Original Investigation

Association of Body Composition With Survival and Locoregional Control of Radiotherapy-Treated Head and Neck Squamous Cell Carcinoma

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IMPORTANCE Major weight loss is common in patients with head and neck squamous cell carcinoma (HNSCC) who undergo radiotherapy (RT). How baseline and posttreatment body composition affects outcome is unknown.

OBJECTIVE To determine whether lean body mass before and after RT for HNSCC predicts survival and locoregional control.

DESIGN, SETTING, AND PARTICIPANT Retrospective study of 2840 patients with pathologically proven HNSCC undergoing curative RT at a single academic cancer referral center from October 1, 2003, to August 31, 2013. One hundred ninety patients had computed tomographic (CT) scans available for analysis of skeletal muscle (SM). The effect of pre-RT and post-RT SM depletion (defined as a CT-measured L3 SM index of less than 52.4 cm^2/m^2 for men and less than 38.5 cm^2/m^2 for women) on survival and disease control was evaluated. Final follow-up was completed on September 27, 2014, and data were analyzed from October 1, 2014, to November 29, 2015.

MAIN OUTCOMES AND MEASURES Primary outcomes were overall and disease-specific survival and locoregional control. Secondary analyses included the influence of pre-RT body mass index (BMI) and interscan weight loss on survival and recurrence.

RESULTS Among the 2840 consecutive patients who underwent screening, 190 had whole-body positron emission tomography–CT or abdominal CT scans before and after RT and were included for analysis. Of these, 160 (84.2%) were men and 30 (15.8%) were women; their mean (SD) age was 57.7 (9.4) years. Median follow up was 68.6 months. Skeletal muscle depletion was detected in 67 patients (35.3%) before RT and an additional 58 patients (30.5%) after RT. Decreased overall survival was predicted by SM depletion before RT (hazard ratio [HR], 1.92; 95% CI, 1.19-3.11; $P = .007$) and after RT (HR, 2.03; 95% CI, 1.02-4.24; $P = .04$). Increased BMI was associated with significantly improved survival (HR per 1-U increase in BMI, 0.91; 95% CI, 0.87-0.96; $P < .001$). Weight loss without SM depletion did not affect outcomes. Post-RT SM depletion was more substantive in competing multivariate models of mortality risk than weight loss–based metrics (Bayesian information criteria difference, 7.9), but pre-RT BMI demonstrated the greatest prognostic value.

CONCLUSIONS AND RELEVANCE Diminished SM mass assessed by CT imaging or BMI can predict oncologic outcomes for patients with HNSCC, whereas weight loss after RT initiation does not predict SM loss or survival.

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Significant weight loss is common in patients with head and neck squamous cell carcinoma (HNSCC).[1,2] In these patients, weight loss is complicated by tumor location and the subsequent local toxic effects of radiotherapy (RT) and chemoradiotherapy (CRT). Because these factors make food intake challenging, patients receiving RT or CRT are offered dietary counseling, nutritional supplementation, and often feeding tubes. However, multiple trials evaluating nutritional interventions have failed to show an improvement in survival.[3] Weight loss is commonly used to screen the risk for poor outcomes in the clinical setting, but contradictory studies leave the relationship between treatment-associated weight loss and survival unclear.[4-6]

Patients undergoing RT continue to lose weight and lean body mass (LBM), even with adequate caloric intake.[1,2,7] Severe LBM wasting that is resistant to nutritional support is the hallmark of cachexia, the paraneoplastic wasting syndrome associated with advanced cancer.[8] The resultant skeletal muscle (SM) depletion is strongly correlated with decreased survival in patients with other solid tumors[9,10]; however, to our knowledge, no published reports have investigated directly the association between the loss of LBM and oncologic outcomes in HNSCC. Although multiple studies have demonstrated a positive correlation between body mass index (BMI) and survival, BMI alone is not a reliable indicator of SM depletion.[9,10] In addition, extant studies reporting LBM in HNSCC, measured by dual-energy x-ray absorptiometry, unfortunately did not include survival data.[1,2,7]

We hypothesize that SM depletion before and after RT is associated with clinically meaningful survival and disease control differentials in patients with HNSCC. Because dual-energy x-ray absorptiometry is used infrequently in routine clinical practice, we used a previously validated computed tomography (CT)-based body-composition method with scans acquired during normal staging procedures (eg, whole-body positron emission tomography [PET]-CT imaging).[9-12] The primary aim of this study is to characterize the association between SM depletion and HNSCC survival. As secondary aims we sought to identify and compare the prognostic significance of LBM, weight loss, and BMI on locoregional control and survival.

Key Points

Question: Does diminished skeletal muscle mass affect survival and locoregional control in patients with head and neck squamous cell carcinoma (HNSCC) who receive radiotherapy?

Findings: In this retrospective review of 190 patients with HNSCC treated with radiotherapy, depleted skeletal muscle mass on presentation or after treatment portended worsened survival, whereas increased body mass index predicted improved survival and locoregional control independent of other known risk factors. Weight loss during treatment had no prognostic significance.

Meaning: Low skeletal muscle mass or body mass index, but not treatment-related weight loss, may identify patients with HNSCC who are at greater risk for death or cancer recurrence.

Methods

Population Cohort and End Points

In this single-center retrospective analysis, the records of 2840 consecutive patients with HNSCC treated with curative-intent RT from October 1, 2003, to August 31, 2013, were screened. All patients were presented at a multidisciplinary tumor board for treatment recommendations. Standard treatment for HNSCC included primary surgery, single-modality RT (66-70 Gy), or concurrent CRT (66-72 Gy), dependent on the site and stage of the tumor and risk factors (to convert radiation absorbed dose to rad, multiply gray by 100). Induction chemotherapy was offered to patients with high-risk, advanced T-stage or N-stage disease at the discretion of the medical oncologist. For patients treated with primary surgery, postoperative RT or concurrent CRT (60 Gy) was offered per previously defined risk factors.[13,14] All patients undergoing RT received pretreatment speech and swallow evaluations and weekly dietary counseling. Feeding tubes were provided per clinician judgement during treatment and were not offered prophylactically. This study was approved by the institutional review board of the University of Texas MD Anderson Cancer Center. Written informed consent was obtained from all study participants.

Final follow-up was completed on September 27, 2014, and data were collected from October 1, 2003, to September 27, 2014. Patients with whole-body PET-CT or abdominal CT scans before and after RT with interscan intervals of less than 12 months were eligible for inclusion (n = 190). Pretreatment PET-CT scans collected as part of the routine staging workup within 60 days of treatment start were considered to reflect pretreatment body composition. Post-RT PET-CT or abdominal CT scans were ordered to evaluate treatment response or disease progression 8 to 12 weeks after RT completion, with height and weight obtained at the time of imaging. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Normal weight, overweight, and obesity were defined as BMI of less than 25.0, 25.0 to 29.9, and 30.0 or greater, respectively.[9] Disease was staged per the American Joint Committee on Cancer using the TNM system.[15]

Overall survival in months was defined as the time from diagnosis to the date of death due to any cause. Disease-specific survival in months was defined as the time from diagnosis to death due to HNSCC; observations were censored at death due to other causes. Duration of locoregional control in months was defined as the interval from diagnosis to the date of locoregional recurrence. The time to event was measured in days and divided by 30.4 to calculate months. Distant recurrences and second primary tumors were censored.

CT Image Analysis

We analyzed CT images of the third lumbar vertebrae (L3), including the CT component of whole-body PET-CT scans and abdominal CT scans.[9,10,12,16] Three adjacent axial images within the same series were selected for analysis of total muscle cross-sectional area (in square centimeters) and the mean cross-sectional area was calculated for each patient. Muscle and fat

tissue were defined by ranges of −29 to 150[16] and −190 to −30 Hounsfield units, respectively.[17,18] After autosegmentation, the contours were corrected manually if necessary. For SM mass, muscles segmented included the rectus abdominus, abdominal wall, psoas, and paraspinal muscle groups. For adipose tissue mass, we contoured intra-abdominal and subcutaneous adipose tissue mass. Lean and fat body mass were contoured by a radiation oncologist with 5 years of postresidency experience (S.C.) using a commercial image-processing platform (Pinnacle 9.6; Phillips Medical Systems). The cross-sectional area of muscle and adipose tissue was normalized for the square of height in meters and reported as the lumbar SM index (SMI) or adipose index as the cross-sectional area in square centimeters divided by the square of the height in meters.[9,10,12] We defined SM depletion a priori as an SMI of less than 52.4 for men and less than 38.5 for women based on multiple prior reports establishing the prognostic utility of CT-derived LBM measures.[9,11] Skeletal muscle mass and fat body mass were calculated from L3 contours, as previously described.[12]

Statistical Analysis

Data were analyzed from October 1, 2014, to November 29, 2015. Differences between groups were assessed using the 2-tailed *t* test (for continuous variables) and Pearson χ^2 test (for categorical variables). Data are presented as mean (SD) or median (95% CI). Survival curves were constructed using the Kaplan-Meier technique. We used the log-rank test to compare survival between groups of patients and obtained hazard ratios (HRs) from the cumulative survivor function. Univariate and multivariate analyses for overall survival were conducted using the Cox proportional hazards model. Hazard ratios and corresponding 95% CIs are reported.

We analyzed the following variables in univariate analysis: age (<65 vs ≥65 years), sex, tumor site (oropharyngeal vs nonoropharyngeal), cancer stage (I-III vs IV), smoking history (ever vs never), treatment modality (induction vs no induction, surgery vs no surgery, CRT vs no CRT), reduction in planned induction or concurrent chemotherapy related to toxic effects,[19] human papillomavirus (HPV) status, and feeding tube provision (yes or no). Variables were selected based on recursive partitioning analysis that demonstrated an influence on survival in head and neck cancers.[20] Because most patients had tumors of the oropharynx, risk factors described by Bonner et al[21] were also included. Treatment modalities were evaluated to minimize any confounding effect on body composition. Variables significant ($P < .05$) at the univariate level or previously shown to predict survival[21] were included in the multivariate analysis. Human papillomavirus status was only available for 53 patients and was therefore excluded from the primary analysis. Tumor site was dichotomized on the basis of improved outcomes in patients with oropharyngeal tumors.[20] We dichotomized T, N, and overall stages per risk stratification by Bonner et al.[21] In multivariate analysis, we compared body composition indices collected before treatment (BMI and SM depletion) and during post-RT follow-up (weight loss, SM depletion [encompassing all patients with SM depletion]) by creating competing multivariate models and sequentially adding each of these collinear variables to the risk stratification model based on clinical criteria.

Model comparison was performed using the corrected Bayesian information criteria (BIC). For censored data, the BIC expression is modified to include the number of deaths rather than the sample size, to approximate weighting of uncensored events in Cox proportional hazards regression.[22] Model selection using BIC guards against overfitting by adding a penalty for the inclusion of additional minimally informative variables. Lower BIC indicate improved model performance and parsimony per the BIC evidence grades presented by Raftery,[23] which assigns superior posterior probability with the lower BIC model. A BIC difference of less than 2 is considered weak (representing a 50%-75% posterior probability of the minimum BIC model being superior to a comparison model); 2 to 6, positive (posterior probability of 75%-95%); 6 to 10, strong (posterior probability of >95%); and greater than 10, very strong (posterior probability of >99%).[23] The BIC expression for each model was verified using the Akaike information criteria, an alternative method to evaluate goodness of fit using similar terms.[24] Statistical analysis was performed using JMP Pro (version 12; SAS Institute Inc), and graphs were built using GraphPad Prism (GraphPad Software Inc) statistical analysis software. *P* values are 2 sided with values less than 0.05 regarded as statistically significant.

Results

Patient Characteristics

Median follow up in this study was 68.6 months, with a mean interval between pre-RT and post-RT CT imaging of 5.7 (2.2) months. Included patients had a mean age of 57.7 (9.4) years at diagnosis. The patient sample was predominately male (160 men [84.2%] vs 30 women [15.8%]). All 190 patients completed RT; the mean radiation dose was 68.7 (2.9) Gy. Single-modality RT was used in 24 patients (12.6%). Seventy-four patients (38.9%) underwent induction chemotherapy before RT with platinum-based regimens. One hundred twenty-seven patients (66.8%) were treated with concurrent chemotherapy, with platinum-based regimens used in 123 of these (96.9%). Surgery was performed in 62 patients (32.6%) and as salvage treatment in 38 patients (20.0%). At the time of censoring, 122 patients (64.2%) remained alive. Forty-five patients (23.7%) in this population had HNSCC-related deaths. Patients with depleted SM exhibited no differences in cancer stage, treatment modality, feeding tube provision, radiation dose, or chemotherapy dose. Obese patients demonstrated a significantly different distribution of cancer site, with more glottic cancers and fewer hypopharyngeal cancers. Characteristics and details of the patient sample separated by pre-RT obesity and SM status are shown in eTable 1 in the Supplement.

Before RT, 67 patients (35.3%) had SM depletion, which increased to 125 patients (65.8%) after RT. Patients presenting with SM depletion before treatment were older by a mean of 4.8 years than those with normal SM (mean age, 60.8 [9.7] vs 56.0 [8.9] years; $P = .001$). In men, mean estimated LBM decreased from 58.4 (9.6) kg (66.8% of body mass) to 51.6 (7.8)

kg after RT (64.5% of body mass), whereas mean estimated LBM in women remained fairly stable, decreasing from 38.0 (7.3) kg (55.0% of body mass) to 35.7 (6.6) kg (55.8% of body mass) after RT (eTable 2 in the Supplement).

SM Depletion and Survival

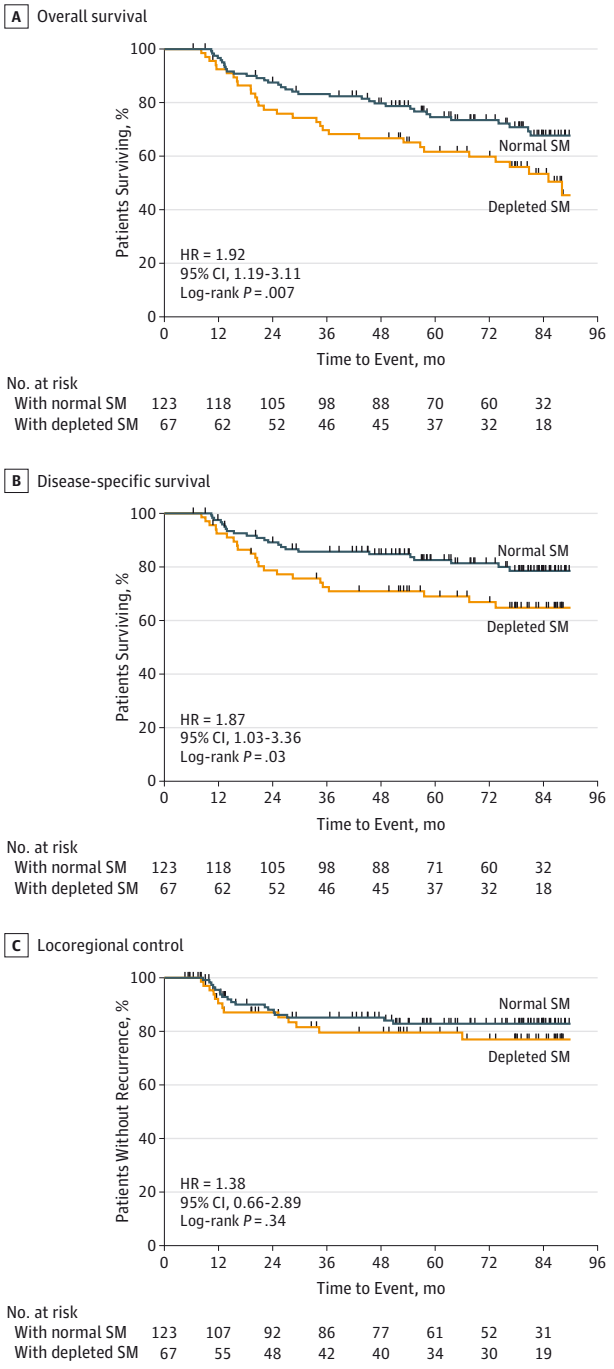
The associations between pre-RT and post-RT SM depletion and overall and disease-specific survival and locoregional control are depicted in **Figure 1**. Patients with depleted SM at baseline were excluded from post-RT SM depletion analyses. Pre-RT SM depletion was significantly associated with shorter overall survival (HR, 1.92; 95% CI, 1.19-3.11; P = .007) and disease-specific survival (HR, 1.87; 95% CI, 1.03-3.36; P = .03). Five-year overall survival was decreased from 75% to 62% in SM-depleted patients. No significant difference in locoregional control was observed (HR, 1.38; 95% CI, 0.66-2.89; P = .34).

Post-RT SM depletion was associated with decreased overall survival (HR, 2.03; 95% CI, 1.02-4.24; P = .04), yielding a decrease in 5-year overall survival from 86% to 64% and a nonsignificant decrease in disease-specific survival (HR, 2.07; 95% CI, 0.90-5.13; P = .09). Post-RT SM depletion also predicted for an increased risk for locoregional recurrence (HR, 3.00; 95% CI, 1.18-7.60; P = .02) (**Figure 2**).

Because oropharyngeal cancer is associated with improved survival, we evaluated the association between SM depletion and outcome independently in oropharyngeal (n = 139) and nonoropharyngeal (n = 51) sites independently. Pre-RT SM depletion was associated with a decrease in overall survival (HR, 1.89; 95% CI, 0.94-4.23; P = .09) and disease-specific survival (HR, 2.85; 95% CI, 1.20-7.20; P = .02) in patients with nonoropharyngeal HNSCC, but not those with oropharyngeal tumors (eFigures 1 and 2 in the Supplement). We found no significant influence of pre-RT SM depletion on locoregional control in either group. Although HPV status was not assessed for most patients with oropharyngeal HNSCC, a total of 37 of the 53 patients for whom HPV status was known were found to be seropositive for HPV by means of immunohistochemistry or polymerase chain reaction. Among these patients, baseline SM depletion demonstrated a decrease in overall survival that was not statistically significant (HR, 2.75; 95% CI, 0.83-13.62; P = .09) (eFigure 1 in the Supplement).

The effect of post-RT SM depletion was larger in the group with nonoropharyngeal HNSCC (HR, 2.96; 95% CI, 1.05-11.78; P = .047), whereas SM-depleted patients with oropharyngeal HNSCC had decreased survival (HR, 2.04; 95% CI, 0.91-4.68; P = .09) and had a significant increase in locoregional recurrence (HR, 5.41; 95% CI, 1.42-35.3; P = .01) (eFigures 1 and 2 in the Supplement). We found no effect of intercurrent surgery (χ^2 = 0.52; P = .47) or feeding tube placement (χ^2 = 1.83; P = .40) on the development of SM depletion. Patients who received a feeding tube had decreased survival compared with those who did not (eTable 3 in the Supplement). Only SM-depleted patients who received a feeding tube exhibited a significant survival decrement (HR, 2.23; 95% CI, 1.37-4.69; P = .01), whereas overall survival for those patients who did not receive a feeding tube was not decreased (eFigure 3 in the Supplement).

Figure 1. The Effect of Skeletal Muscle (SM) Depletion Before Radiotherapy on Survival and Locoregional Recurrence

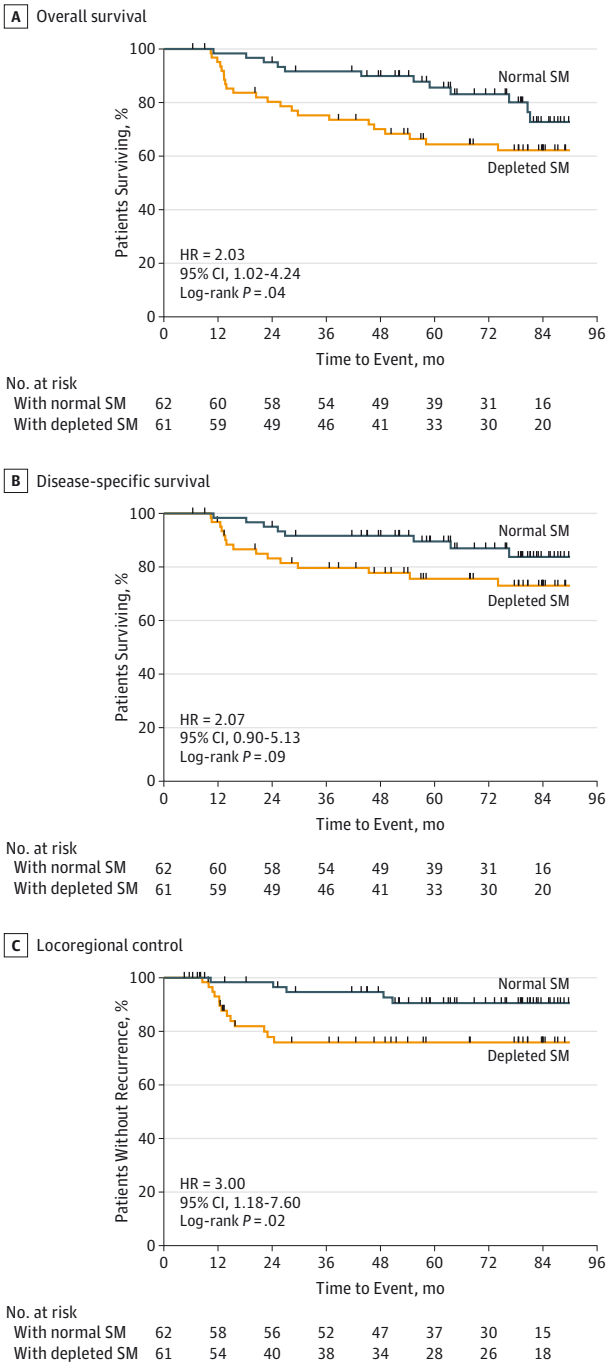


Patients with depleted SM on presentation demonstrated decreased overall and disease-specific survival compared with patients with normal SM. We found no difference in locoregional control between these groups. HR indicates hazard ratio.

Weight Loss and Survival

Weight loss alone did not correlate with survival, whether measured in the total patient population or only those patients with normal SM at baseline (r = −0.010; P = .85) (eFigure 4A in the Supplement). Weight loss of greater than

Figure 2. The Effect of Skeletal Muscle (SM) Depletion After Radiotherapy (RT) on Survival and Locoregional Recurrence



Patients who developed SM depletion after the initiation of RT demonstrated decreased overall survival compared with patients with normal SM. The decrease in disease-specific survival was not significant. Locoregional control was decreased significantly in these patients. HR indicates hazard ratio.

5% was not associated with decreased survival, instead showing a trend toward survival advantage (HR, 0.48; 95% CI, 0.21-1.28; P = .09) (eFigure 4B in the Supplement). Patients with pre-RT SM depletion lost significantly less weight (mean weight loss, 5.2 [4.0] kg) compared with patients who developed post-RT SM depletion (mean weight loss, 7.6 [4.5] kg) or those whose SM remained normal (mean weight loss, 8.3 [6.3] kg; $F_{2,187}$ = 6.84; P = .01) (eFigure 4C in the Supplement).

BMI and Survival

Higher BMI was associated with improved survival in a linear fashion (HR per 1-U increase in BMI, 0.91; 95% CI, 0.87-0.96; P < .001). This effect was driven by improved disease-specific survival (HR, 0.90; 95% CI, 0.84-0.95; P < .001), consistent with improved locoregional control (HR, 0.91; 95% CI, 0.85-0.98; P = .01). We then divided BMI into normal (<25.0), overweight (25.0-29.9), and obese (≥30.0) categories for survival curve plotting. Overweight (HR, 0.42; 95% CI, 0.24-0.73; P = .002) and obese (HR, 0.30; 95% CI, 0.15-0.55; P < .001) patients demonstrated increased overall survival compared with normal-weight patients (HR, 1.00) (**Figure 3**A). No significant difference in overall survival was observed between overweight and obese patients (HR, 0.70; 95% CI, 0.35-1.37; P = .30). Increased disease-specific survival was observed in overweight (HR, 0.34; 95% CI, 0.17-0.68; P = .002) and obese (HR, 0.26; 95% CI, 0.11-0.54; P < .001) (Figure 3B) patients. Locoregional control was improved in obese patients compared with normal-weight patients (HR, 0.39; 95% CI, 0.15-0.98; P = .046), but no differences were observed between normal-weight and overweight patients (HR, 0.69; 95% CI, 0.31-1.56; P = .37) or between overweight and obese patients (HR, 0.57; 95% CI, 0.21-1.42; P = .23) (Figure 3C). The SMI was significantly correlated with BMI in men (r = 0.6; P < .001) and women (r = 0.6; P = .001) (eFigure 5A in the Supplement). Obese patients had a greater SMI and adipose index at baseline and at follow-up when compared with nonobese patients (P < .001; eFigure 5B in the Supplement). No obese patients met criteria for SM depletion. Between imaging assessments, obese patients lost approximately twice as much mass as nonobese patients, including greater loss of LBM and fat body mass (P < .01; eFigure 5C in the Supplement).

Multivariate Risk Model

Multivariate Cox proportional hazard analysis demonstrated that pre-RT SM depletion, post-RT SM depletion (inclusive of all SM-depleted patients), and baseline BMI are each significantly associated with overall survival when independently added to the multivariate clinical model. The pre-RT multivariate model that included BMI exhibited strong superior performance compared with the model that included SM depletion (ΔBIC = 5.9). Pre-RT SM depletion was no longer prognostic when BMI was included in the multivariate model. Among post-RT metrics, SM depletion demonstrated a greater than 95% posterior probability of improving on a model that included weight loss (ΔBIC = 7.9). Comparison of all metrics revealed that BMI was the best-performing factor, followed by post-RT SM depletion. Weight loss had no significant effect on survival in the multivariate analysis. Univariate and multivariate models are presented in eTables 3 and 4 in the Supplement.

Discussion

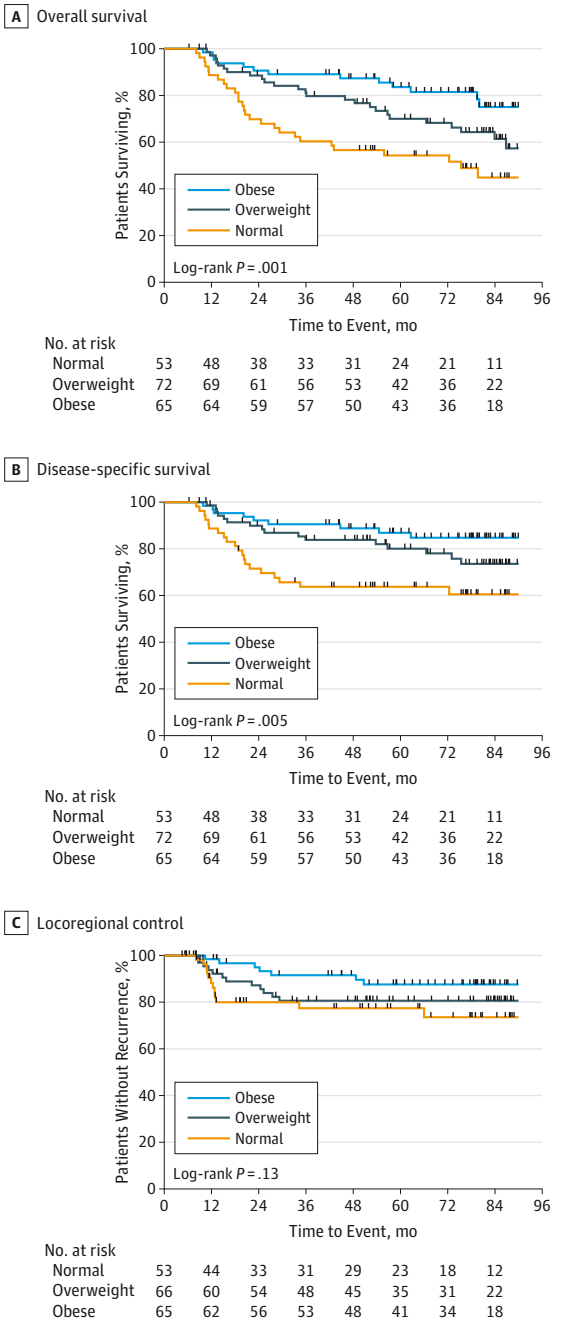
To our knowledge, our study is the first retrospective analysis of LBM, BMI, and survival in patients with HNSCC and makes a provocative case for the importance of body composition in predicting survival after definitive RT. Depletion of SM was easily identifiable from routine CT imaging and was frequent in patients with HNSCC before and after RT. We found that BMI and SM depletion are powerful prognostic indicators of mortality independent of conventional prognostic factors, such as cancer stage, age, site, sex, smoking history, and treatment factors. Conversely, weight loss during treatment, commonly used to screen for patients in need of additional support, had no prognostic value. Our findings were further supported by the observation that BMI and post-RT SM depletion add prognostic value to a multivariate risk model for patients with HNSCC.

The association of pre-RT SM depletion with survival in patients with HNSCC is consistent with reports in other cancer populations.[10,25] Whether association is because SM depletion is a marker of more advanced disease, extreme toxic effects, or reduced physiologic reserve to combat disease is unclear. This distinction is important, because targeted aggressive nutritional support should improve survival if inadequate metabolic reserve is the primary culprit.[26] In the DAHANCA 25 (Danish Head and Neck Cancer Study), progressive resistance training was shown to be viable to counteract decreases in function and LBM.[27] In a subset of patients, the study showed a nonstatistically significant benefit of protein and creatinine supplementation after resistance training. Whether such interventions directed toward patients with depleted SM will ultimately influence survival, particularly given the strong effect of pre-RT SM depletion on survival in patients receiving a feeding tube, remains unknown. Indeed, the results of this study argue that reactive nutritional supplementation is inadequate to overcome the increased risk associated with SM depletion. However, in the absence of effective cachexia therapeutics, the benefit of early and aggressive nutritional support for patients with SM depletion should be evaluated directly.

That weight loss itself failed to predict worsened survival may reflect the diminution of weight loss in SM-depleted patients. Therefore, weight loss alone cannot be used reliably to stratify by risk patients with HNSCC undergoing RT. This finding supports a recent movement to consider weight loss only within the context of other factors, such as BMI, in the determination of clinical significance.[28] No difference in feeding tube frequency was observed between SM-depleted and normal-SM patients, and feeding tube placement did not affect SM loss, reflecting that post-RT SM depletion is a multifactorial process not purely mediated by nutritional deficiencies.

In contrast to the recent study by Martin et al,[10] the effect of SM depletion on survival was not independent of BMI. Because SMI and BMI were collinear in this data set, we could not compare the effects of these 2 factors directly. In multivariate analysis, BMI completely accounted for the effect of SM depletion on survival, yet the inverse was not true. Therefore, the association between BMI and survival likely represents the combined protective effects of increased LBM and metabolic reserve as excess calorie stores. Thus our data add context to the previously reported positive prognostic effects associated with increasing BMI in HNSCC. Furthermore, these data

Figure 3. The Effect of Body Mass Index (BMI) on Survival and Locoregional Recurrence



Increasing BMI (calculated as weight in kilograms divided by height in meters squared) on presentation predicted improved overall and disease-specific survival. We found no significant increase in locoregional control associated with increased BMI. Normal weight, overweight, and obesity were defined as BMIs of less than 25.0, 25.0 to 29.9, and 30.0 or greater, respectively. HR indicates hazard ratio.

suggest BMI is an adequate, and possibly superior, replacement for SMI to stratify patients with HNSCC by risk at the time of presentation. Our findings are in keeping with the obesity paradox that although obesity increases mortality risk in the general population, it positively affects survival in patients with catabolic conditions.[29] Of particular note, patients with BMI of 30.0 or greater exhibited a trend for improved locoregional control, with no difference in cancer stage or age, which indicates less aggressive tumor biology. Because obesity and SM depletion were mutually exclusive, the aforementioned effects of SM depletion on survival simply may represent more advanced disease at presentation. If true, a focus on early detection may obviate this survival discrepancy. In the absence of better diagnostics to stratify tumor biology, this interpretation warrants reexamination in future prospective trials and invokes a new opportunity to screen for biomarkers associated with advanced or aggressive disease.

This study has several limitations. As with all retrospective studies, heterogeneous patient populations preclude overgeneralization of our results. Abdominal CT imaging is not routinely performed in patients with HNSCC, and not all patients receive staging and follow-up PET-CTs, so some bias in sampling is possible. The interval between pre-RT and post-RT imaging varied, making this study insensitive to changes in trajectory that occur between these points. For example, some patients may have recovered muscle mass during the interval between RT and follow-up, whereas others may have continued to lose muscle mass after RT cessation. Our multivariate model comparing cachexia measures was limited by staging homogeneity, a well-discussed weakness in HNSCC risk stratification. Although the prognostic value of SM depletion appeared to persist in HPV-seropositive patients with oropharyngeal HNSCC, inclusion of so few patients with known HPV status necessarily limits our interpretation of the data.

Conclusions

Patients with HNSCC and low SM mass at presentation or after treatment exhibit decreased overall and cancer-specific survival. Body mass index was also significantly associated with survival, and lower BMI on presentation conferred increased mortality. The association of SM depletion and BMI with survival is independent of previously described risk factors, including cancer stage, age, sex, and treatment modality. Conversely, weight loss after RT initiation predicts neither SM depletion nor survival. Skeletal muscle mass and BMI each demonstrate increased prognostic value, compared with weight loss, and therefore may more accurately distinguish patients who benefit from nutritional supplementation. Our data suggest BMI or SM mass can be used to stratify patients with HNSCC undergoing curative RT by risk, but this should be confirmed in prospective trials.

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REFERENCES

1. Jager-Wittenaar H, Dijkstra PU, Vissink A, et al. Changes in nutritional status and dietary intake during and after head and neck cancer treatment. *Head Neck*. 2011;33(6):863-870.

2. Jackson W, Alexander N, Schipper M, Fig L, Feng F, Jolly S. Characterization of changes in total body composition for patients with head and neck cancer undergoing chemoradiotherapy using dual-energy x-ray absorptiometry. *Head Neck*. 2014;36(9):1356-1362.

3. Garg S, Yoo J, Winquist E. Nutritional support for head and neck cancer patients receiving radiotherapy: a systematic review. *Support Care Cancer*. 2010;18(6):667-677.

4. Ghadjar P, Hayoz S, Zimmermann F, et al; Swiss Group for Clinical Cancer Research (SAKK). Impact of weight loss on survival after chemoradiation for locally advanced head and neck cancer: secondary results of a randomized phase III trial (SAKK 10/94). *Radiat Oncol*. 2015;10:21.

5. Langius JA, Bakker S, Rietveld DH, et al. Critical weight loss is a major prognostic indicator for disease-specific survival in patients with head and neck cancer receiving radiotherapy. *Br J Cancer*. 2013;109(5):1093-1099.

6. Karnell LH, Sperry SM, Anderson CM, Pagedar NA. Influence of body composition on survival in patients with head and neck cancer [published online December 24, 2014]. Head Neck. doi:10.1002/hed.23983.

7. Silver HJ, Dietrich MS, Murphy BA. Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck cancer treated with concurrent chemoradiation after low-dose induction chemotherapy. *Head Neck*. 2007;29(10):893-900.

8. Grossberg AJ, Scarlett JM, Marks DL. Hypothalamic mechanisms in cachexia. *Physiol Behav*. 2010;100(5):478-489.

9. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. 2008;9(7):629-635.

10. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol*. 2013;31(12):1539-1547.

11. Parsons HA, Baracos VE, Dhillon N, Hong DS, Kurzrock R. Body composition, symptoms, and survival in advanced cancer patients referred to a phase I service. *PLoS One*. 2012;7(1):e29330.

12. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab*. 2008;33(5):997-1006.

13. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2001;51(3):571-578.

14. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head Neck*. 2005;27(10):843-850.

15. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AHCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

16. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol (1985)*. 1998;85(1):115-122.

17. Heymsfield SB, McManus CB. Tissue components of weight loss in cancer patients: a new method of study and preliminary observations. *Cancer*. 1985;55(1)(suppl):238-249.

18. Kvist H, Sjöström L, Tylén U. Adipose tissue volume determinations in women by computed tomography: technical considerations. *Int J Obes*. 1986;10(1):53-67.

19. Arrieta O, De la Torre-Vallejo M, López-Macías D, et al. Nutritional status, body surface, and low lean body mass/body mass index are related to dose reduction and severe gastrointestinal toxicity induced by afatinib in patients with non–small cell lung cancer. *Oncologist*. 2015;20(8):967-974.

20. Cooper JS, Farnan NC, Asbell SO, et al. Recursive partitioning analysis of 2105 patients treated in Radiation Therapy Oncology Group studies of head and neck cancer. *Cancer*. 1996;77(9):1905-1911.

21. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol*. 2010;11(1):21-28.

22. Volinsky CT, Raftery AE. Bayesian information criterion for censored survival models. *Biometrics*. 2000;56(1):256-262.

23. Raftery AE. Bayesian model selection in social research. *Sociol Methodol*. 1995;25:111-163.

24. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr*. 1974;19:716-723.

25. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res*. 2009;15(22):6973-6979.

26. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME. Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck*. 2005;27(8):659-668.

27. Lønbro S, Dalgas U, Primdahl H, et al. Lean body mass and muscle function in head and neck cancer patients and healthy individuals: results from the DAHANCA 25 study. *Acta Oncol*. 2013;52(7):1543-1551.

28. Martin L, Senesse P, Gioulbasanis I, et al. Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol*. 2015;33(1):90-99.

29. Kalantar-Zadeh K, Horwich TB, Oreopoulos A, et al. Risk factor paradox in wasting diseases. *Curr Opin Clin Nutr Metab Care*. 2007;10(4):433-442.