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Pretreatment fat-free mass index correlates with early death in patients with head and neck squamous cell carcinoma

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Abstract

Background: A significant proportion of patients with head and neck squamous cell carcinoma (HNSCC) are malnourished at diagnosis. In this study, we investigated how pretreatment body mass index (BMI) and fat-free mass index (FFMI) correlate with early death, and whether these measurements are useful markers of prognosis for risk stratification of head and neck cancer patients.

Methods: Patients ($n = 404$) with newly diagnosed, curable HNSCC and WHO performance status 0–2 were prospectively included and met with a study representative before treatment initiation, as well as up to four follow-up visits. All patients provided an estimate of body weight at 6 months prior to diagnosis. Bioelectrical impedance analysis (BIA) was performed for all patients before treatment initiation.

Results: Most patients had oropharyngeal (46%), oral cavity (28%), or laryngeal cancer (12%). Forty-five (11%) patients met the standardized criteria for malnutrition according to the Global Leadership Initiative on Malnutrition (GLIM) at diagnosis. FFMI at diagnosis was lower in patients who died within 6 and 12 months after the start of treatment than in patients who survived these time points ($p = 0.035$ and $p = 0.005$, respectively).

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Conclusions: In this study, pretreatment FFMI was an independent prognostic factor for death within 6 and 12 months after the start of treatment in patients with HNSCC. Pretreatment BMI was not an independent risk factor for death within 6 and 12 months after treatment termination. Thus, FFMI may be useful for risk stratification of patients with head and neck cancer.

KEYWORDS

body composition, early death, head and neck cancer, malnutrition, oral oncology

1 | BACKGROUND

Head and neck cancer (HNC) is a global health problem and accounts for approximately 650 000 new cases and 330 000 deaths worldwide every year.[1] Early death after diagnosis is a significant problem within HNC, as almost 10% of these patients are reported to die within 6 months.[2,3] Early death in HNC may be caused by patient-, cancer-, and treatment-related factors, including malnutrition.[3] A better understanding of these risk factors could contribute to improved care and thereby increased survival rates.[4]

A substantial number of patients with HNC are already at risk of malnutrition at the time of diagnosis.[5,6] A poor nutritional status drives the loss of skeletal muscle (sarcopenia), which in combination with low-grade inflammation leads to cancer-related cachexia and increased mortality.[7–9] Smoking is a risk factor for HNC and also has several negative effects on body composition.[10,11] Patients with HNC are at high risk of malnutrition due to the location of the tumor in the upper aerodigestive tract. The treatment, including surgery, radiotherapy, and chemotherapy, gives rise to side effects, such as dysphagia and decreased appetite, and contributes to both local and systemic inflammation.[12–14]

Malnutrition may be avoidable, and early recognition of a cachectic body composition before and during treatment can identify patients in need of specific interventions, and potentially act as a prognostic factor among patients with HNC.

Bioelectrical impedance analysis (BIA) is a noninvasive method for measuring body mass composition via the body's electrical properties, and has been used for over 40 years in different settings.[15] BIA measures the resistance and reactance of body tissues. Measures related to skeletal muscle mass (SMM), such as fat-free mass (FFM) and fat-free mass index (FFMI), can be derived from these resistance and reactance values.[16] The measurement of body mass composition with BIA is a simple procedure that can identify HNC patients with signs of sarcopenia who are consequently at increased risk of treatment-related complications and mortality.

The primary aim of this study was to investigate whether pretreatment body mass index (BMI) and FFMI correlate with early death (within 6 months and within 12 months) after start of treatment, in order to establish the significance of pretreatment BMI and FFMI as markers of prognosis for risk stratification of patients with HNSCC.

2 | MATERIALS AND METHODS

2.1 | Study subjects

The Regional Ethical Review Board in Uppsala reviewed and approved the study (No. 2014/447). This study is part of a larger multicenter study registered at ClinicalTrials.gov, NCT03343236, and was carried out in accordance with the current Helsinki Declaration of the World Medical Association. This study was a multicenter, prospective cohort study. In total, 463 patients were included in this prospective study. Fifty-nine patients were excluded because they were not assessed by BIA. A cohort of 404 patients with head and neck squamous cell carcinoma (HNSCC) from three tertiary centers in Sweden were included from October 2015 until May 2022.

Inclusion criteria were newly diagnosed, previously untreated HNSCC, a curative treatment intent and a World Health Organization (WHO) performance status of 0–2.[17] Exclusion criteria included previous treatment for malignant neoplasms within the last 5 years (except for skin cancer), severe alcoholism, cognitive impairments, pacemaker or inability to understand Swedish. Blood samples were coded and stored in the Uppsala Biobank (approved RCC 2015-0025).

All 404 patients underwent BIA at diagnosis. Patients were treated according to the Swedish national guidelines and treatment options were discussed at multidisciplinary tumor board meetings. All patients were staged according to the 8th edition of the Union for International Cancer Control staging system.[18] Tumor response to treatment and loco-regional status were assessed by head and neck surgeons or general ENT physicians at

3-month intervals. Response to treatment was defined as complete response or nonresponse. Patients with complete response showed no evidence of disease, whereas patients with nonresponse included patients with locoregional failure after first line treatment or distant metastasis within 1 year after start of treatment.

Patients were under nutritional surveillance and were offered nutritional supplemental therapy when indicated. No physical exercise program was added to the study design. According to the study protocol, a follow-up visit with a study representative was arranged before treatment, at 7 weeks after the start of treatment, and at 3, 6 and 12 months after the termination of treatment. All 404 patients were followed up for at least 12 months. Weight loss during the 6 months prior to diagnosis was self-reported by the patients. BMI was calculated at all the visits as body weight divided by the square of height (kg/m^2). FFMI was calculated as FFM divided by the square of height (FFM/m^2). To diagnose malnutrition according to GLIM previous to the start of treatment, phenotypic and etiological criteria were used. Phenotypic criteria were body weight loss (either >5% within the past 6 months or >10% beyond 6 months), body mass index (<20 kg/m^2 if <70 years or <22 kg/m^2 if >70 years) or FFMI measured by BIA (<17 FFM/m^2 for males and <15 FFM/m^2 for females). Etiologic criteria were partial or no food intake, with the need for nutritional support, or C-reactive protein (CRP) level >5 mg/L.[19,20] The patients' body composition was measured using an 8-electrode BIA device (BC-418MA, Tanita Corporation, Tokyo, Japan).

Patient factors, such as smoking habits (pack-years; cigarette packages multiplied by the number of years), were recorded before treatment started. Data on disease-related factors, such as tumor site, TNM classification, stage and treatment modalities were collected.

2.2 | Statistical analysis

The data are presented as the mean, standard deviation and range for continuous variables, and as numbers and percentages for categorical variables. For comparisons between two groups, the independent *t*-test was used. To adjust for confounding, two-way analysis of variance test (with the Bonferroni method as post hoc test) and linear regression were used for continuous variables. The chi-square test was used for comparison of categorical variables, and Fisher's exact test for comparison of dichotomous variables. Exact binominal confidence intervals were estimated for proportions. Logistic and linear regression analysis was used to control for confounding in comparisons of dichotomous variables. For correlation analysis, both Pearson (parametric calculations) and Spearman (nonparametric calculations) tests were used. A Kaplan–Meier plot was used to describe the overall survival for the subgroups, and the difference between subgroups was analyzed with a log-rank test. Cox regression was used for multivariable analyses. All significance tests were two-tailed and were conducted at 5% significance level. IBM SPSS Statistics for Macintosh, Version 27.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

3 | RESULTS

3.1 | Patient characteristics

This prospective cohort study enrolled patients with oropharyngeal cancer (185 patients, 46%), oral cavity cancer (113 patients, 28%) or laryngeal cancer (47 patients, 12%), as well as 59 patients (14%) who had primary tumors in other sites. The mean age of patients overall was 63 years (range, 22–89 years). Two hundred and eighty-seven (71%) patients were male, and 117 (29%) were female. Table 1 provides details of patient characteristics. Patients with laryngeal cancer had the largest number of pack-years (25.0 pack-years), on average 16 pack-years more than patients with oral cavity cancer and oropharyngeal cancer (95% CI: 8.4–24.4) ($p < 0.001$) and (95% CI: 8.5–23.5) ($p < 0.001$), respectively, and 13 pack-years more than the other sites (95% CI: 4.3–22.3) ($p < 0.001$). No significant age differences were noticed regarding stages and sites at diagnosis. Ninety-two percent ($n = 171$) of all the oropharyngeal cancer patients were p16-positive. Forty-five (11.4%) of all patients met the standardized criteria for malnutrition according to GLIM at the start of treatment. None of the patients underwent prophylactic percutaneous endoscopic gastrostomy placement and no patient received tube feeding or parenteral nutritional feeding at time of diagnosis.

3.2 | Weight loss and BMI 6 months prior to diagnosis

The mean BMI for the whole cohort at 6 months prior to diagnosis was estimated at 27.5 kg/m^2 (range, 17.6–47.3 kg/m^2). The mean loss of weight in the whole cohort from 6 months prior to diagnosis to date of diagnosis was 1.9 kg. Patients with stage I or stage II disease had a self-reported mean weight loss of 1.4 kg during the 6 months prior to diagnosis and a mean BMI loss of 0.48 kg/m^2,

whereas patients with stage III or stage IV disease had a mean weight loss of 2.7 kg ($p = 0.006$) and a mean BMI loss of 0.89 kg/m^2 ($p = 0.005$). Patients with oropharyngeal cancer had a mean body weight of 87.5 kg 6 months prior to diagnosis, whereas oral cancer patients had a mean body weight of 80.9 kg ($p = 0.006$) (Table 2). The oral cavity cancer patients lost a mean of 1.5 kg more than the oropharyngeal patients (3.0 kg vs. 1.5 kg) during the 6 months prior to diagnosis ($p = 0.034$).

TABLE 1 Patient characteristics.

Group	Cohort
Total number of subjects (*n*)	404
Age, years	
Mean (standard deviation, SD)	63 (11)
Sex, *n* (%)	
Male	287 (71.0)
Female	117 (29.0)
Smoking, pack-years mean (range)	11.7 (0–105)
C-reactive protein at diagnosis, mg/L mean (range)	7.4 (0.2–226)
Stage, *n* (%)	
I	159 (39)
II	86 (21)
III	82 (20)
IV	77 (20)
Treatment modality, *n* (%)	
Surgery	53 (13)
Surgery + radiotherapy	85 (21)
Chemoradiotherapy	126 (31)
Radiotherapy	140 (35)
Tumor site, *n* (%)	
Oropharynx	185 (46)
Oral cavity	113 (28)
Larynx	47 (12)
Hypopharynx	10 (2)
Nasopharynx	18 (4)
Cancer of unknown primary	20 (5)
Sinonasal	11 (3)

3.3 | BMI and FFMI at diagnosis

At diagnosis, no significant differences in BMI were found between the different stages and sites. Men had a mean BMI of 27.4 kg/m^2 at diagnosis, while the mean BMI in women was 25.4 kg/m^2 ($p < 0.001$) (Table 3). The mean FFMI at diagnosis in patients with oropharyngeal and oral cavity cancer was 20.0 and 18.9 kg/m^2 ($p = 0.004$), respectively. There was no significant difference between the tumor stages regarding FFMI at diagnosis. Men had a mean FFMI of 20.6 kg/m^2 at diagnosis, while the mean FFMI in women was 16.6 kg/m^2 ($p < 0.001$). Higher age correlated to lower FFMI at diagnosis, and for every additional year of age the patient had 0.07 kg/m^2 lower FFMI at diagnosis ($p < 0.001$). A multivariable linear regression with FFMI as the dependent variable showed that age ($p < 0.001$), sex ($p < 0.001$), and patient-estimated weight loss during the 6 months prior to diagnosis ($p = 0.018$) were significant independent factors for FFMI at diagnosis. Male sex, younger age, and minimal weight loss correlated with a high FFMI at diagnosis. Tumor site was not a significant independent factor for FFMI at diagnosis.

3.4 | Response to treatment within 1 year after treatment

Seventy-nine (19.6%) patients demonstrated nonresponse to treatment within 1 year after the start of treatment. Of these, 58 (73%) were diagnosed at stage III–IV, and 21 (27%) patients were diagnosed at stage I–II ($p < 0.001$). Both weight loss and loss of BMI during the 6 months prior to diagnosis was higher in the nonresponding group compared to the responding group (2.9 kg vs. 1.7 kg) ($p = 0.005$) and (1.0 kg/m^2 vs. 0.56 kg/m^2) ($p = 0.004$), respectively. Malnutrition according to GLIM at time of diagnosis was correlated to nonresponse to treatment, 14 (31%) of the patients

TABLE 2 Mean body weight and body mass index (BMI) 6 months prior to head and neck cancer diagnosis.

Factor	Male	Female	Oropharynx	Oral cavity	Larynx	Other sites	Stage I–II	Stage III–IV	Total
Weight, kg mean (SD)	89.3 (14.8)	71.6 (14.6)	87.5 (16.0)	80.9 (18.7)	80.5 (13.9)	83.7 (15.7)	85.1 (16.5)	83.1 (17.1)	84.3 (16.8)
BMI, kg/m^2 mean (SD)	28.0 (4.4)	26.2 (5.0)	27.8 (4.4)	27.4 (5.4)	27.0 (3.9)	27.2 (4.4)	27.5 (4.5)	27.4 (4.9)	27.5 (4.6)

TABLE 3 Body composition of patients with head and neck cancer at diagnosis and weight loss prior to diagnosis, grouped by sex, site, and stage.

Factor	Male	Female	Oropharynx	Oral cavity	Larynx	Other sites	Stage I–II	Stage III–IV	Total
BMI, kg/m^2 mean (SD)	27.4 (4.3)	25.4 (5.0)	27.2 (4.4)	26.3 (5.2)	26.6 (4.1)	26.7 (4.5)	26.9 (4.5)	26.6 (4.8)	26.8 (4.6)
FFM, kg mean (SD)	65.7 (8.3)	45.5 (4.9)	63.1 (11.0)	56.1 (12.7)	57.7 (10.7)	58.7 (11.0)	60.6 (11.9)	58.8 (11.7)	59.9 (11.8)
FFMI, kg/m^2 mean (SD)	20.6 (2.1)	16.6 (1.5)	20.0 (2.5)	18.9 (3.0)	19.3 (2.5)	19.1 (2.5)	19.5 (2.7)	19.4 (2.7)	19.5 (2.7)
Weight loss,[a] kg mean (SD)	1.9 (4.3)	2.0 (4.5)	1.6 (4.4)	3.0 (4.5)	1.3 (4.4)	1.4 (3.8)	1.4 (4.3)	2.7 (4.4)	1.9 (4.4)

[a]Patient self-reported unintentional weight loss during 6 months leading up to diagnosis.

with malnutrition were nonresponders compared to only 63 (17%) of the patients in the nonmalnutrition group ($p = 0.002$).

3.5 | Pretreatment BMI and FFMI and risk of early death

Pretreatment BMI was not a significant predictor of death within 6 or within 12 months. Ten (2.2%) patients died within 6 months after start of treatment. These patients had a lower mean pretreatment FFMI than that of patients who survived more than 6 months (17.6 kg/m^2 vs. 19.5 kg/m^2, respectively, $p = 0.035$). Only one patient who died within 6 months after treatment had been diagnosed with stage I–II (10%) disease, compared to nine patients who were diagnosed with stage III–IV disease (90%) ($p < 0.001$) (Table 4). Deceased patients within 6 months from start of treatment were on average 9 years older than the group of patients surviving 6 months (72 years vs. 63 years) ($p = 0.003$). Two (1%) patients with treatment response died within 6 months from start of treatment compared to 8 patients (10%) of the nonresponse group ($p < 0.001$). There were no significant differences between tumor site, pack-years, malnutrition at diagnosis and weight loss 6 months prior to diagnosis, regarding death within 6 months.

Twenty-five (6.2%) patients died within 12 months after start of treatment. The mean difference in pretreatment FFMI between patients who died within 12 months from start of treatment and those who survived for more than 12 months was 1.3 kg/m^2 (18.2 kg/m^2 vs. 19.5 kg/m^2, $p = 0.005$). Sixteen (64%) of the patients who were deceased within 12 months after start of treatment were diagnosed at stage IV, while an additional six (24%) patients were diagnosed at stage III, compared to only three patients (12%) who were diagnosed at stage I or stage II ($p < 0.001$). Fourteen (56%) of the patients who died within 12 months after start of treatment had oral cavity cancer, compared to six (24%) oropharyngeal cancer patients, two (8%) laryngeal cancer patients and three (12%) patients with cancer in other sites ($p = 0.014$). Twenty (80%) of the 25 patients who died within 12 months from start of treatment were nonresponders to treatment ($p < 0.001$) (Figure 1A). There was a significant correlation between malnutrition at diagnosis and death within 12 months from start of treatment ($p < 0.001$). There was no significant impact for pack-years, age, or weight loss 6 months prior to diagnosis regarding death within 12 months.

We observed that nonresponse to treatment predicted death within 12 months after start of treatment, whereas high pretreatment FFMI was a protective factor against death, according to a multivariable Cox regression model (Table 5). In this multivariable analysis, we found no independent impact for malnutrition, stage or site regarding death within 12 months after treatment. Figure 1A,B shows a Kaplan–Meier curve for death within 12 months after diagnosis. The mean FFMI for those surviving 12 months was 19.5 kg/m^2, which was used as a cut-off value for the Kaplan–Meier curve (Figure 1B).

4 | DISCUSSION

In this real-life, prospective study, we explored the effects of pretreatment body mass composition on early death in patients with HNSCC. In our study, 11.4% of the patients were malnourished before the start of treatment. A low FFMI at diagnosis correlated with death within 6 months and within 12 months after treatment completion. This implies that body mass composition can be used to identify patients with HNSCC at risk of early death.

In previous studies, various BIA variables have been used to predict treatment outcomes in HNSCC and other cancer types.[20–23] In this study, we used FFMI as the

TABLE 4 Incidence of recurrence and death within 6 and within 12 months after start of treatment for patients with head and neck cancer.

	Responder, *n* (%)		Death within 0–6 months, *n* (%)		Death within 0–12 months, *n* (%)	
Factor	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Male	233 (81)	54 (19)	4 (1)	283 (99)	12 (4)	275 (96)
Female	92 (79)	25 (21)	6 (5)	111 (95)	13 (11)	104 (89)
Oropharynx	162 (88)	23 (12)	2 (1)	183 (99)	6 (3)	179 (97)
Oral cavity	82 (73)	31 (27)	5 (4)	108 (96)	14 (12)	99 (88)
Larynx	37 (79)	10 (21)	0 (0)	47 (100)	2 (4)	45 (96)
All other sites	44 (75)	15 (25)	3 (5)	56 (95)	3 (5)	56 (95)
Stage I–II	224 (91)	21 (9)	1 (1)	244 (99)	3 (1)	242 (99)
Stage III–IV	101 (64)	58 (36)	9 (6)	150 (94)	22 (18)	137 (86)
Total	325 (80)	79 (20)	10 (3)	394 (97)	25 (6)	379 (94)

body composition variable to estimate the total muscle mass. Body mass composition can be calculated using different approaches. Other than BIA, commonly used methods are CT-based estimates of SMM of the third lumbar or third cervical vertebra, and dual-energy x-ray absorptiometry (DEXA), which is considered to be the gold standard.[24,25] Our results were in line with previous publications indicating that body mass composition measured with CT or BIA can be used as a predictor of prognosis.[26–28] The results of the present study strengthen this hypothesis even further, given that it describes a larger cohort than the previous ones.

Important pretreatment differences were demonstrated between the two major groups of patients with oral cavity and oropharyngeal cancer. Our data showed that FFMI at diagnosis was higher in oropharyngeal cancer than in oral cancer patients. Patients with oropharyngeal cancer in general tend to be younger, with fewer comorbidities and a less sedentary lifestyle, which could contribute to a more favorable body composition at diagnosis.[29] A challenge to improve the understanding of the importance of pretreatment FFMI as a predictor of early death is the body composition trajectory prior to diagnosis. Well-established patient-related risk factors of low pretreatment FFMI include high age, poor nutritional intake, a sedentary lifestyle, and alcohol abuse.[30–32] Cancer can lead to decreased FFMI through proinflammatory cytokines that are produced as part of a systemic inflammatory response.[33] Additionally, tumor-related dysphagia can lead to decreased caloric intake and thus reduce FFMI. In our study, in addition to age and sex, patient-estimated weight loss during the 6 months prior to diagnosis was found to affect FFMI at diagnosis, which has not been shown in previous studies. This finding may indicate that patients with less weight loss prior to diagnosis are better able to maintain muscle mass. However, we are aware that the patient-estimated weight may not be accurate, and thus, a bias could possibly have affected the analysis.

A fundamental finding was that baseline FFMI was an independent prognostic factor of early death after treatment completion. The FFMI values, which can be regarded as a rough measure of protein balance and physical activity, were significantly lower in patients who succumbed to their disease within 12 months, compared to patients who survived longer. Willemsen et al. demonstrated that, in a prospective series including 137 patients with locally advanced HNC, low pretreatment FFMI measured using BIA was a negative prognostic indicator.[34] Similarly, a recent retrospective study identified low pretreatment FFMI as a prognostic factor in patients with normal or high BMI who were treated for lung cancer, breast cancer or upper gastrointestinal cancer, using BIA for body mass composition measurements.[35] Other studies have also shown that low FFMI is a risk factor for mortality and postoperative complications, both in unselected cohorts of hospitalized patients and in cancer patients.[36–39] Yilmaz et al., however, did not find any association between FFMI and mortality in patients with hematological malignancies.[40]

This study further demonstrated that weight loss, calculated from patient-reported weight at 6 months prior to diagnosis to start of treatment, was associated with treatment response failure but not with survival. Thus, weight loss during follow-up after treatment of HNSCC may be regarded as an early warning sign of recurrence. Langius et al. have previously found that weight loss in patients with HNC, both before and during radiotherapy, had a negative impact on disease-specific survival.[41] Another retrospective study documented weight loss from

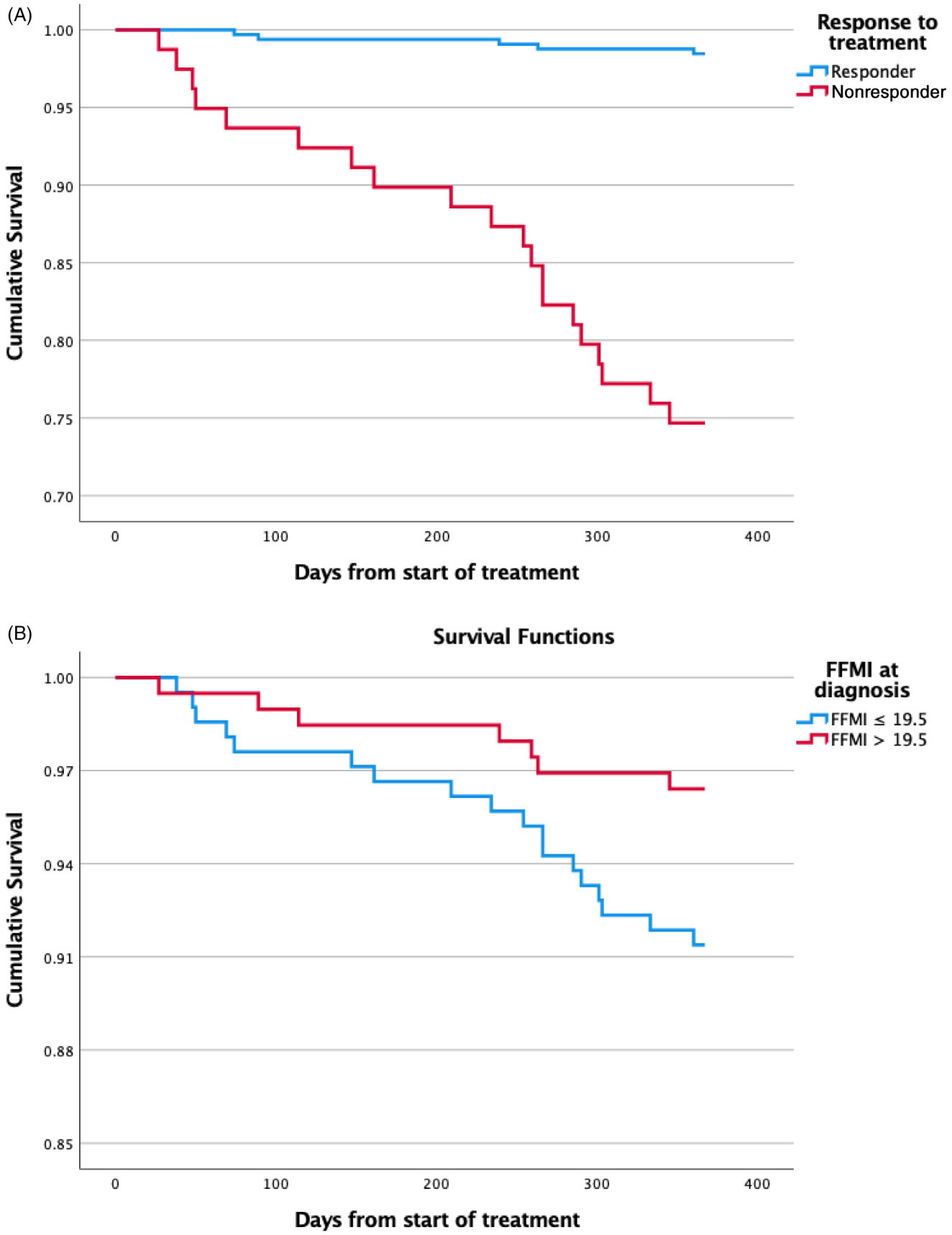

FIGURE 1 (A) Kaplan–Meier curve of 1-year survival after treatment in the cohort of 404 patients with head and neck cancer, based on response to treatment ($p < 0.001$). (B) Kaplan–Meier curve of 1-year survival based on fat-free mass index (FFMI) in the cohort of 404 patients with head and neck cancer ($p = 0.037$). The mean FFMI for patients that survived 12 months from start of treatment was 19.5 kg/m^2 and was used as a cut-off value. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Cox-regression ratio for death within 12 months after start of treatment.

Variable	Sig. *p*-values	Hazard ratio	95% CI for HR	
			Lower	Upper
Malnutrition	0.818	1.104	0.476	2.561
Oropharynx	0.243	1.000	–	–
Oral cavity	0.520	1.427	0.483	4.220
Larynx	0.447	0.515	0.093	2.849
Other sites	0.287	0.444	0.100	1.981
Stage I	0.077	1.000	–	–
Stage II	0.492	0.422	0.036	4.943
Stage III	0.327	2.347	0.427	12.904
Stage IV	0.090	4.351	0.795	23.804
Treatment response	<0.001	11.039	3.757	32.432
FFMI	0.012	0.819	0.701	0.957

Note: Included variables are malnutrition, tumor site, stage at diagnosis, treatment response, and fat-free mass index (FFMI) at diagnosis. Site: oral cavity, larynx, and other sites versus oropharynx. Stage: II, III, and IV versus I.

6 months prior to diagnosis in patients with various solid tumors, including HNC, and found that >10% weight loss was associated with worse survival. Interestingly, >10% weight gain was also related to a bleaker prognosis.[42] A number of other studies have linked low BMI at diagnosis with decreased survival.[43,44]

There have been conflicting reports regarding the association between obesity and prognosis in patients with HNC. Several previous epidemiological studies have indicated that overweight or obese patients (BMI >25 and >30 kg/m^2, respectively) with various types of cancer might have longer survival—a finding that has been referred to as the "obesity paradox."[45–47] At least in our cohort, where short-term outcomes were studied, BMI at diagnosis did not correlate with death within 12 months after the start of treatment. A recent prospective study of 80 patients with HNC, who were assessed using BIA, showed that cancer cachexia was prevalent in all stages (thereby giving lower SMM), but was most common in patients with advanced stage disease.[48] Sarcopenia seen in patients with HNSCC has multifactorial causes, of which decreased intake of food and cancer-induced systemic inflammation are probably most important.[49] Dysphagia is a common symptom among patients with HNSCC, and can be attributed to the tumor and/or as a side effect of treatment.[50,51] In addition to toxicity-related dysphagia, both radiotherapy and chemotherapy activate a local and systemic immune response.[52,53] Although the immunogenicity of the different treatment modalities has been shown to have beneficial antitumor effects, muscle wasting leading to cancer cachexia is an unwanted side effect.[13,54,55]

Previous studies have underlined the importance of monitoring changes in body composition and thereby SMM in HNC.[56,57] The measurement of body mass composition with BIA is noninvasive, is readily available at many centers, and is considered a more accurate indicator of the patient's nutritional status than use of only BMI, as the latter does not inherently distinguish between fat and fat-free mass. Furthermore, BIA is reported to correlate well with CT-based estimates.[58] A significant advantage of BIA over other validated methods of body mass estimation (e.g., DEXA, CT) is the absence of radiation, which allows for repeated risk-free measurements. According to the European Society for Clinical Nutrition and Metabolism guidelines, as well as the Global Consensus Report published in 2019, patients with cancer should be screened for malnutrition, regardless of BMI and weight history.[20,59] In accordance with this, we also propose that BIA evaluation should be considered as part of the standard workup for HNSCC patients. In addition, it is a more accurate indicator of malnutrition than single measurements of body weight, and may also identify overweight patients with poor muscle mass who are at risk but who might otherwise be overlooked. In order words, the use of repeated BIA measurements could be a tool to guide the development of a personalized approach in the nutritional treatment of patients with HNSCC. Patients who are identified as being malnourished with loss of FFM might be considered for active physical therapy and nutritional consultation early on, before cachexia is established.[60,61]

Among the strengths of this prospective cohort study are the considerable size of the cohort and the prospective nature of data collection. In addition, the information gathered on patient body weight 6 months prior to diagnosis adds further depth to our data and has only

been reported in a few previous studies on HNSCC. The main weakness of this study is the heterogeneous nature of the patients, with different sites of HNSCC included, as well as the varying treatment modalities, both of which are common problems in HNSCC research.

5 | CONCLUSIONS

Low FFMI is displayed in a substantial number of patients before treatment of HNSCC and was an independent prognostic factor predicting early death within 6 and within 12 months from the start of treatment in the present cohort. Decrease in BMI and weight 6 months prior to treatment correlated with treatment response. The analysis of body mass composition with BIA could help to detect patients with HNSCC at risk of early death. We suggest further studies to establish a more thorough understanding of the relationship between body composition, survival and secondary inflammation in patients with HNSCC.

AUTHOR CONTRIBUTIONS

Charbél Talani: Statistical analyses, interpretation of data, manuscript writing. Thorsteinn Astradsson: Data collection, interpretation of data, manuscript writing. Antti Mäkitie: Design of work, critical revision and contribution to manuscript. Lovisa Farnebo: Statistical analyses, study design, critical revision and contribution to manuscript. Ylva Tiblom Ehrsson: Data collection, study design, interpretation of data, critical revision and contribution to manuscript. Göran Laurell: Data collection, study design, interpretation of data, critical revision and contribution to manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The Regional Ethical Review Board in Uppsala reviewed and approved the study (No. 2014/447). This study is part of a larger multicenter study registered at clinicaltrials.gov, NCT03343236, and was carried out in accordance with the current Helsinki Declaration of the World Medical Association. Informed consent was obtained from all subjects involved in the study.

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