynx n(%)	14(23.3)	6(23.1)	8(23.5)	
Larynx n(%)	14(23.3)	8(30.8)	6(17.6)	
Salivary glands n(%)	6(10)	3(11.5)	3(8.8)	
Others/unknown n(%)	10(16.7)	3(11.5)	7(20.6)	
T stage				0.049
T1 n(%)	18(30)	8(30.1)	10(29.4)	
T2 n(%)	19(31.7)	11(42.3)	8(23.5)	
T3 n(%)	6(10)	4(15.4)	2(5.9)	
T4 n(%)	8(13.3)	2(7.7)	6(17.6)	
Tx n(%)	9(15)	1(3.8)	8(23.5)	
N stage				0.495
N0 n(%)	25(41.6)	14(53.8)	11(32.4)	
N1 n(%)	15(25)	5(19.2)	10(29.4)	
N2 n(%)	10(16.7)	6(23.1)	4(11.8)	
Nx n(%)	10(16.7)	1(3.8)	9(26.5)	
IMRT				0.660
Yes n(%)	12(20)	5(19.2)	7(20.6)	
Chemotherapy				0.242
Yes n(%)	21(35)	7(26.9)	14(41.2)	
Radiation dose				0.786
40Gy n(%)	2(3.3)	0(0)	2(5.9)	
60Gy n(%)	18(30)	9(34.6)	9(26.5)	
64Gy n(%)	1(1.7)	0(0)	1(2.9)	
66Gy n(%)	6(10)	3(11.5)	3(8.8)	
68Gy n(%)	23(38.3)	10(38.5)	13(38.2)	
70Gy n(%)	9(15)	3(11.5)	6(17.6)	
Unknown n(%)	1(1.7)	1(3.8)	0(0)	
Smoking				0.917
Present smoker n(%)	11(18.3)	6(23.1)	5(14.7)	
Former smoker n(%)	34(56.7)	12(46.2)	22(64.7)	
Never smoker n(%)	15(25)	8(30.1)	7(20.6)	
Baseline weight loss* n(%)	12(20)	7(26.9)	5(14.7)	0.187

*Patients who reported weight loss on EORTC QLQ-H&N 35 form, no quantification required

Table 2 Patients' BMI, hemoglobin and albumin before and during treatment

	All	**BMI <25 (n=26)**	**BMI ≥25 (n=34)**	**P-value**
BMI				
0 Gy mean, range	25.7, 16.9	22.5, 6.5	28.2, 10.3	0.418
20 Gy mean, range	25.5, 16.9	22.3, 6.8	28.0, 12.5	0.820
40Gy mean, range	25.2, 17.4	22.1, 7.7	27.6, 11.4	0.071
60Gy mean, range	24.5, 15.8	21.9. 7.9	26.8, 10.1	0.389
Hb				
0Gy [g/dl]; mean, range	13.7, 7.5	13.3, 6.4	14.1, 6.5	0.275
20Gy [g/dl]; mean, range	13.8, 6.3	13.4, 5.1	14.0, 6.3	0.105
40Gy [g/dl]; mean, range	13.2, 6.4	13.0, 5.0	13.4, 6.4	0.342
60Gy [g/dl]; mean, range	12.9, 6.4	12.7, 4-9	13.2, 6.4	0.405
Albumin				
0 Gy [g/l]; mean, range	42.2, 15.3	42.3, 15.3	42.1, 11.1	0.818
20 Gy [g/l]; mean, range	41.2, 24.4	40.5, 23.5	41.4, 12.9	0.424
40 Gy [g/l]; mean, range	40.0, 22.3	40.5, 17.4	39.5, 22.3	0.396
60 Gy [g/l]; mean, range	38.9, 19.8	39.1, 17.2	38.4, 18.9	0.549

Table 3 Relationship between quality of life (EORTC QLQ-C30) in patients with BMI ≥25 vs <25

EORTC QLQ-C30 Functional scales	Start of treatment BMI≥25 Mean, SD, P-value	Start of treatment BMI<25 Mean, SD	End of treatment BMI≥25 Mean, SD, P-value	End of treatment BMI<25 Mean, SD	Difference BMI≥25 Mean, SD, P-value	Difference BMI<25 Mean, SD
Physical Functioning	83.1, 17.5, 0.321	84.5, 15.1	69.1, 25.5, 0.453	65.3, 22.4	14.0, 16.6, 0.479	22.7, 24.3
Role functioning	71.1, 26.1, 0.602	76.4, 25.5	44.8, 31.2, 0.213	43.6, 38.5	28.2, 26.8, 0.653	34.2, 33.5
Emotional functioning	81.5, 19.3, 0.342	87.2, 20.3	75.0, 24.5, 0.733	77.2, 22.5	7.3, 26.9, 0.586	10.6, 28.3
Cognitive functioning	89.2, 19.2, 0.184	86.1, 17.5	78.3, 25.2, 0.187	67.8, 30.4	12.8, 17.3, 0.407	18.6, 30.9
Social functioning	71.1, 28.8, 0.637	73.6, 26.0	60.1, 30.9, 0.843	60.9, 34.7	10.7, 20.9, 0.639	15.9, 34.7
Global health scale	68.6, 21.8, 0.310	65.6, 24.6	48.3, 25.7, 0.527	47.8, 25.5	21.9, 19.4, 0.820	21.6, 26.7
Symptom scale						
Fatigue	32.3, 25.6, 0.816	31.9, 21.8	53.7, 30.5, 0.236	62.3, 25.9	-22.6, 24.3, 0.611	-31.3, 25.3
Nausea and vomiting	13.0, 21.2, 0.281	17.4, 26.2	33.3, 30.0, 0.471	25.4, 28.8	-19.2, 29.3, 0.670	-9.8, 32,4
Pain	15.2, 18.5, 0.919	18.1, 20.8	44.4, 30.7, 0.078	53.6, 34.8	-30.6, 26.3, 0.230	-38.6, 35.0
Single-item question						
Dyspnea	22.5, 21.3, **0.033**	16.7, 26.0	22.2, 22.0, 0.401	30.4, 31.6	-1.1, 20.5, 0.349	-15.2, 22.4
Insomnia	26.5, 29.3, 0.395	33.3, 34.0	25.6, 27.2, 0.343	34.8, 34.0	1.1, 27.0, 0.135	-3.0, 34.0
Loss of appetite	17.6, 29.9, 0.732	22.2, 35.0	57.8, 37.1, 0.826	66.7, 34.1	-40.0, 37.5, 0.768	-44.4, 38.5

Constipation	17.2, 23.7, 0.607	20.8, 27.5	46.7, 38.8, 0.922	47.8, 38.7	-31.0, 46.2, 0.961	-34.8, 39.1
Diarrhea	14.1, 23.6, 0.773	13.9, 21.8	17.8, 31.2, 0.253	13.6, 19.7	-2.3, 35.6, 0.778	4.7, 21.8
Financial difficulties	13.7, 26.1, 0.652	18.1, 31.1	15.6, 24.3, 0.263	30.3, 35.5	-1.1, 28.3, 0.340	-12.7, 30.7

Table 4 Relationship between quality of life (EORTC QLQ-H&N35) in patients with BMI ≥25 vs <25

EORTC QLQ-H&N35	Start of treatment BMI≥25 Mean, SD, P-value	Start of treatment BMI<25 Mean, SD	End of treatment BMI≥25 Mean, SD, P-value	End of treatment BMI<25 Mean, SD	Difference BMI≥25 Mean, SD, P-value	Difference BMI<25 Mean, SD
Pain	17.2, 16.3, 0.423	18.0, 15.7	49.4, 28.4, 0.339	48.2, 26.6	-33.9, 23.3, 0.594	-30.4, 29.4
Swallowing	6.9, 12.0, 0.081	11.6, 16.1	45.7, 31.6, 0.281	45.3, 28.1	-38.2, 35.0, 0.651	-35.6, 26.8
Senses problems	14.2, 24.7, 0.352	26.7, 28.9	50.6, 31.7, 0.217	55.8, 30.0	-35.6, 35.8, 0.405	-31.2, 25.3
Speech problems	13.1, 14.6, 0.268	23.1, 25.8	39.8, 27.3, 0.137	47.0, 31.0	-26.1, 29.1, 0.351	-25.8, 25.5
Trouble with social eating	9.8, 12.5, 0.478	18.8, 23.0	48.3, 26.7, 0.652	49.9, 27.5	-38.3, 27.3, 0.958	-34.3, 30.2
Trouble with social contact	4.2, 6.8, 0.518	6.1, 11.0	23.0, 24.8, 0.288	28.9, 29.9	-18.4, 22.1, 0.479	-22.6, 30.4
Less sexuality	30.1, 29.5, 0.345	34.8, 37.1	53.2, 32.3, 0.450	41.6, 33.8	-28.3, 33.1, **0.019**	-8.8, 44.5
Teeth	4.9, 16.7, 0.095	10.1, 23.4	14.9, 27.6, 0.845	10.6, 21.5	-9.2, 26.6, 0.399	-4.8, 12.0
Opening mouth	17.6, 27.5, 0.248	9.3, 15.3	40.2, 33.8, 0.467	39.1, 34.3	-19.5, 31.5, **0.034**	-30.4, 37.5
Dry mouth	29.4, 29.3, 0.197	41.3, 26.0	64.4, 33.3, **0.042**	62.3, 27.2	-34.5, 32.7, 0.528	-23.2, 29.2
Sticky saliva	27.3, 24.2, 0.318	34.7, 32.6	71.4, 31.1, 0.168	68.1, 34.1	-44.0, 31.5, 0.387	-37.7, 36.7
Coughing	20.6, 16.4, 0.087	21.3, 27.0	35.6, 28.1, 0.744	43.5, 29.2	-12.6, 27.3, 0.536	-26.1, 26.5
Felt ill	16.7, 22.1, 0.707	17.8, 22.2	43.7, 32.2, 0.824	45.5, 28.3	-29.9, 28.7, 0.397	-29.8, 27.1
Pain killers	44.1, 50.4, 0.752	40.0, 50.0	86.7, 34.6, 0.288	95.5, 21.3	-43.3, 50.4, 0.424	-54.5, 51.0
Nutritional supplements	3.0, 17.4, **0.001**	36.0, 49.0	46.7, 50.7, 0.123	68.2, 47.7	-44.8, 50.6, 0.543	-36.4, 49.2
Feeding tube	0.0, 0.0, **0.037**	12.5, 33.8	30.0, 46.6, 0.075	54.5, 51.0	-27.6, 45.5, 0.072	-22.7, 68.5
Weight gain	30.3, 46.7, 0.311	43.5, 50.7	7.4, 26.7, 0.707	4.8, 21.8	22.2, 57.7, 0.394	40.0, 50.3
Weight loss	14.7, 35.9, 0.181	29.2, 46.4	62.1, 49.4, 0.909	63.6, 49.2	-51.7, 50.9, 0.275	-36.4, 49.2

Table 5a General condition, skin and mucosal changes during radiation treatment for patients with BMI ≥25 vs <25

	0Gy	20Gy	40Gy	60Gy
ECOG performance status, BMI≥25 Mean, SD, P-value	2.7, 2.3, 0.512	1.9, 1.2, 0.298	2.5, 1.5, 0.921	3.2, 1.7, 0.572
ECOG performance status, BMI<25 Mean, SD	2.9, 2.3	2.0, 0.7	2.5, 1.3	2.9, 1.4
Skin changes*, BMI≥25 Mean, SD, P-value	6.4, 1.7, 0.704	3.3, 2.5, 0.237	2.9, 2.1, 0.292	3.2, 1.5, 0.240
Skin changes*, BMI<25 Mean, SD	6.0, 2.2	2.5, 2.2	2.0, 1.0	2.9, 0.8
Mucosal changes*, BMI≥25 Mean, SD, P-value	6.3, 1.9, 0.271	1.8, 1.2, **0.010**	2.9, 1.3, 0.415	3.6, 1.4, 0.368
Mucosal changes*, BMI<25 Mean, SD	5.5, 2.5	3.0, 1.8	2.9, 1.2	3.3, 1.0

*none vs all grades combined
Not provided standardized oral care information for prevention of mucositis

Table 5b Relationship between dermatitis and mucositis grade 3-4 in patients with BMI ≥25 vs <25

	20Gy	40Gy	60Gy
Dermatitis, BMI≥25 Mean, SD, P-value	1.0, 0.0, 0.154	1.2, 0.4, 0.525	1.6, 0.5, 0.269
Dermatitis, BMI<25 Mean, SD	1.1, 0.3	1.1, 0.3	1.7, 0.5
Mucosal changes, BMI≥25 Mean, SD, P-value	1.0, 0.2, **0.003**	1.4, 0.5, 0.191	1.7, 0.5, 0.655
Mucosal changes, BMI<25 Mean, SD	1.3, 0.5	1.6, 0.5	1.8, 0.4

no patients grade 3-4 at 0 Gy

Table 6 Patients' verbal answer about the instructions they received from health care providers before or during the treatment, converted to a three-tiered score. All patients received standardized oral care kits. Comparison between patients with BMI ≥25 vs <25

Study specific questionnaire	Start of treatment BMI≥25 Mean, SD, P-value	Start of treatment BMI<25 Mean, SD	End of treatment BMI≥25 Mean, SD, P-value	End of treatment BMI<25 Mean, SD
Information about nutrition	1.7, 0.5, 0.104	1.5. 0.5	1.7, 0.6, 0.323	1.5, 0.6
Information about food and drinks that should be avoided	1.8, 0.4, 0.565	1.7, 0.5	2.0, 0.5, **0.011**	1.6, 0.6

Discussion

During initial analyses of the prospective study [20-23], the authors developed a hypothesis that patients with normal and low BMI had more nutrition problems and therefore need more tube feeding than patients with overweight. The secondary analyses in the present exploratory study indicate that there were no significant differences, but they also show that BMI affected HRQOL and toxicity during radiation therapy. Head and neck cancer patients with high BMI (≥ 25) faced several challenges compared to patients with BMI < 25 before, during and after radiation treatment, except from mucosal changes after two weeks of treatment. This finding is in line with Fang et al. [26] who showed that higher BMI was associated with worse QOL for breast cancer patients before, during and after RT. The results are not consistent with those reported by Al-Naggar et al. [27] who examined QOL of breast cancer patients in Yemen and found a difference between underweight and overweight patients for emotional wellbeing. However, comparisons across both different disease types and cultures are difficult to interpret.

Our study is the first to demonstrate that there is a connection between head and neck cancer patients' BMI, their HRQOL and the individualized dietary counseling in the treatment period. The data presented here also illustrate that a considerable number of functions and symptoms are similar between the two BMI groups examined during RT for head and neck cancer. Before treatment overweight patients had more dyspnea than normal weight patients. As might be expected intuitively, lower rates of feeding tube use and lower intake of nutritional supplements were found in this subgroup. In a previous study, Van Bokhorst-de van der Schueren et al. [28] evaluated the use of perioperative nutritional support on QOL in 49 malnourished head and neck cancer patients. They found that patients who received preoperative tube-feeding and nutritional supplements experienced dyspnea relief [28]. Høgdal [29] has in a master thesis examined pretreatment HRQOL in 81 patients suffering from head and neck cancer. She found that these patients had more dyspnea before RT than normal population [29]. This finding might be related to the fact that half of these patients are smokers [29]. In Høgdals thesis [29] it was not focused on patients' weight or BMI status. Other studies have also reported higher baseline dyspnea scores in head and neck cancer patients [25,30,31]. In our study patients with BMI ≥ 25 had more dyspnea than patients with BMI < 25, in the absence of significant differences in smoking status between the groups (objective measures of lung function were not performed). This result can

possibly be explained by links between obesity and chronic diseases such as hypertension, coronary heart disease and congestive heart failure. Hammerlid et al [32] evaluated the connection between QOL and nutritional status and energy intake for head and neck cancer patients. They found no significant differences, but the malnourished patients scored worse on 12 of the 16 functional domains/symptoms [32].

Besides dyspnea, we found significant differences between the two groups regarding use of nutritional supplements and feeding tubes at baseline. Tumor location and size might lead to nutritional difficulties before treatment [33,34]. Some studies have reported an association between poor nutrition and development of mucositis [35-37]. The potential mechanism of the association between BMI and oral mucositis is uncertain [38]. Oral mucositis is one of the most serious problems connected to head and neck cancer radiotherapy [39,40], and severe cases may require feeding tube placement. The data presented here, illustrate how oral mucositis develops in the two BMI groups during radiotherapy. At baseline there were no significant differences between the groups, but after two weeks of radiation treatment patients with BMI ≥ 25 had less mucosal changes than patients with BMI < 25. After this time period, oral mucositis did not differ significantly between the groups. Saito et al. [38] examined whether low BMI could be a risk factor for oral mucositis. In their study, 33 patients with oral cancer received radiotherapy and they found that low BMI (< 22) may be a risk factor of moderate to severe oral mucositis. Virtually all patients who receive radiation therapy for head and neck cancer develop some degree of oral mucositis [39]. The incidence of oral mucositis has been reported to vary in relation to various patient characteristics, including low body mass index, altered oral intake and poor functional status, but the data supporting these potential non-dosimetric risk factors are inconsistent. At least in part, small group sizes and variations in RT technique and exposed mucosa surface might explain why variable correlations have been observed.

In the present study a significant correlation was also shown between overweight and problems with opening mouth and less sexuality during radiation treatment. Høgdal [29] found comparable correlations in the same HRQOL domains. Since risk factors for restricted mouth opening in head and neck cancers include tumor location and proximity to relevant muscles [41] imbalances might confound QOL results, but we found no significant correlation between BMI and location or T stage.

Our patients with BMI ≥ 25 had more problems with dry mouth after RT than patients with BMI < 25. This is interesting since there is a possibility that weight loss and contour changes in the neck region could account for accidental increase in dose to the salivary glands. This could explain the finding in the higher BMI group, but the number of patients was small. Kakoei et al. [42] highlighted the relationship between low QOL and dry mouth among patients irradiated for head and neck cancer. Head and neck cancer patients who underwent radiotherapy began to experience xerostomia after start of treatment, and this lead to a decrease in QOL during radiotherapy [42]. Previous studies have demonstrated that xerostomia, which is caused by permanent damage to the salivary glands in the irradiated region, is a common and important complaint amongst patients who undergo head and neck radiotherapy [43,44]. According to other studies, the effect of xerostomia on oral health and QOL is very important [42, 45]. In a study conducted in 2006, Pow et al. [44] compared the effect of intensity modulated radiotherapy (IMRT) vs. conventional radiotherapy on salivary flow and QOL. They found consistent improvement over time in the IMRT group, with xerostomia-related symptoms significantly less common than in the conventional radiotherapy group [44]. None of these studies have focused on patients' BMI. We found no significant imbalance in IMRT use between

the two BMI groups. Possibly, in the absence of adaptive radiotherapy with re-planning based on new CT scans, obese patients might experience relatively larger changes in anatomy, which might result in higher than anticipated dose to the salivary glands [46].

During treatment patients with BMI ≥ 25 received less information about food and drink that should be avoided than normal weight patients. The authors did not compare patient recollection with the actual nutritional advice and information provided, which is a weakness of our study. It is tempting to speculate that identical information policies would have contributed to better QOL and fewer side effects in overweight patients, which had less mucositis despite poorer counseling. However, this hypothesis needs prospective testing. Access to other sources of information including publicly available brochures and websites as well as communication with fellow patients might compensate for imbalances.

The clinical manifestations of radiation injury and its nutritional consequences have been well described [47]. Several studies have shown a relationship between nutrition support, weight gain and improved QOL [48,49]. Ravasco et al. [7] performed a prospective randomized controlled trial with 75 patients with head and neck cancer to determine the effect of dietary counseling on outcome and QOL during and 3 months after radiotherapy [7]. They found that during RT, dietary counseling improved all QOL function scores in association with an adequate dietary intake and nutritional status [7]. The results from the present study provide important information about head and neck cancer patients treated with radiotherapy and the association of overweight with HRQOL, comparable to a previous breast cancer study [26]. Implications for practice include the need for health care providers to be aware of the impact that overweight and low weight has on patients' HRQOL. Patients in the low BMI group had already commenced nutritional support with supplements and tube feeding before treatment, and this group continued to need greater nutritional support during treatment. Health care providers should be aware of patients' need for nutritional information and support. A main limitation of our study is the short period of follow-up. Additional longitudinal studies should examine whether or not overweight patients persistently experience more problems with dry mouth and opening their mouth. Another weakness of the present study is the lack of information about patients' compliance with dietary and oral care counseling. Regardless of BMI, all patients should be informed about nutritional recommendations during treatment and receive appropriate follow-up care and rehabilitation for reduced swallowing and mouth opening function.

Acknowledgements

We thank the study participants who shared their experiences during a difficult period of their lives. We also thank the research assistants Anne J. Dalheim, Solveig Hanssen, and Janne Heidi Tunstad for their participation in data collection and cooperation in the study.

Conflict of interest

Both authors have read and approved the manuscript; we have no conflicts of interest to declare or financial support from industry sources to disclose.

References:

1. Lees J (1999) Incidence of weight loss in head and neck cancer patients on commencing radiotherapy treatment at a regional oncology centre. European Cancer Care 8:133-136

2. Mekhail TM, Adelstein DJ, Rybicki LA, Larto MA, Saxton JP, Lavertu P (2001) Enteral nutrition during the treatment of head and neck carcinoma. Cancer 91:1785-1790

3. Head BA, Heitz L, Keeney C, Myers J, Appana SN, Studts L, Bumpous J, Pfeifer M (2011) The relationship between weight loss and health-related quality of life in persons treated for head and neck cancer. Support Care Cancer 19:1511-1518

4. Beaver ME, Matheny KE, Roberts DB, Myers JN (2001) Predictors of weight loss during radiation therapy. Otolaryngology Head and Neck Surgery 125:645-648

5. Delafuente JC (1991) Nutrients and immune responses. Reumatic Diseases Clinics of North America 17:203-212

6. Copeland EM, Daly JM, Dudrick SJ (1977) Nutrition as an adjunct to cancer treatment in the adult. Cancer Research 37:2451-2456

7. Ravasco P, Monteiro-Grillo I, Marques VP, Camilo ME (2005) Impact of nutrition on outcome: A prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. Head and Neck 27:659-668

8. Borggreven PA, Verdonck-de Leeuw IM, Muller M, Heiligers LCH, de Bree R, Aaronson NK, Leemans CR (2007) Quality of life and functional status in patients with cancer of the oral cavity and oropharynx: pretreatment values of a prospective study. European Archives of Otorhinolaryngology 264:651-657

9. Funk G, Hynds L (1997) Baseline and post-treatment assessment of the general health status of head and neck cancer patients compared with United States population norms. Head and Neck 19:675-683

10. Maciejewski O, Smeets R, Gerhards F, Kolk A, Kloss F, Stien JM, Kasaj A, Koch F, Grosjean M, Riediger D, Yetka SS (2010) Gender specific quality of life in patients with oral squamous cell carcinomas. Head and Face Medicine 6:21

11. Michelson H, Bolund C, Nilsson B, Brandberg Y (2000) Health-related quality of life measured by the EORTC QLQ-C30. Reference values from a large sample of the Swedish population. Acta Oncologica 39:477-484

12. Hammerlid E, Ahlner-Elmqvist M, Bjordal K, Björklund A, Evensen JF, Boysen M, Jannert M, Kaasa S, Sullivan M, Westin T (1999) A prospective multicenter study in Sweden and Norway of mental distress and psychiatric morbidity in head and neck cancer patients. British Journal of Cancer 80:766-774

13. De Leuw JRJ, de Graeff A, Ros WJG, Blijham GH, Hordijk G-J, Winnubst JAM (2000) Prediction of depressive symptomology after treatment of head and neck cancer: The influence of pre-treatment physical and depressive symptoms, coping, and social support. Head and Neck 22:799-807

14. List MA, Lee Rutherford J, Stracks J, Haraf D, Kies MS, Vokes EE (2002) An exploration of the pretreatment coping strategies of patients with carcinoma of the head and neck. Cancer 95:98-104

15. De Graeff A, de Leeuw RJ, Ros WJG, Hordijk G-J, Blijham GH, Winnubst JAM (2001) Sociodemographic factors and quality of life as prognostic indicators in head and neck cancer. European Journal of Cancer 37:332-339

16. Duffy SA, Terrell JE, Valenstein M, Ronis DL, Copeland LA, Connors M (2002) Effect of smoking, alcohol, and depression on the quality of life of head and neck cancer patients. General Hospital Psychiatry 24:140-147

17. Lebel S, Devins GM (2008) Stigma in cancer patients whose behavior may have contributed to their disease. Future Oncology 4:717-733

18. Pai PC, Chuang CC, Tseng CK, Tsang NM, Chang KP, Yen TC, Liao CT, Hong JH, Chang JTC (2012) Impact of pretreatment body mass index on patients with head-and-neck cancer treated with radiation. International Journal of Radiation Oncology Biology Physics 83:e93-e100

19. Ramsay SE, Whincup PH, Shaper AG, Wannamethee SG (2006) The relations of body composition and adiposity measures to ill health and physical disability in elderly men. American Journal of Epidemiology 164:459-469

20. Egestad H & Emaus N (2014) Changes in health related quality of life in women and men undergoing radiation treatment for head and neck cancer and the impact of smoking status in the radiation treatment period, European Journal of Oncology Nursing; http://dx.doi.org/j.ejon.2014.04.003

21. Egestad, H (2013) The significance of fellow patients for head and neck cancer patients in the radiation treatment period. European Journal of Oncology Nursing;17.(5) 618-624

22.Egestad H (2013): How does the radiation therapist affect the cancer patients' experience of the radiation treatment? European Journal of Cancer Care, 22 (5) 580-588

23. Egestad H (2013) Radiographers relationship with head and neck cancer patients. Journal of Radiotherapy in Practice 2013 ; 12, 245-254

24. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez J, Filiberti A, Flechtner H, Fleishman SB, de Haes JCJM, Kaasa S, Klee M, Osobam D, Razavi D, Rofe PB, Schraub S, Sneeuw K, Sullivan M, Takeda F (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials on oncology. Journal of the National Cancer Institute 85:365-376

25. Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D, Ahlner- Elmqvist M, Maher EJ, Meyza JW, Brèdart A, Söderholm AL, Arraras JJ, Feine JS, Abendstein H, Morton RP, Pignon T, Huguenin P, Bottomly A, Kaasa S (2000) A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. European Journal of Cancer 36:1796-1807

26. Fang P, Tan KS, Troxel AB, Rengan R, Freedman G, Lin LL (2013) High body mass index is associated with worse quality of life in breast cancer patients receiving radiotherapy. Breast Cancer Research and Treatment DOI 10.1007/s10549-013-26663-2

27. Al-Naggar RA, Nagi NMS, Ali MMS, Almuasli M (2011) Quality of life among breast cancer patients in Yemen. Asian Pacific Cancer Prevention 12:2335-2341

28. Van Bokhorst-de van der Schueren MAE, Langendoen SI, Vondeling H, Kuik DJ, Quak JJ, van Leeuwen PAM (1999) Perioperative enteral nutrition and quality of life of severely malnourished head and neck cancer patients: a randomized clinical trial. Clinical Nutrition 19:437-444

29. Høgdal N (2010) Funktionel status og helbredelsesrelatert livskvalitet hos pasienter med cancer cavi oris og cancer oropharynges ved start av strålebehandling (Functional status and quality of life in patients with cancer cavi oris and oropharynx at the start of radiotherapy). Masteroppgave I Helsefagvitenskap ved Det medisinske fakultet, seksjon for helsefag. (Master in Health Sciences Faculty of Medicine). University of Oslo, Norway.

30. Hammerlid E, Taft C (2001) Health-related quality of life in long-term head and neck cancer survivors: a comparison with general population norms. British Journal of Cancer 84:149-156

31. Hjermstad MJ, Fayers PM, Bjordal K, Kaasa S (1998) Using reference data on quality of life – the importance of adjusting for age and gender, exemplified by the EORTC QLQ-C30 (+3). European Journal of Cancer 34:1381-1389

32. Hammerlid E, Wirblad RD, Sandin RN, Mercke C, Edström MD, Kaasa S, Sullivan M, Westin T (1998) Malnutrition and food intake in relation to quality of life in head and neck cancer patients. Head and Neck 20:540-548

33. van den Berg MG, Rasmussen-Conrad EL, van Nispen L, van Binsbergen JJ, Merkx MA (2008) A prospective study on malnutrition and quality of life in patients with head and neck cancer. Oral Oncology 44:830-837

34. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME (2003) Nutritional deterioration in cancer: the role of disease and diet. Clinical Oncology 15:443-450

35. Raber-Durlacher JE (1999) Current practices for management of oral mucositis in cancer patients. Support Care Cancer 7:71-74

36. Raber-Durlacher JE, Weijk NI, Abu Saris M, de Koning B, Zwinderman AH, Osanto S (2000) Oral mucositis in patients treated with chemotherapy for solid tumors: a retrospective analysis of 150 cases. Support Care Cancer 8:366-371

37. Dreizen S (1990) Oral complications of cancer therapy. Description and incidence of oral complications. NCI Monographs 9:11-15

38. Saito N, Imai Y, Muto T, Sairenchi T (2012) Low body mass index as a risk factor of moderate to severe oral mucositis in oral cancer patients with radiotherapy. Support Care Cancer 20:3373-3377

39. Vera-Llonch M, Oster G, Haigwara M, Sonis S (2006) Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma – risk factors and clinical consequences. Cancer 106:329-336

40. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, Komaroff E, Nalysnyk L, Zilberberg MD (2003) Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiotherapy and Oncology 66:253-262

41. Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP (2003) Oral sequelae of head and neck radiotherapy. Critical Reviews in Oral Biology & Medicine 14:199-212

42. Kakoei S., Haghdoost A-A, Rad M, Mohammadadalizadeh S, Pourdamghan N, Nakhaei M, Bahador M (2012) Xerostomia after radiotherapy and its effect on quality of life in head and neck cancer patients. Archives of Iranian Medicine 15:214-218

43. Dirix P, Nuyts S, Vander Poorten V, Delaere P, Van den Bogaert W (2008) The influence of xerostomia after radiotherapy on quality of life: results of a questionnaire in head and neck cancer. Support Care Cancer 16:171-179

44. Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JST, Leung LH, Leung WK (2006) Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasophargeal carcinoma: initial report on a randomized controlled clinical trial. International Journal of Radiation Oncology Biology Physics 66:981-991

45. Lin SC, Jen YM, Chang YC, Lin CC (2008) Assessment of xerostomia and the impact on quality of life in head and neck cancer patients undergoing radiotherapy, and validation of the Taiwanese version of the xerostomia questionnaire. Journal of Pain and Symptom Management 36:141-148

46. You SH, Kim SY, Lee CG, Keum KC, Kim JH, Lee IJ, Kim YB, Koom WS, Cho J, Kim SK, Kim GE (2012) Is there a clinical benefit to adaptive planning during tomotherapy in patients with head and neck cancer at risk for xerostomia? Am J Clin Oncol 35:261-266

47. Chao KSC, Perez CA, Brady LW (1999) Fundamentals of patient management. In: Chao K.S.C., Perez C.A., Brady L.W. editors. Radiation oncology: management decisions. Philadelphia: Lippincott-Raven 1-13

48. Jamieson C, Norton B, Day T, Lakeman M, Powell-Tuck J (1997) The quantitative effect of nutrition support on quality of life in outpatients. Clinical Nutrition 16:25-28

49. Tchekmedyian S, Fesen M, Price L, Ottery F (2003) Ongoing placebo-controlled study of oxandrolone in cancer-related weight loss. International Journal of Radiation Oncology Biology Physics 57:283-284