Nutritional and body composition changes affecting head and neck cancer patients during oncological treatment

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Memòria presentada per Lorena Arribas Hortigüela per optar al títol de doctor per la Universitat de Barcelona

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Cambios nutricionales y de composición corporal que afectan a los pacientes con cáncer de cabeza y cuello durante el tratamiento oncológico

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Memòria presentada per optar al grau de doctor/a per la Universitat de Barcelona

A mis amores, Nacor, Nahia y Leire

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SUMMARY

The use of imaging techniques routinely used for diagnosis and the assessment for treatment response in oncology allow us to analyze the changes in body composition that occur during treatment and how these changes impact on oncologic outcomes such as survival or toxicity. In addition, we can observe the efficacy of nutritional support through these images.

My main objective for this thesis was to evaluate the nutritional and body composition changes affecting patients with head and neck squamous cell carcinoma (HNSCC) during cancer treatment.

Initially we designed a prospective study to analyze the body composition and nutritional changes that occur during conservative treatment in patients with locally advanced HNSCC at different time points. All patients were closely monitored throughout the treatment implementing nutritional support according to clinical practice guidelines. We observed that 30% of patients were malnourished at diagnosis. However, after the induction chemotherapy, there was an increase in weight and muscle mass with a significant improvement in nutrition impact symptoms such as dysphagia and odynophagia. Nevertheless, a significant nutritional deterioration occurred by the end of concomitant treatment with bio-radiotherapy or chemo-radiotherapy with 95% of patients becoming severely/moderately malnourished. Our findings suggest that induction chemotherapy may help improve nutritional status by ameliorating nutrition impact symptoms. This improvement could contribute to minimize the significant deterioration that occurs despite an intensive nutritional support along the oncological treatment.

An additional aimed was to describe the changes in muscle and fat mass during the chemo-radiation in locally advanced HNSCC patients and evaluate the clinical predictors implicated in this loss. A longitudinal retrospective study was carried out focusing in the analysis of CT images pre-treatment and at the evaluation of tumor response at 3 months after finishing radiotherapy, to quantify muscle and adipose tissue. Nutritional support was provided according to ESPEN guidelines and adjusted body weight (ABW) was used in overweight/obese patients to define their nutritional targets. Patients lost a significant amount of weight, muscle and fat mass during the concomitant treatment. Patients with higher body mass index tended to lose more fat mass but also more muscle. In multivariate regression, only ABW independently predicted muscle and fat loss suggesting that the use of ABW to set nutrition targets in overweight/obese patients may be insufficient. It should be highlighted the urgent need for the development of nutritional guidelines to treat obese cancer patients in order to improve oncological outcomes.

We used the repeated images at baseline and after treatment in same cohort of patients to describe the changes in skeletal muscle and fat over time at different anatomical levels to determine whether those changes are systemic or localized. Precision testing was performed calculating the % coefficient of variation, the root-mean-square standard deviation and the corresponding 95% least significant change values for four anatomical levels: upper arm, thigh, chest and abdomen. The median time between scans was 224 (SD 31 days). The least significant change values for muscle varied from 0.7 to 2.4% depending on anatomic level; with the lowest precision error to detect change in the thigh. Muscle wasting appears to be systemic and while present in limbs and trunk is significant higher in the thigh that in the chest abdomen and upper arm.

As reduced muscle mass has been associated with increased treatment complications worsening survival in several tumor types, we evaluated the impact of reduced skeletal muscle on prognosis and immune-related adverse events (IrAEs) in patients of recurrent/metastatic HNSCC treated with immune checkpoints inhibitors (ICI). Skeletal muscle was quantified using a CT scan at diagnosis. We observed that low skeletal muscle mass was an independent factor for overall survival in the univariate and multivariate analysis. There was no association between low skeletal muscle and IrAEs of any grade.

RESUMEN *(en español)*

El uso de técnicas de imagen utilizadas habitualmente para el diagnóstico y la valoración de respuesta al tratamiento oncológico permite analizar los cambios en la composición corporal (CoC) que se producen durante el tratamiento y cómo estos cambios repercuten en los resultados oncológicos, como la supervivencia o la toxicidad. Además, podemos observar la eficacia del soporte nutricional a través de estas imágenes.

El principal objetivo de esta tesis ha sido evaluar los cambios nutricionales y de CoC que afectan a los pacientes con carcinoma escamoso de cabeza y cuello (CECC) durante el tratamiento oncológico.

Inicialmente diseñamos un estudio prospectivo para analizar la CoC y los cambios nutricionales que se producen durante el tratamiento conservador en pacientes con CECC localmente avanzado. Todos los pacientes tuvieron seguimiento nutricional implementando el soporte nutricional de acuerdo con las guías de práctica clínica. Hemos observado que el 30% de los pacientes estaban desnutridos en el momento del diagnóstico. Sin embargo, tras la quimioterapia de inducción, aumentó el peso y la masa muscular con una mejora significativa de los síntomas de que limitaban la ingesta (disfagia y odinofagia). No obstante, se produjo un deterioro nutricional significativo al final del tratamiento concomitante (bio-radioterapia o quimio-radioterapia), con un 95% de desnutrición grave/moderada. Nuestros hallazgos sugieren que la quimioterapia de inducción puede ayudar a mejorar el estado nutricional mejorando aquellos síntomas que limitan la ingesta. Esta mejora podría contribuir a minimizar el importante deterioro que se produce a pesar del soporte nutricional intensivo a lo largo del tratamiento oncológico.

Un objetivo adicional ha sido describir los cambios en la masa muscular y la grasa durante la quimio-radioterapia concomitante en pacientes con CECC localmente avanzado y evaluar los predictores clínicos implicados en esta pérdida. Se realizó un estudio longitudinal retrospectivo centrado en el análisis de las imágenes de TC previas al tratamiento y en la valoración de respuesta a los 3 meses tras finalizar el tratamiento, para cuantificar músculo y grasa. Se proporcionó soporte nutricional según las guías ESPEN utilizando el peso ajustado (PA) en los pacientes con sobrepeso/obesidad para definir sus objetivos nutricionales. Los pacientes perdieron una cantidad significativa de peso, masa muscular y grasa durante el tratamiento concomitante. Aquellos pacientes con un mayor índice de masa corporal (IMC) tendían a perder más grasa, pero también más músculo. En el análisis multivariado, sólo el IMC predijo de forma independiente la pérdida muscular y grasa, lo que sugiere que el uso del PA para establecer objetivos nutricionales en pacientes con sobrepeso/obesidad puede ser insuficiente. Cabe destacar la necesidad urgente de desarrollar guías nutricionales para el tratamiento nutricional de pacientes obesos con cáncer con el fin de mejorar los resultados oncológicos.

Además, hemos utilizado las imágenes del diagnóstico y tras el tratamiento concomitante de esta misma cohorte de pacientes para describir los cambios de CoC a lo largo del tiempo en diferentes niveles anatómicos para determinar si estos cambios son sistémicos o localizados. Se realizaron pruebas de precisión calculando el % de coeficiente de variación y los correspondientes valores del mínimo cambio significativo al 95% para cuatro niveles anatómicos: brazo, muslo, tórax y abdomen. La mediana del tiempo transcurrido entre las exploraciones fue de 224 (DE 31 días). Los valores del mínimo cambio significativo para el músculo variaron entre el 0,7 y el 2,4% según el nivel anatómico; el error de precisión más bajo para detectar el cambio se produjo en el muslo. El deterioro muscular parece ser sistémico y, aunque está presente en las extremidades y el tronco, es significativamente mayor en el muslo que en el tórax, el abdomen y el brazo.

Por otro lado, se ha evaluado el impacto de la reducción del músculo esquelético en el pronóstico y los efectos adversos inmuno-relacionados (EAI) en pacientes con CECC recurrente/metastásico tratados con inmunoterapia. El músculo esquelético se cuantificó mediante TC al diagnóstico. Hemos observado que la baja masa muscular era un factor independiente de supervivencia global en el análisis univariante y multivariante. No hubo asociación entre la baja masa muscular y los EAI.

Contents

LIST OF ABBREVIATIONS

ABW: Adjusted Body Weight

BIA: Bioimpedance Analysis

BMI: Body Mass Index

BMR: Basal Metabolic Rate

BSA: Body Surface Area

CRP: C-reactive Protein

CRT: Chemo-Radiotherapy

CSA: Cross-Sectional Area

CT: Computed-Tomography

CTCAE: Common Terminology Criteria for Adverse Events

CV: Coefficient of Variation

DXA: Dual-energy X-ray Absorptiometry

ECOG-PS: Eastern Cooperative Oncology Group Performance Status

EPA: Eicosaepentanoic acid

ESPEN: European Society for Clinical Nutrition and Metabolism

FFM: Fat Free Mass

FM: Fat Mass

GLIM: Global Leadership Initiative on Malnutrition

HB: Harris-Benedict equation

HGS: Hand Grip Strength

HNC: Head and Neck Cancer

HNSCC: Head and Neck Squamous Cell Carcinoma

HR: Hazard Ratio

HT: Height

HU: Hounsfield unit

ICI: Immune Checkpoints Inhibitors

ICO: Catalan Institute of Oncology

iCT: Induction Chemotherapy

irAEs: Immune-related Adverse Events

ISCD: International Society for Clinical Densitometry

L3: third Lumbar vertebra

LSC: Least Significant Change

MST: Malnutrition Screening Tool

MUST: Malnutrition Universal Screening Tool

NRS2002: Nutritional Risk Screening 2002

OR: Odds Ratio

OS: Overall Survival

PD-(L)-1: Programmed cell Death (ligand)-1

PET-CT: Positron Emission Tomography-Computed Tomography

PFS: Progression Free Survival

PG-SGA: Patient Generated Subjective Global Assessment

QoL: Quality of life

R/M: Recurrence/Metastatic

RMS-SD: Root-Mean-Square Standard Deviation

RT: Radiotherapy

SD: Standard Deviation

SMA: Skeletal Muscle Area

SMI: Skeletal Muscle Index

SMM: Skeletal Muscle Mass

TATA: Total Adipose Tissue Area

TATI: Total Adipose Tissue Index

TKI: Tyrosine-Kinase Inhibitors

WT: Weight

INCLUDED ARTICLES AND IMPACT FACTOR

Articles' reference	Impact factor#	Journal rank in the category#
Arribas L, Hurtós L, Taberna M, Peiró I, Vilajosana E, Lozano A, Vazquez S, Mesía R*, Virgili N*. **Nutritional changes in patients with locally advanced head and neck cancer during treatment** Oral Oncology 2017;71: 67-74	5.337	**Dentistry, Oral Surgery & Medicine 7/91** **Q1**
Arribas L, Sabaté-Llobera A, Taberna M, Pallares N, Narro Marin A, Virgili N, Hurtós L, Peiró I, Vilajosana E, Lozano A, Baracos V.E*, Mesía R*. **Adequacy of nutritional support using computed-tomography (CT) in patients with head and neck cancer (HNC) during chemo-radiotherapy (CRT)** Eur J Clin Nutr 2021; 75 (10):1515-1519	4.016	**Nutrition & Dietetics 39/89** **Q2**
Arribas L, Sabaté-Llobera A, Cos Domingo M, Taberna M, Sospedra M, Martin L, González- Tampán R, Pallarés N, Mesía R*, Baracos VE*. **Assessing dynamic change in muscle during treatment of patients with cancer: precision testing standards** Clin Nutr, 2022; 41: 1059-1065	7.325	**Nutrition & Dietetics 2/116** **Q1**
Arribas L, Plana M, Taberna M, Sospedra M, Vilariño N, Oliva M, Pallarés N, González-Tampán AR, Del Rio LM, Mesia R*, Baracos VE*. **Predictive value of skeletal muscle mass in recurrent / metastatic head and neck squamous cell carcinoma patients treated with immune checkpoint inhibitors** Front Oncol 2021; Jun 25;11:699668	6.244	**Oncology 62/242** **Q2**

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GENERAL INTRODUCTION

Malnutrition and cancer

Cancer-associated malnutrition is generally acknowledged to differ from deficiency of nutrients in the absence of underlying disease [1]. Metabolic changes in patients with cancer caused by the tumor or by the cancer alter the ability to utilize nutrients leading to weight loss. Depletion in body mass during the course of oncological treatment has been shown to have a prognostic significance [2] and is associated with reduced response rate during chemotherapy and increased toxicity [3]. A robust grading system incorporating the independent prognosis significance of both body mass index (BMI) and % of weight loss was developed as a diagnostic criteria for cancer-associated weight loss [2].

Figure 1 shows the relationship between % weight loss and BMI to overall survival. A gradient of decreasing survival was observed with increasing % weight loss and decreasing BMI: the highest risk in the lower right-hand corner of the figure (grade 4; median survival, 4.3 months), and the least risk in the upper left corner (grade 0; median survival, 20.9 months).
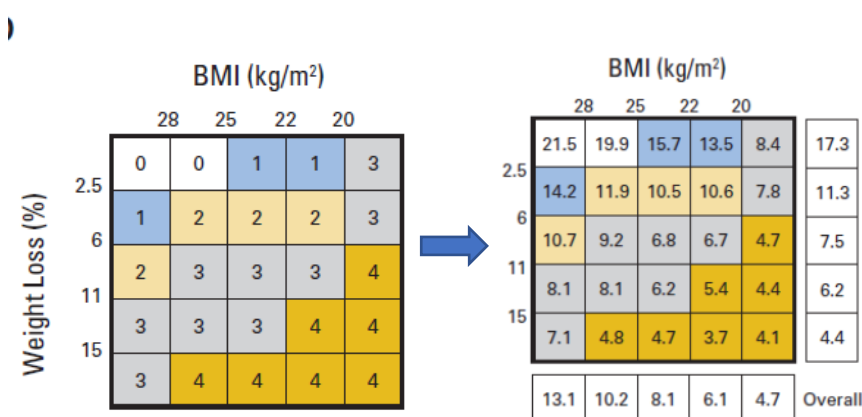
Source: Martin L et al. J Clin Oncol, 2015

Cancer patients are likely to be malnourished and the prevalence of malnutrition ranges from 20% to 70% or more depending on age, cancer type and stage or the definition of malnutrition used [4,5]. In a study of 23,904 cancer patients, 58% had moderate to severe malnutrition according to Patient Generated Subjective Global Assessment (PG-SGA), a nutritional questionnaire validated for cancer patients, but only 29% of these patients received nutritional care [6]. It has been suggested that a significant number of patients with cancer die of cancer-associated malnutrition instead of the malignant disease itself [1]. In fact, cancer associated malnutrition has been shown to have an important impact in quality of life and added healthcare costs [7–9]

Low dietary intake is endemic in cancer patients. In addition, the uncontrolled catabolic drive that characterizes malnutrition in cancer makes it difficult for the nutritional support alone to have clear clinical benefits [1]. In the early stages of cancer-associated malnutrition, malnutrition may be reversible; however, in later stages of the disease, it has been difficult to attain significant improvements in nutritional status, although it has been suggested that with the right combination of therapies, even patients with advanced disease may exhibit anabolic potential [10]. A number of individual studies have demonstrated positive impacts of nutritional interventions on relevant outcomes where dietitian-led clinics and intensive dietary counselling can reduce nutrition-related admissions [11,12] and the hospital length of stay [13]. Improved energy and protein intake [14,15] and

weight [16,17] were noted in some studies and these increases led to improved quality of life (QoL), functioning and nutritional status [18].

Quantitative assessment of body composition also allows us to evaluate the effectiveness of the nutritional support applied. There are evidence-based Clinical Practice Guidelines for nutrition in oncology (ESPEN) available [19]. These guidelines have a focus on dietetic consultation, oral nutritional supplements and escalation to tube feeding per indication. Accordingly, patients presenting with impaired dietary intake, pre-diagnosis weight loss and low BMI, receive aggressive nutrition support during treatment. However, specific nutritional guidelines are lacking for obese cancer patients for whom correct nutritional management is less evident [20,21]. Currently, the use of "adjusted body weight" (ABW) is well extended between nutrition professionals to set nutrition targets also for cancer patients without knowing whether this practice could exacerbate nutritional deterioration.

The poor oncological outcomes associated with cancer-associated malnutrition are driven mainly by the depletion of skeletal muscle [22,23]. Cancer patients have been shown to have a rate of muscle loss 24-fold higher than that observed in healthy aging adults [24,25] which is 1-1.4%/year [26]. Fat mass also plays an important role of weight loss and lately some studies have shown the relationship between inflammatory factors such as IL6 and fat loss by promoting lypolisis [27,28]. In the last decade, diagnostic imaging acquired from the routine clinical practice, enable quantifying these losses [29,30].

Malnutrition in head and neck cancer

Head and neck cancer (HNC) include a wide range of malignant tumors that originate in the different structures of this region of the body. Of these cancers, squamous cell carcinoma of the head and neck accounts for over 90% of HNC [31]. More than 60% of patients with squamous-cell cancer of the head and neck present with stage III or IV disease, which is characterized by large tumors with marked local invasion, evidence of metastases to regional nodes, or both. Locally advanced disease carries a high risk of local recurrence (15 to 40%) and distant metastasis, with a poor prognosis (5-year overall survival, <50%) [32]. Its presentation causes aesthetic alterations and disturbance of functions as phonation, swallowing, hearing and breathing [33]. The surgical option could compromise all these basic functions, therefore an alternative for the treatment of these tumors in advanced stages is a conservative treatment [34]. For locally advanced disease, these are based on the association of radiotherapy (RT) alone or with concomitant chemotherapy [35], or bioradiotherapy [36,37] and, in some cases with previous induction chemotherapy [38]. HNC patients are specially at high risk of malnutrition due to tumor site and treatment [39]. In recent years antineoplasic treatments have contributed to improve locoregional control and survival [40,41], however, acute toxicity caused by these treatments may exacerbate nutritional deterioration by compromising dietary intake [42]. Concurrent chemoradiotherapy is associated with higher rates of toxicity and complications when compared with surgery or radiation alone [43,44]. Some of the treatment toxicities can persist long-term and become chronic: swallowing dysfunction, xerostomia, dental problems, taste alterations, and weight loss have a significant impact on patient's quality of life [45,46]. In addition to the nutritional support, symptom-management (i.e., analgesia), psycho-oncological counseling, and speech and language rehabilitation therapy will be essential to improve their quality of life.

The prevalence of malnutrition according to PG-SGA in HNC patients at diagnosis ranges from 42-77% and worsens throughout the treatment [47,48]. Early detection of malnutrition helps to implement an individualized nutritional intervention to improve oncological outcomes [49,50] and minimize acute toxicities, treatment interruptions and enhance survival [51]. Nutritional support teams are not always well established as part of the multidisciplinary HNC teams and dietetic resources are usually limited; therefore, the coordination with other health professionals may help to improve the adherence to the nutritional support [52]. Nutritional support is an essential part of the multidisciplinary care from the diagnosis through the oncological treatment [53]. The teamwork and support among the different professionals responsible for cancer patients' care allows us to adjust the nutritional intervention to the clinical situation and to treat early toxicities and the evolution of the disease [54]. Medical management of symptoms combined with nutrition therapy is

increasingly conceptualized as being part of the multidisciplinary team effort involving clinical dietitians.

Nutrition care is a priority in patients with HNC due to their multifactorial risk of developing severe malnutrition and the association of malnutrition with poor prognosis [55]. The nutritional and muscle depletion suffered by patients with HNC throughout the course of treatment may be due to symptoms that limit intake depending on the tumor location, toxicity produced by the treatment or inadequate nutritional support. Nutritional intervention in HNC patients is summarized in Figure 3A, B.

A few clinical guidelines for the nutritional management of HNC patients have been published [46,56]. These guidelines have significantly raised awareness on the impact of nutrition in HNC patients among oncologists and surgeons, increasing the number of early nutritional assessments and making it part of the treatment decision, particularly in patients with uncertain prognosis.

Numerous prognostic factors have been described in HNC [33]: those related to the patient (age, patient's general condition or performance status (PS) and smoking)[57], malnutrition according to PG-SGA [58], those related to the tumor (location, stage, human papillomavirus or Epstein-barr virus infection and histologic grade) [59,60] and those related to treatment [61]. Malnutrition and weight loss prior to the start of treatment is considered a poor prognostic factor [62–64]. In recent years, it has been shown that this weight loss occurs mainly at the expense of muscle mass. Sarcopenia defined as a reduction in muscle mass can occur regardless of age and is common in chronic diseases, including cancer [22,65] and is often classified in relation to the risk of specific disease outcomes. Reduced muscle mass has been shown to have a negative clinical outcome in cancer patients including HNC patients [66–68].

Figure 3. Nutritional intervention in HNC patients
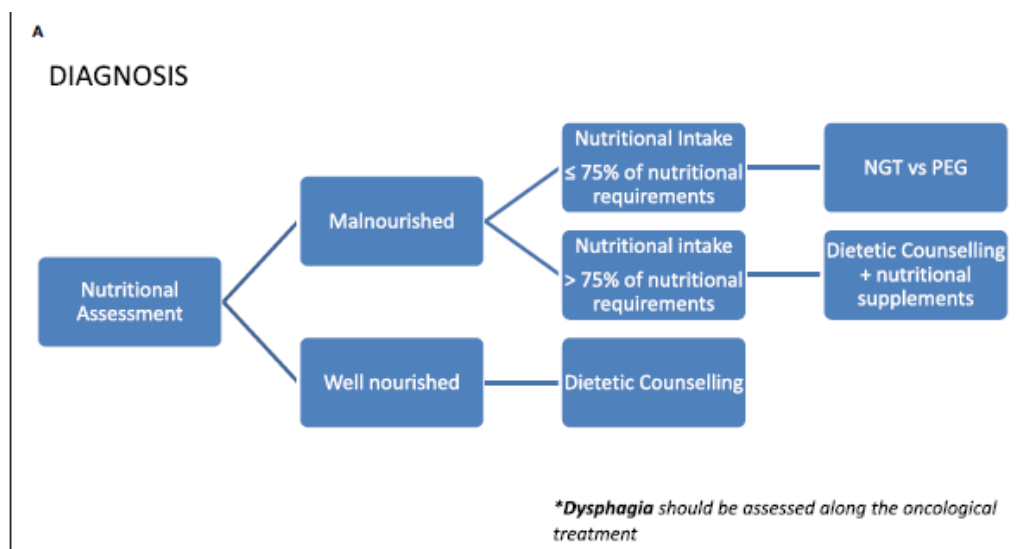
NGT: Nasogastric tube; PEG: Percutaneous endoscopic gastrostomy

Source: Taberna M et al. Front Oncol 2020

NUTRITIONAL INTERVENTION IN HEAD AND NECK CANCER PATIENTS

FIGURE 1 | (A) Nutritional intervention in HNC patients according to the nutritional status. (B) Nutritional intervention in HNC patients according to the treatment plan.
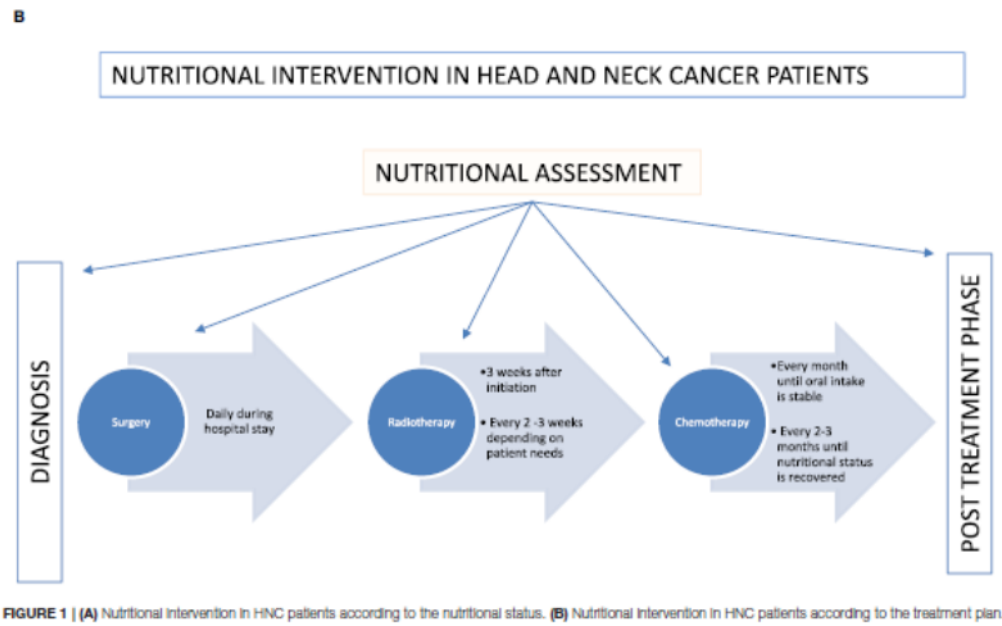
Source: Taberna M et al. Front Oncol 2020

Body composition analysis

As mentioned above, muscle loss is probably the most clinically relevant feature of weight loss in cancer. Therefore, to identify those patients with muscle loss can become a huge challenge.

Computed tomography (CT) is now considered the reference standard method of body composition assessment in terms of specificity and precision and is of particular convenience in oncology research as these scans are readily available because they are used as part of routine diagnosis and staging. Axial CT images at the level of the third lumbar (L3) vertebrae can be retrospectively analyzed to precisely segment skeletal muscle and adipose tissue (subcutaneous, visceral and intermuscular) (Figure 4). Using a commercially available image analysis software, muscle and adipose tissues can be evaluated based on Hounsfield unit (HU) thresholds: −29 to +150 for skeletal muscle [69], −190 to −30 for subcutaneous and intermuscular adipose tissue [69] and −150 to −50 for visceral adipose tissue [70]. Muscles in this area include the psoas, paraspinal muscles (erector spinea, quadratus lumborum) and the abdominal wall muscles (transversus abdominus, external and internal oblique, rectus abdominus). Measurements at L3 level as the skeletal muscle area (SMA) obtained at this level is a good correlate for whole body muscle in healthy individuals (r 0.92) [71]. From this, skeletal muscle index (SMI) can be calculated by adjusting SMA by the patient's height (total SMA (cm^2)/height (m^2)) and patients are often compared on this basis. Regression formulae are available to estimate whole-body compartments using these data (in a sex-specific manner).

In the oncology setting, consensus-based cut points to define low muscle mass or sarcopenia are lacking, and a variety have been devised [72]. In 2013, Martin et al. [73] identified both sex and BMI-specific cut points for SMI that best predicted survival (men: <43 cm^2/m^2 if BMI ≤24.9 kg/m^2 and <53 cm^2/m^2 if BMI ≥25 kg/m^2; women: <41 cm^2/m^2) [73] in a large cohort of 1473 patients with lung and gastrointestinal (GI) cancer, which are more applicable to non-obese cohorts. Using optimal stratification methodology, several other studies have reported cut points for SMI associated with mortality in a number of cancer cohorts [72], these range 36–55.8 cm^2/m^2 for men and 29–46.6 cm^2/m^2 for women including Asian population. Several factors influence patient's muscularity (ethnicity, age, sex, physical activity and magnitude of adiposity) [74]; hence, published cut points may not be applicable to all cancer populations [72]. Other studies have defined sarcopenia based

16

on more data-orientated approaches, categorizing SMI based on predetermined percentiles, such as quartiles [75], tertiles [25,76,77] or based on the median [78,79].

As BMI does not describe adipose tissue and muscle distribution, the need for quantifying the total adipose tissue (including visceral, subcutaneous and intermuscular adipose tissue) and muscle mass has been a need to evaluate fat and muscle mass as predictor factors for oncological outcomes [2,80]. CT allows the precise quantification of both muscle and adipose tissue and has led to a large volume of research which has increased our understanding of the importance of abnormal body composition phenotypes, such as low muscle mass (sarcopenia) as important prognostic indicators of unfavorable outcomes in patients with cancer [10].

Chemotherapy can often be associated with severe toxicity that can result in dose delays, dose reduction and early treatment termination, referred to as dose limiting toxicities. Moderate to severe toxicities can lead to interruption, deferral or even cessation of treatment. Severe toxic events can result in hospitalizations and can even be life-threatening [10]. Recent evidence suggests that variability in body composition of cancer patients may be a source of disparities in the metabolism of cytotoxic agents resulting in increased toxicity [81–83].

The widespread use of body surface area (BSA), relying on height and weight alone [84], in dosing chemotherapy drugs presents a problem because this approach does not normalize all of the variability in drug metabolism and pharmacokinetics. Body composition variation is a potential source of drug metabolism variations, if that is affected by proportions of muscle and adipose tissue. There are large discrepancies in muscle mass between people of the same BSA, resulting in potential variations in exposure when calculations are based on a simple BSA formula [85–87]. A 4–10-fold variation in drug clearance is possible in individuals with a similar BSA and there is concern that this approach to dosing is invalid [88,89]. Bodyweight comprises two major components (muscle and adipose tissue), these being the main sites of distribution of hydrophilic and lipophilic drugs [90,91]. Therefore, variability in individual muscle and adipose tissue may lead to changes in the volume of distribution of drugs and therefore adversely affect the tolerance of cytotoxic drugs [92].

It is also important to note that sarcopenic patients are highly susceptible to acute medical events that exacerbate chemotherapy-related toxicity [93]. In addition, low concentrations of circulation plasma proteins (e.g. albumin), which is commonly seen in those with malnutrition or systemic inflammation (or both) may also affect the distribution of highly protein-bound drugs [91,94,95]. As imaging techniques in body composition become more widely used, this may represent an opportunity for a more personalized approach to chemotherapy dosing.

Lastly, the combination of sarcopenia and obesity has been shown to have particularly poor clinical outcomes. This may be related to the combined negative effects of both conditions or may be related to poor detection of sarcopenia in a cohort whose muscle loss is masked by excess adiposity. Sarcopenic obesity specifically has been associated with poorer survival in a number of cohorts [96].

Figure 4. Computed tomography body composition analysis of the third lumbar vertebrae

Subcutaneous adipose tissue

Visceral adipose tissue

Intermuscular adipose tissue

Skeletal muscle
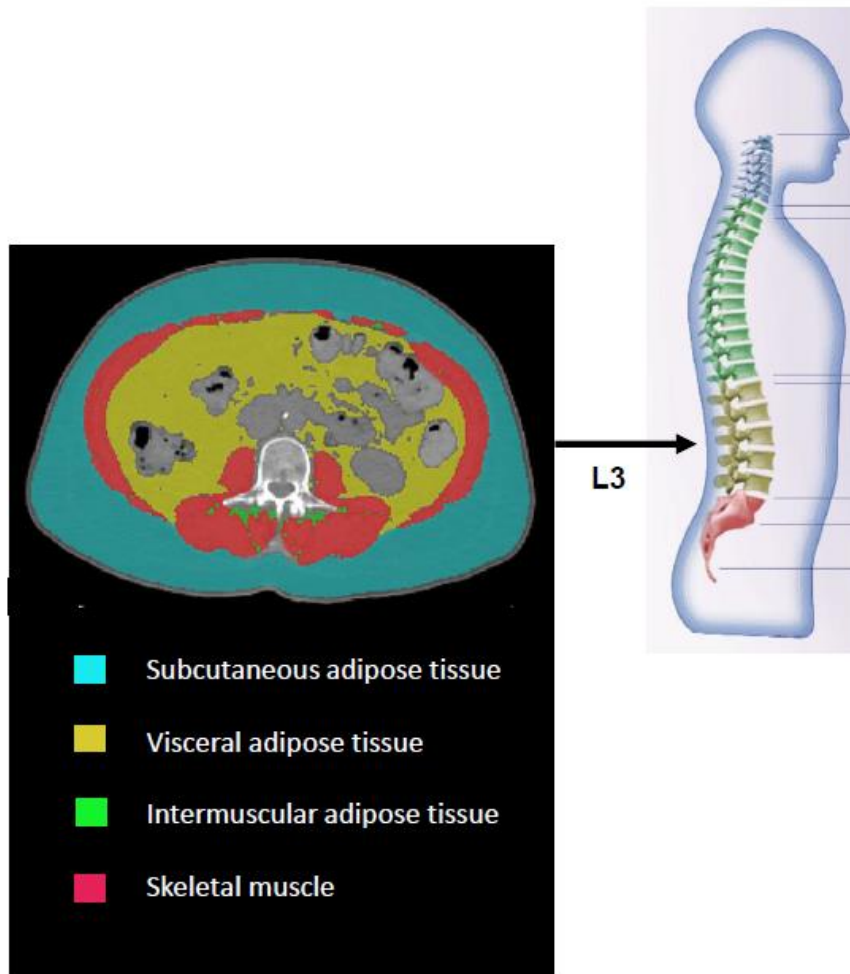
Body composition changes over time during cancer treatment and precision test

In the last decade, muscle quantification has gained clinical relevance as it has been related to functionality, nutritional status, tolerance to oncological treatment and prognosis [66,67,97]. PET/CT imaging allows quantitative and qualitative measurement of adipose tissue and muscle tissue leading to numerous publications evaluating oncological outcomes such as survival, surgical complications or treatment toxicity [97–101]. Many of these studies quantify in a single time, without taking into account some errors associated with making a single measurement. Other studies that measure changes over time do not evaluate any repeatability measurements. Very few studies mentioned intra-observer (or inter-observer) coefficient of variability, however none of the studies published stated to be using a radiological standard for precision testing. An example of these standards is the establishment of specific requirements for Dual-energy X-ray Absorptiometry (DXA) by The International Society for Clinical Densitometry (ISCD) for diagnosis and longitudinal measurements in body composition [102]. Likewise, for bone densitometry, the requirements to perform precision studies at regular intervals by each individual observer involved with a minimum acceptable precision are mandatory. The least significant change (LSC) value is a key performance metric for repeated measures over time and evaluates the minimum amount of change that can be considered statistically significant and is calculated based on the precision error [103,104]. For a change between two images to be considered statistically significant, it must exceed the value of LSC, otherwise the change can be attributed to the measurement itself [103]. Lately there has been an increase in publications evaluating muscle changes in oncology

patients, but it should be noted that the measurement of these changes must be performed in a standardized manner using precision tests to ensure that the changes are actually due to their biological nature and not due to measurement error. This is especially important for small changes that may occur in a short period of time.

Despite the advances in muscle assessment and its prognostic and predictive value, there are still many unresolved questions. One of them is whether the muscle loss that occurs in cancer patients occurs uniformly throughout the body or is localized to a specific region. Most of the studies published to date use the third lumbar vertebra (L3) as the landmark for calculating total body muscle mass. This practice was adopted because of the high correlation of this region with the total amount of body adipose and muscle tissue [71]. In addition, images covering the whole body are not performed in routine clinical practice. However, despite all this, we do not know if the L3 region is representative of the whole body when assessing muscle loss over time. Many of the factors associated with this muscle loss in cancer patients are mostly systemic. However, some animal studies have shown that some muscle tissues are more susceptible to loss depending on the type of fiber they present [105]. In addition, the reduction of physical activity in bedridden patients causes muscle loss, especially in the lower limbs [106,107]. Even today we do not know the effect that oncological treatments alone or combined with other treatments such as exercise, nutritional intervention or hormone therapy have on the muscle over time. Therefore, it is unknown whether the loss of muscle mass is systemic or localized to a greater extent in a specific region. The increasing use of PET/CT in staging HNC helps us to extend the evaluation to different anatomical regions and compare them with each other.

Sarcopenia as predictive biomarker in head and neck cancer patients

The impact of sarcopenia on survival in cancer has been extensively studied over the past decade. Most studies report a significant decrease in overall survival and complications in patients with sarcopenia compared with those without sarcopenia, irrespective of the primary cancer site and stage [10,108]. These results have also been described in HNC [66,109–115].

One of the issues with the use of CT scans in muscle mass evaluation for HNC is that diagnostic is frequently used to evaluate cervical or thoracic images. As a result, investigations of sarcopenia in patients with HNC have lagged until recently, facilitated by the availability of the CT component of whole-body Positron Emission Tomography Computed Tomography (PET-CT). In the absence of imaging to the level of L3, some studies used either the third cervical vertebra (C3) [111,113,116] or second (T2) [117] or fourth (T4) [66] thoracic vertebra. However, a recent systematic review conclude that the current level of evidence is inadequate to provide definitive recommendations for the use of alternative vertebral slice to L3 in CT scans of cancer patients for the evaluation of SMM [118].

In the HNC surgical population, sarcopenia has been found to be an independent negative prognostic indicator for patient undergoing total laryngectomy for: pharyngocutaneous fistula, prolonged hospital stay and reduced overall survival [119]; and both all complications and wound complications [120]. A recent meta-analysis [121] shows that sarcopenia is independently associated with reduced overall survival in patients with HNC undergoing radiotherapy and holds a clinically meaningful prognostic value. Pre-treatment sarcopenia was associated with reduced overall survival (HR 2.07; 95%CI 1.47-2.92, p<0.0001, I^2=49%) with similar findings for post-treatment sarcopenia (HR 2.93; 95%CI, 2.00-4.29, p < 0.00001, I^2= 0%) with moderate to low heterogeneity exhibited amongst studies respectively. Two other meta-analysis [122,123] have been published including studies from HNC with different treatment modalities (surgery, radiotherapy, chemotherapy and combinations). Both publications conclude that the presence of pre-treatment sarcopenia has a significant negative impact on overall survival for HNC compared with its absence. All these publications include studies with all stages and HNC locations but none of the studies have been performed in metastatic or recurrent HNC patients.

Among patients with head and neck squamous cell carcinoma (HNSCC), between 5-10% are diagnosed with metastatic disease [33]. Additionally, despite aggressive multimodal strategies about 60% of patients treated with radical intention for a locally advanced disease will eventually recur [124]. Until the introduction of immunotherapy agents, the median survival was 10.1 months, with a 82% rate of grade 3–4 adverse events using the historic standard first-line EXTREME

(combining platinum and 5-fluorouracil (5-FU) and cetuximab) [125]. Patients with progressive disease after platinum-based chemotherapy have a poor prognosis with a one-year survival under 5% [126]. Hereby, there is an urge need for improved therapy in the recurrent and metastatic (R/M) population.

Patients with metastatic disease at diagnosis and those with recurrent disease not salvageable with local treatment currently have the same oncologic treatment [31,32]. Targeting the programmed cell death (ligand)-1 (PD-(L)1) pathway has shown significant activity, and improved overall survival (OS) in patients with previously treated R/M HNSCC, associated with fewer grade 3 or 4 toxicities than standard therapy [127–129]. These results have led to approval of two anti-PD1 agents (pembrolizumab and nivolumab) as 2nd line treatment for patients with R/M HNSCC who experience disease progression on or after a platinum-based therapy [128,129]. More recently pembrolizumab has been approved in the 1st line setting, alone or in combination with chemotherapy [130]. Despite improving the results compared with older strategies, approximately 70% of patients do not benefit from immune checkpoints inhibitors (ICI) as they have progression as the best response, enhancing the need for predictive biomarkers [128,130] to select patients who clearly benefit from them.

The urgent need to find new predictors factors in patients treated with ICI has led to different investigators to study sarcopenia as an independent factor for overall survival and also for immune-related adverse events (irAEs). Several studies have shown the poor effect of sarcopenia on patients including lung cancer [131,132], melanoma [133,134] and urothelial carcinoma receiving ICI immunotherapy [135]. Also the incidence rate of irAEs of any grade increase compared to those without sarcopenia [132,133,136]. However, whether sarcopenia is a predictive factor for clinical outcomes in R/M HNSCC receiving ICIs remains unclear.

RATIONALE OF THE THESIS

Our understanding of the nutritional and body composition changes in HNC patients are progressively improving during the last years. Nevertheless, there are still some important gaps in knowledge that remain unclear. We have tried to answer some of these gaps in knowledge in this thesis:

1) As explained above, patients with HNC become malnourished during oncologic treatment. But we also know that some oncologic treatments in HNC help to reduce tumor size with the consequent benefit in the improvement of symptoms that limit oral intake due to tumor location. We want to evaluate body composition and nutritional status throughout the treatment in those patients with locally advanced disease who received intensive nutritional support.

2) Since imaging techniques are being used to assess body composition and its changes, we want to relate the nutritional support with the changes in body composition that occur along the oncological treatment and evaluate which may be the most significant predictors involved in this depletion.

3) Up to now, we have learned that both baseline body composition and its changes can associate with poor clinical oncologic outcomes. However, these changes over time have not been properly measured in a standardized way as with other methods of analysis, such as DXA. Therefore, we propose the need to perform a precision test before analyzing the changes over time using CT images to ensure that the changes are real and not due to measurement error.

4) On the other hand, given the pathophysiology of muscle loss, it has been postulated that muscle loss over time is systemic, but some studies in immobilized patients have confirmed muscle atrophy with specific group of muscles. In this thesis, we want to explore whether muscle loss in locally advanced HNC patients undergoing oncological treatment is systemic or regional.

5) With the emergence of new treatments, especially immunotherapy, and the improvement in survival, we want to evaluate whether, like other treatments, body composition has also a negative impact on survival and toxicity in HNC patients.

HYPOTHESIS

1. HNC patients suffer significant nutritional and body composition depletion throughout cancer treatment despite intensive and individualized nutritional support. This depletion persists over time after the end of treatment.

2. The calculation of a precision test in the analysis for the different compartments of the body through imaging techniques could help to differentiate with certainty whether the changes that occur over time are biological changes or due to measurement error.

3. The loss of muscle mass and adipose tissue is systemic.

4. Sarcopenia could be an independent prognostic biomarker of survival and predictor of severe toxicity in patients with recurrent or metastatic head and neck squamous cell carcinoma with indication for immunotherapy treatment.

OBJECTIVES

Primary objectives

1) To assess the body composition changes and nutritional status throughout the treatment in patients with locally advanced squamous cell carcinoma of the head and neck.

2) To evaluate a precision test at four different anatomical levels (arm, thigh, thorax and abdomen) to discriminate biological changes from measurement error.

3) To evaluate muscle mass as a prognostic biomarker of survival and progression-free survival in patients with recurrent or metastatic head and neck squamous cell carcinoma treated with immunotherapy.

Secondary objectives

1) To evaluate the clinical predictors of muscle and adipose tissue loss during treatment in patients with locally advanced head and neck squamous cell carcinoma during concomitance with chemo-radiotherapy.

2) To determine whether the loss of muscle mass and adipose tissue is systemic or localized.

3) To analyze the association between muscle mass and the occurrence of immunotherapy-related adverse effects in patients with recurrent and/or metastatic head and neck squamous cell carcinoma.

RESULTS

List of articles from the project that have been included in the thesis:

- **Arribas L**, Hurtós L, Taberna M, Peiró I, Vilajosana E, Lozano A, Vázquez S, Mesía R*, Virgili N*. **Nutritional changes in patients with locally advanced head and neck cancer during treatment.** Oral Oncology 2017;71: 67-74

- **Arribas L**, Sabaté-Llobera A, Taberna M, Pallares N, Narro Marin A, Virgili N, Hurtós L, Peiró I, Vilajosana E, Lozano A, Baracos V.E*, Mesía R*. **Adequacy of nutritional support using computed-tomography (CT) in patients with head and neck cancer (HNC) during chemo-radiotherapy (CRT).** Eur J Clin Nutr 2021; 75 (10):1515-1519

- **Arribas L,** Sabaté-Llobera A, Cos Domingo M, Taberna M, Sospedra M, Martin L, González- Tampán R, Pallarés N, Mesía R*, Baracos VE*. **Assessing dynamic change in muscle during treatment of patients with cancer: precision testing standards**. Clin Nutr, 2022; 41: 1059-1065

- **Arribas L,** Plana M, Taberna M, Sospedra M, Vilariño N, Oliva M, Pallarés N, González- Tampán AR, Del Rio LM, Mesía R*, Baracos VE*. **Predictive value of skeletal muscle mass in recurrent / metastatic head and neck squamous cell carcinoma patients treated with immune checkpoint inhibitors.** Front Oncol 2021; Jun 25;11:699668

*Equally contributed as senior author

ARTICLE 1

Arribas L, Hurtós L, Taberna M, Peiró I, Vilajosana E, Lozano A, Vazquez S, Mesía R*, Virgili N*.

Nutritional changes in patients with locally advanced head and neck cancer during treatment.

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Nutritional changes in patients with locally advanced head and neck cancer during treatment

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ARTICLE INFO

ABSTRACT

Objective: The purpose of the study is to evaluate changes in body composition and nutritional status that occur throughout the oncological treatment in head and neck cancer patients.

Methods: A prospective cohort observational study in patients diagnosed with head and neck squamous cell carcinoma (HNSCC) that underwent treatment with induction chemotherapy (iCT) followed by chemoradiotherapy or bioradiotherapy were invited to participate. All patients had dietetic counseling from the diagnosis and a close monitoring throughout the treatment implementing nutritional support as needed.

Results: From June 2011 until October 2012, 20 patients were included. Nutritional and anthropometric parameters were collected at diagnosis, post iCT, after radiotherapy, 1 and 3 months post radiotherapy. According to Patient Generated Subjective Global Assessment, 30% of patients were malnourished at diagnosis. After iCT there was an increase in weight, body mass index (BMI) and fat free mass (FFM) with almost complete improvement in dysphagia and odynophagia. Nevertheless a significant nutritional deterioration (p = 0.0022) occurred at the end of radiotherapy with 95% of patients becoming severe or moderate malnourished. Nutritional parameters such as weight, BMI and hand grip strength also decrease significantly during treatment.

Conclusions: Despite an intensive nutritional support from the diagnosis throughout the oncological treatment in advanced HNSCC cancer patients, nutritional status deteriorates during radiotherapy. Our findings suggest that iCT may help improve nutritional status by ameliorating the symptoms that limit the oral intake. This improvement in the nutritional status could contribute to minimize further deterioration. Further investigations are needed involving novel approaches to avoid nutritional deterioration.

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Introduction

Head and neck squamous cell carcinoma (HNSCC) includes a wide range of malignant tumors that originate in the different structures of this region of the body. Its presentation causes aesthetic alterations and disturbance of functions as phonation, swallowing, hearing and breathing [1]. The surgical option compromises all these basic functions, therefore an alternative for the treatment of these tumors in advanced stages is a conserva-

tive treatment [2]. These are based on the association of radiotherapy (RT) with concomitant chemotherapy [3], or bioradiotherapy [4,5] and, in some cases previous induction chemotherapy (iCT) [6]. HNSCC patients are specially at high risk of malnutrition due to tumor site and treatment [7]. In recent years antineoplasic treatments have contributed to improve locoregional control and survival [8,9], however, acute toxicity caused by these treatments may exacerbate nutritional deterioration by compromising dietary intake by odynodysphagia (mucositis related), anorexia or xerostomia [10].

The prevalence of malnutrition in HNSCC patients at diagnosis ranges from 42 to 77% and worsen throughout the treatment [11,12]. Nutritional support is an essential part of the multidisciplinary care from the diagnosis through the oncological treatment [13]. An early detection of malnutrition helps to implement an individualized nutritional intervention to improve oncological outcomes [14,15] and minimize acute toxicities, treatment interruptions and enhance survival [16]. The teamwork and support among the different professionals responsible for cancer patients' care allows us to adjust the nutritional intervention to the clinical situation and to treat early toxicities and the evolution of the disease [17].

Weight loss in cancer patients is one of the independent negative factors in prognosis and development of complications [18]. In recent years, several studies have demonstrated the importance, not only on the weight but the changes in body composition throughout cancer treatment [19,20]. Muscle loss determines the limiting dose of some antineoplasic drugs due to the high volume of distribution in adipose tissue (patients with more adipose tissue have a slower drug elimination) [21–23]. Many patients with HNSCC have a body mass index (BMI) above normal values contributing in many cases to masking a decreased muscle mass [12].

Furthermore, primary sarcopenia includes not only loss of muscle mass but age-related functionality [24]. Life expectancy and obesity increased in developed countries, have contribute to determine the body composition of patients with cancer. Far from the idea of an emaciated oncological patient, only 10% of all cancer patients are underweight (BMI$\leq$18.5 kg/m^2) at the diagnosis [18].

The objective of our study is to evaluate in a prospective cohort the changes in body composition and nutritional status that occur throughout the oncological treatment in HNSCC patients.

Methods

Study population

This is a prospective cohort observational study conducted in a single center, the Catalan Institute of Oncology (ICO)/Hospital Universitari de Bellvitge from June 2011 until October 2012. Patients (age$\geq$ 18 years) diagnosed with locally advanced HNSCC that underwent oncoespecific and radical treatment with iCT followed by chemoradiotherapy or RT plus cetuximab were invited to participate in the study. Eligibility criteria included pathologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx and nasopharynx with no history of recurrent disease. Patients were excluded if they were unable to understand and speak Spanish, had a definitive diagnosis of dementia or lacked capacity to understand the purpose of the study.

The iCT scheme was based on taxanes and cisplatinum (TPF-like) [25]. Cisplatinum 100 mg/m^2 every 21 days or cetuximab 250 mg/m^2 weekly (loading dose of 400 mg/m^2) was used in patients with concomitant RT. Patients were referred to concomitance chemoradiotherapy or RT plus cetuximab according to the

head and neck multidisciplinary committee decision; previous toxicity to iCT or patients inclusion on a clinical trial protocol [26].

The study protocol was approved by the Hospital Universitari de Bellvitge Ethics Committee for Clinical Research (PR231/11). All patients provided written informed consent.

Procedures

An oncology dietitian collected data at diagnosis (baseline), after finishing iCT/prior to begin RT (visit 1), after finishing RT (visit 2), 1 month after RT (visit 3) and 3 months after the end of treatment (visit 4). Data included were nutritional and anthropometric parameters, serum albumin (mg/dl), tumour location, tumour staging (TNM 7th edition), oncological treatment, toxicity according to the CTCAE scale version 4.0 (Common Terminology Criteria for Adverse Events) [27] and follow-up data.

Height (ht) and weight (wt) were measured using standard protocols [28]. BMI was calculated as $[(wt in kg)/(ht in m)^2]$. Percent wt loss was calculated as $\{[usual body wt-actual body wt]/ usual body wt\}*100$.

Dietary intake was estimated by a 24-h recall conducted by the oncology dietitian each time. Dietary intake data were analyzed using the Dietsource® software version 3.0 to estimate the calories and protein intake.

Energy requirements were estimated using Harris–Benedict (HB) equation [29,30] and Mifflin-St Jeor (MS) equation [31] using the adjusted body weight for patients with BMI$\geq$ 25 kg/m^2. 1.5 per physical activity was added as all patients had no incapacity and 1.2 per active oncology disease. Daily protein requirements were estimated at 1.5 g/kg actual body wt [29].

Muscle functionality was evaluated by handgrip strength (HGS) in the dominant hand, using Jamar dynamometer (Hydraulic Hand Dynamometer, SI Instruments PtyLtd, Adelaide, Australia). Three successive measurements were taken and the maximal measurement was used for the analysis [32].

Nutritional status was evaluated by the Patient Generated Subjective Global Assessment (PG-SGA) validated in cancer patients [33,34]. The first section of the assessment that includes actual weight, height, food intake, symptoms, activity and functionality was completed by the participant, with the help of the dietitian when needed [33]. The oncology dietitian performed the remainder form (diagnoses, metabolic demand and physical exam). Individuals were categorized as being well nourished (A), moderately malnourished or risk of malnutrition (B) or severely malnourished (C). Dietetic counseling was given to all patients from the diagnosis. Oncology dietitian adapted their diet to improve their nutritional intake, especially emphasizing on the protein intake and the fractionation of intakes along the day. Only when nutritional requirements were not met with dietetic intervention, nutritional supplementation was prescribed according to the individual needs.

Body composition was assessed by bioimpedance (BIA). Data were recorded at each visit using TANITA bioelectrical impedance analysis device (TANITA BC-418MA segmental; Biológica tecnología médica, SL, Barcelona, Spain). Measurements were made at 10 min after the participant assumed a supine position using standard protocols for BIA [35].The BIA variables collected were fat free mass (FFM) and basal metabolic rate (BMR).

Statistical analysis

A descriptive analysis of each of the variables was made using descriptive statistics. Changes of the anthropometric parameters, food intake, serum albumin and nutritional support in each visit were evaluated, calculating the average of these parameters at each visit and a 95% confidence interval was estimated.

The Pearson correlation coefficient with 95% confidence interval was predicted for the association between the difference of baseline and the end of treatment in HGS and the FFM and the association between different parameters and the BMR.

Time from first visit to death (survival) and disease progression was analyzed. The Kaplan-Meyer curve was estimated with its confidence interval. The log-rank test was used to compare the survival curves with PG-SGA. We used the Cox regression model to quantify the risk of death between nutritional groups, estimating hazard ratios with their confidence interval for PG-SGA, oncological stage, 3-months weight loss, baseline BMI, baseline HGS, FFM and serum albumin.

Statistical significance was set at a probability level ≤ 0.05. The statistical package used to treat the data and perform the statistical analysis has been the R version 3.2.5 for Windows.

Results

From the 23 patients included in the study one deceased during the treatment and 2 were treated with surgery due to lack of response to iCT. These 3 patients were excluded for the final analysis (analysis per protocol). Table 1 shows baseline demographic and clinical characteristics of all patients included. The mean age was 53 years (SD 7). All patients were male except for 1 female. Tumour location was mainly hypopharynx and larynx in advanced stages IVb. 70% of the patients were treated with chemoradiotherapy after iCT.

Weight loss in the last 3 months prior to diagnosis was not statistically significant (p = 0.13 [95% CI −7.51 to 9.35]). Nutritional status varied throughout the treatment (Table 2). Since there is small number of patients on bioradiotherapy treatment (n=6) we cannot evaluate significant changes in any nutritional parameters between the chemoradiotherapy and bioradiotherapy. At diagnosis, 30% of patients showed severe or moderate malnutrition (B +C) with dysphagia in 55% (11/20) and odynophagia in 50% (10/20) that limited their oral intake. All patients had dietetic counseling from diagnosis, 15% (n=3) required nutritional supplementation and only one patient (5%) required gastrostomy placement for enteral nutrition.

After iCT, the symptoms such as dysphagia and odynophagia were resolved almost entirely and only one patient remained with dysphagia (grade 3–4). According to PG-SGA, nutritional status had a significant nutritional deterioration (p = 0.0022) at the end of RT (visit 2) with 95% (19/20) of patients becoming severe or moderate malnourished (B + C). Other nutritional parameters such as weight loss, BMI, FFM and HGS also decrease significantly over the course of treatment (Fig. 1). Patients lost a mean of 7.09 kg (95% CI 5.05–9.12; p < 0.0001) 3 months after the end of the treatment and BMI dropped an average of 2.46 kg/m2 (95% CI 1.75–3.17; p < 0.0001). Functionality was also affected globally with a strength loss of 3.76 kg (p = 0.007; 95% CI 1.17–6.36) at the end of treatment. The FFM increased slightly after iCT, decreasing subsequently after concomitance **(p = 0.37 [95% CI −0.98 to 2.49]). The changes in nutritional parameters (weight, BMI, FFM, HGS) do not show significant changes until 3 months after RT (p = 0.00003 [95% CI 1.40–3.83]). It was not possible to establish a correlation between the HGS and the FFM difference throughout the treatment, with a Pearson correlation of 0.34 (95% CI −0.19 to 0.71). The value of albumin decreased non-significantly throughout the treatment (p = 0.5216; 95% CI −1.23 to 2.52). There was no association between the decline in albumin level and weight loss (Pearson correlation: −0.19; 95% CI [−0.61; 0.30]).

Acute toxicity throughout the concomitance treatment is shown in Table 3. Mucositis and odynophagia affected 85% (15% with grade 3–4) and 75% (10% with grade 3–4) of patients respec-

Table 1
Baseline demographic and clinical characteristics of the study sample at baseline.[*]

Characteristics	No. of patients (n = 20)	SD
Age, years	53.70	7.11
Male	19	95
Body weight, kg	71.36	13.14
BMI, kg/m^2	25.20	4.11
Pre-diagnosis weight loss, kg	2.31 p = 0.13[a]	6.37
Hand grip strength, kg	35.87	8.10
Serum albumin, g/l	44.35	3.07
Energy intake, kcal/d	2016.20	358.47
Protein intake, g/d	84.75	23.86
Tumour location	n	%
Oral cavity	2	10
Hypopharynx	7	35
Larynx	6	30
Oropharynx	3	15
Nasopharynx	1	5
Unknown	1	5
Staging		
Stage III	4	20
Stage IVa	5	25
Stage IVb	11	55
Concomitance with RT		
CDDP	14	70
Cetuximab	6	30

[*] Values are mean; standard deviation (SD) or frequency (%).
[a] Pair t-test.

tively during the concomitance, decreasing to 45% and 20%, 1 month after the end of treatment. At 3 months post treatment, xerostomia G1-2 (60%) and anorexia G1-2 (45%) remained as an acute toxicity.

All patients received dietetic counseling from the diagnosis. A close monitoring was carried out by the oncology dietitian to implement nutritional intervention according to patient's needs. Despite a gradual decrease in energy and protein intake throughout the treatment, it was not significant (p = 0.80 [95% CI −262.91 to 401.32] and p = 0.23 [95% CI −6.16 to 24.02], respectively) (Fig. 2). Nasogastric tube was required by 7 patients (35%) and maintained this need up to visit 3. The need for enteral nutrition along the treatment was 42.10 days (SD 15.88; IQR 52.75–28.75). After concomitance, malnutrition was reversed in 15% of patients (n=3) improving the nutritional status. At 3 months post-treatment, 30% (n=6) were well nourished and 90% of patients (n=18) were on a regular diet.

A strong correlation between the baseline energy expenditure calculation according to BIA and the MS equation (Pearson correlation 0.84; 95% CI (0.66: 0.95) and the HB equation (Pearson correlation 0.88; CI 95% (0.68, 0.96) was observed (Fig. 3).

After 4 years of follow-up, 14 patients were alive (overall survival of 70%). All the deceased patients presented stage IVb at diagnosis and died due to disease progression. No significant relationship could be established between the parameters of weight loss, BMI, FFM and functionality with overall survival. Comparison of survival curves versus PG-SGA suggests differences between survival curves in favor of well-nourished patients (Test log-rank A vs B: Chi^2 = 6.4, p = 0.0117).

Discussion

This study aims to evaluate the nutritional changes that occur during and up to 3 months after the end of the conservative treatment in HNSCC patients. At diagnosis, 70% of our patients were well nourished and did not lose a significant amount of weight. In contrast, in our previous study [11], we found good nutritional status in 51.7% of patients at diagnosis. However this study included patients with metastasic and recurrences diseases.

Table 2
Changes in nutritional parameters along the treatment.

Variables	Baseline	Visit 1	Visit 2[a]	Visit 3	p- value	95%IC[†]	Visit 4[b]	p- value	95%IC[‡]
PG-SGA (n, %)									
A (Well nourished)	14 (70)	12 (60)	1 (5)	3 (15)			5 (25)		
B (moderately malnourished or suspected of malnutrition)	3 (15)	6 (30)	10 (50)	13 (65)			7 (35)		
C (severely malnourished)	3 (15)	2 (10)	9 (45)	4 (20)			8 (40)		
Weight (kg)[*]	71.36 (13.14)	71.67 (12.47)	66.42 (9.89)	66.49 (10.05)	p = 0.016	1–8.73	63.92 (10.89)	<0.0001[c]	5.05–9.12
BMI (kg/m2)[*]	25.20 (4.11)	25.43 (3.81)	23.61 (3.30)	23.60 (3.19)	p = 0.010	0.42–2.77	22.71 (3.56)	<0.0001[c]	1.75–3.17
Hand grip strength (kg)[*]	35.87 (8.10)	34.37 (8.91)	32.98 (7.71)	32.05 (6.83)	p = 0.049	0.02–7.62	32.10 (7.70)	p = 0.0069[c]	1.17–6.36
FFM (kg)[*]	53.69 (8.16)	55.96 (9.06)	51.54 (5.89)	52.08 (6.70)	p = 0.37[e]	−0.98 to 2.49	50.05 (7.66)	p = 0.00003[c]	1.40–3.83
Serum albumin (mg/dl)[*]	44.35 (3.07)	39.58 (3.01)	41.20 (4.65)	42.95 (2.97)			43.75 (3.21)	p = 0.52[c]	−1.23 to 2.52
Energy intake (kcal/d)[*]	2016.20 (358.47)	2274.68 (951.81)	1892.46 (620.18)	1858.53 (711.94)			1947.0 (627.96)	p = 0.80[d]	−262.91 to 401.32
Protein intake (g/d)[*]	84.75 (23.86)	80.84 (43.85)	79.47 (31.80)	76.51 (30.93)			75.22 (25.64)	p = 0.23[c]	−6.16 to 24.02

[*] Mean, standard deviation (SD).
[†] Difference (baseline vs visit 3) 95% confidence interval.
[‡] Difference (baseline vs visit 4) 95% confidence interval.
[a] Wilcoxon signed rank sum test (baseline vs visit 2): V = 10, p-value = 0.0021.
[b] Wilcoxon signed rank sum test (baseline vs visit 4):V = 0, p-value = 0.01154.
[c] Paired t-test (baseline vs visit 4).
[d] Wilcoxon signed rank test(baseline vs visit 4): V = 102, p-value = 0.7983.
[e] Paired t-test (baseline vs visit 3).

Baseline: Visit at diagnosis.
Visit 1: post IC.
Visit 2: post RT.
Visit 3: 1 month post RT.
Visit 4: 3 months post RT.
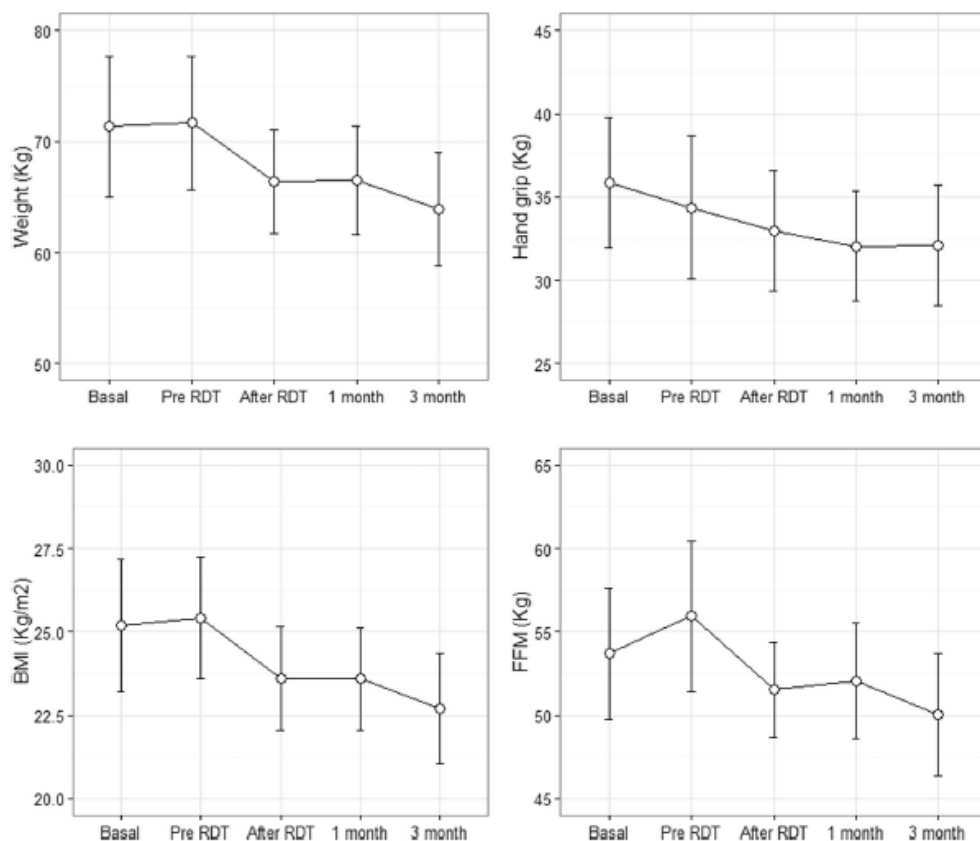
Fig. 1. Weight, BMI, HGS and FFM across treatment.

There were positive changes in body weight and energy intake during the iCT as most patients gain weight (n=13) and increased energy intake (n=14). These results are in agreement with Silver HJ et al. [36] study. The improvement of the symptoms that initially limited the oral intake may have contributed to these changes during the iCT. In our study dysphagia and odynophagia

Table 3
Toxicity due to concomitance.

	Visit 1		Visit 2		Visit 3		Visit 4	
	Number patients (%)							
Odynophagia								
G1-2	1	(5%)	13	(65%)	4	(20%)	4	(20%)
G3-4	0		2	(10%)	0		0	
Dysphagia								
G1-2	0		6	(30%)	4	(20%)	3	(15%)
G3-4	0		2	(10%)	0		0	
Asthenia								
G1-2	9	(45%)	5	(25%)	9	(45%)	5	(25%)
A/Dysgeusia								
G1-2	10	(50%)	8	(40%)	10	(50%)	5	(25%)
Nausea and vomits								
G1-2	3	(15%)	1	(5%)	0		0	
Anorexia								
G1-2	4	(20%)	4	(20%)	8	(40%)	9	(45%)
Mucositis								
G1-2	4	(20%)	14	(70%)	9	(45%)	1	(5%)
G3-4	0		3	(15%)	0		0	
Radiodermatitis								
G1-2	1	(5%)	11	(55%)	1	(5%)	1	(5%)
G3-4	0		3	(15%)	0		0	
Xerostomia								
G1-2	3	(15%)	9	(45%)	13	(65%)	12	(60%)

*Wilcoxon signed rank test: V = 102, p-value = 0.7983

**Test t: t = 1.2437, df = 18, p-value = 0.2296
**Diferencia de medias 8.93 95%CI -6.16-24.02
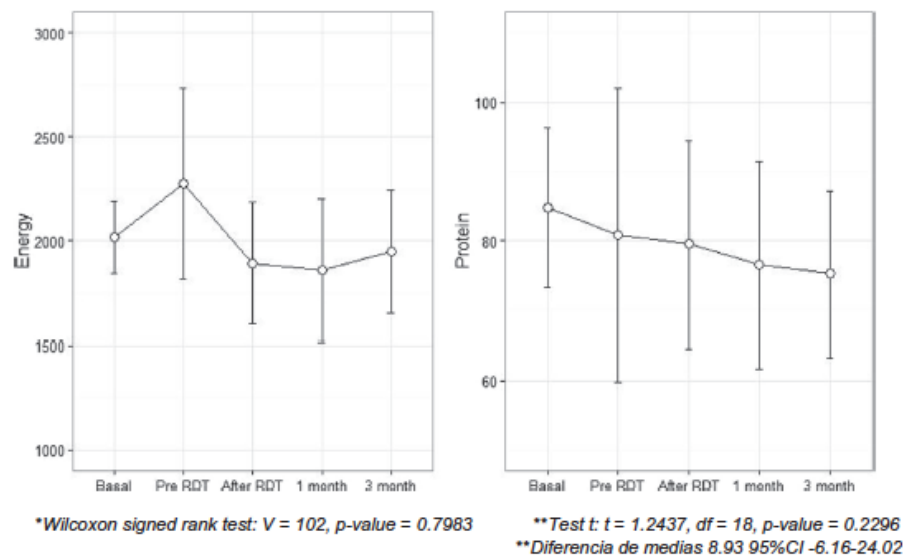
Fig. 2. Dietary intake throughout the treatment.

were the most frequent symptoms that affected our patients at diagnosis but after the iCT only one patient remained with dysphagia. There was also an increase in FFM despite a progressive deterioration in functionality according to the HGS. Data in the literature described that muscle mass and functionality are two different concepts and both can have clinical benefits [37,38].

Despite an intensive nutritional support along the oncological treatment, 95% of patients became malnourished and lost a median of 7.09 kg (IC95% 5.05–9.12), p < 0.0001 during the RT period. Some studies reported that early and intensive nutritional intervention can be beneficial in terms of minimize weight loss, improve quality of life and performance in head and neck cancer patients during RT [39]. Adherence to the nutritional treatment is usually complicated due to the acute toxicity: nausea and vomiting during chemotherapy, profuse thick saliva and odynodysphagia during chemoradiotherapy. In our hospital nutritional support is integrated as part of

the head and neck multidisciplinary unit and all patients are assessed in a multimodal supportive care [13,17] trying to optimize the best nutritional intervention according to the oncological treatment.

Once started the concomitance treatment all parameters (weight, FFM, BMI, energy and protein intake and HGS) decreased along with results reported in the literature [36,40–42]. Toxicity such as mucositis, odynophagia, dysphagia and anorexia affect our patients which may interfere to meet their nutritional requirements. Garcia-Peris P et al. [61] and Silver HJ et al. [47] described an increase in the BMR in head and neck cancer patients during treatment. Our patients, although maintaining a fair energy intake before and after treatment (before treatment was 2018.20 kcal/d (SD 358.47) and 1892.46 kcal/d (SD 620.18) after treatment), still failed to meet their nutritional requirements. We manage to maintain FFM and HGS up to one month after the concomitance in spite
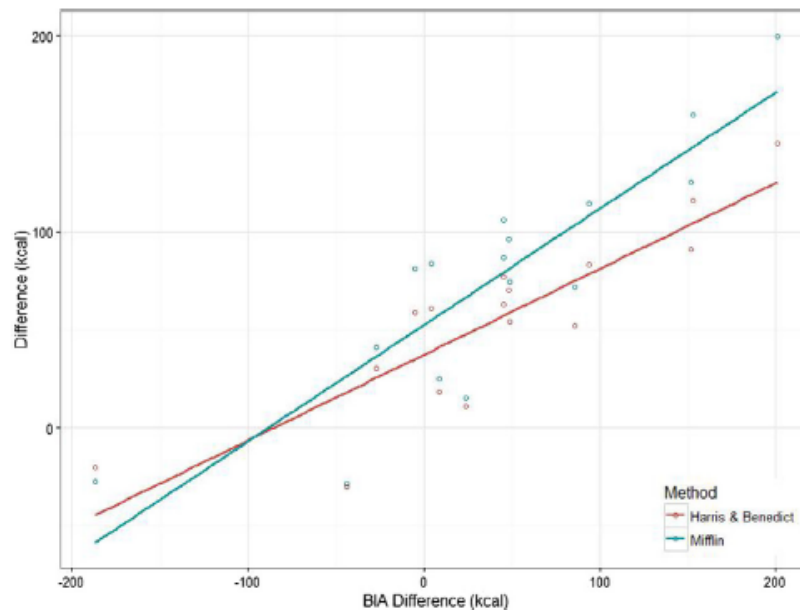
Fig. 3. Correlation between the baseline energy expenditure correlation according to BIA and the Mifflin-StJeor equations.

of a significant deterioration in weight and BMI. Probably the increase in FFM during the iCT minimizes the loss of it by the end of the treatment. One of the possible explanations is that although patients did not follow a standardized exercise program, we emphasized the importance of the physical activity and we provide them with small daily goals to incorporate in their daily life to increase physical activity. It may be helpful for future studies to add other test of physical activity from the lower limbs such as gait speed test or sit-to-stand test used for oncology elderly patients to measure physical performance [43–45]. In our study it becomes evident the nutritional deterioration that occurs in these patients even at 3 months post treatment. It is essential to maintain a close monitoring to optimize nutritional support and improve nutritional status as soon as possible.

There are still controversies about the use of prophylactic gastrostomies in head and neck cancer patients [46–48]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend the use of gastrostomies when enteral nutrition is needed over 6 weeks [29]. In our sample the need for enteral nutrition was 42.10 days (SD 15.88) delivered by nasogastric tube (n=7 patients) except for one patient that had a gastrostomy inserted before initiating the oncological treatment. We feel that a close monitoring from the oncology dietitian improves nutritional status and the return to a regular diet. 90% of our patients manage a regular diet after 3 months post treatment.

Furthermore, many studies have demonstrated the image of L3 at the computerized tomography (CT) as the reference method to measure body composition [49,50]. However head and neck cancer patients do not have this image available in a regular daily basis. Some authors have reported the use of BIA along the treatment as a method with a good consistency in application providing useful information [51–54], specially to assess FFM [41,53]. In addition, the noninvasive nature of BIA makes it particularly well suited for measuring longitudinal changes [52].

Inflammation has been also associated with key clinical outcomes and should be considered as part of nutritional assessment [40]. However we only consider albumin for the purpose of this study. The decrease of the albumin level was not significant

(p = 0.5216 [95%CI −1.23 to 2.52]) along the treatment and a correlation could not be established with the weight loss. It may be useful to associated C-reactive protein (CRP) with albumin level to note metabolic changes [40,55,56] throughout the oncological treatment in future studies.

This study has some limitations that should be noted. Firstly, the equations that employ the impedance measures are used to generate an estimation of fluid and other body composition compartments [57]. The validity and interpretation of maintenance in FFM through the treatment in our population need to be taken cautiously as the body composition values are estimated from changes in voltage across the body [58]. Secondly, the 24-h dietary recall may not be representative of the average daily intake of the patient. Some authors used 3 days food intake record [59,60]to better estimated the average intake. Thirdly, as mentioned earlier, we did not record CRP for the purpose of the study. We do not measure CRP on a daily basis unlike albumin level that comes with the blood sample previous to each cycle of chemo or bioradiotherapy. Fourthly, inclusion criteria for longitudinal studies with advanced head and neck cancer can be challenging to recruit and enroll a larger number of participants. Given these limitations and the single-center site for our data collection, additional research with a larger sample (including more females) could validate our findings.

In summary, despite an intensive nutritional support from the diagnosis throughout the oncological treatment in advanced HNSCC patients, nutritional status deteriorates. Our findings suggest that iCT in advanced HNSCC patients may help improve nutritional status by ameliorating the symptoms that limit the oral intake. This improvement in the nutritional status together with an intensive nutritional intervention could contribute to minimize further deterioration. We manage to maintain FFM according to BIA and HGS emphasizing energy and protein intake and physical activity until one month after treatment. Future investigations need to be done in advanced head and neck cancer patients involving novel approaches that combine nutritional support, anti-inflammatory agents and resistance physical activity to avoid interruptions along the treatment or dose adjustment due to poor performance status or weight loss to improve oncological survival.

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Conflict of interest statement

All authors declare that they have no financial relationship or any interest with any party related to this manuscript. Authors have full control of all primary data and agree to allow the journal to review the data if requested.

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ARTICLE 2

Arribas L, Sabaté-Llobera A, Taberna M, Pallares N, Narro Marin A, Virgili N, Hurtós L, Peiró I, Vilajosana E, Lozano A, Baracos V.E*, Mesía R*.

Adequacy of nutritional support using computed-tomography (CT) in patients with head and neck cancer (HNC) during chemo-radiotherapy (CRT).

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ARTICLE

Nutrition in acute and chronic diseases

Adequacy of nutritional support using computed tomography (CT) in patients with head and neck cancer (HNC) during chemo-radiotherapy (CRT)

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Abstract

We assessed forty HNC patients receiving treatment with curative intent. Specific quantitative muscle and fat changes were evaluated using CT. Nutrition support was provided according to ESPEN guidelines, with adjusted body weight (ABW) in overweight/obese patients used to define their nutritional targets. Linear regression models were used to evaluate clinical predictors of tissue loss. Mean overall losses were body weight (−10.5%), and CT-defined muscle (−8.4%) and fat mass (−24.8%), $p < 0.001$. A subset of 20 patients had high muscle loss (−14.7%) with concurrent negative energy balance as reflected by considerable fat loss (−29.7%); those tended to have higher baseline body mass index (26.2 vs. 23.3 kg/m^2, $p = 0.063$). In multivariate regression, only ABW independently predicted muscle loss ($p < 0.001$) and fat loss ($p = 0.002$). Nutrition support according to guidelines was appropriate for a subset of patients. ABW use to set nutrition targets in overweight/obese patients would appear to be insufficient, based on large tissue losses.

Introduction

Quantitative assessment of muscle loss over time during cancer treatment is rarely described despite low skeletal muscle mass (SMM) being a well-known prognostic factor [1]. Reduced food intake, disease burden and tumour response are factors associated with wasting of muscle and adipose tissue [2].

Adjusted body weight (ABW) was suggested as a logical means to account for the percentage of the obese weight that is most metabolically active [3] and is frequently used in clinical practice. Clinical management guidelines for obese cancer patients [4] do not include nutritional protocols.

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SPRINGER NATURE

We aimed to describe the changes in muscle mass during CTR chemo-radiation in locally advanced HNC patients and evaluate the clinical predictors implicate in this loss. A secondary analysis focused on the predictors of fat mass (FM) loss.

Material and methods

Population and study design

This longitudinal retrospective study was approved by the local Ethics Committees (PR365/18). All patients provided written informed consent. We focused on a curative intent treatment for locally advanced HNC based on induction chemotherapy followed by CRT [5]. Patients had a staging positron emission tomography–computed tomography (PET/CT) scan pre-treatment and at the evaluation response at 3 months of finishing RT.

Clinical and nutritional data

Clinical data included age, primary tumour site, stage and treatment response. Additional information regarding severe toxicity according to the CTCAE version 4.0 (2009) [6] were also collected.

All patients were assessed by an oncology dietitian during treatment. Nutritional data were collected at baseline (before starting treatment) and at evaluation of the tumour response according to RECIST criteria, version 1.1 [7]. These data included body mass index (BMI) [(weight (kg)/ height (m^2)], % weight loss in the last 3 months, nutritional status, type of nutritional support, serum albumin and nutrition impact symptoms (anorexia, dysphagia and ody-nophagia). Patients with BMI ≥ 25 kg/m^2 had their nutri-tional requirements calculated according to the ABW [3].

Image analysis

PET/CT scans at the 3rd lumbar vertebra were chosen as the reference point [8] using SliceOmatic$^©$ software (v5.0 Rev 8, Tomovision, Magog, Canada). Cross-sectional areas of muscle and adipose tissue were determined using tissue-specific HU range [8]. The muscle cross-sectional area was reported as SMI (cm^2/m^2). Sarcopenia was defined according to published thresholds [9]. Estimated kilograms of SMM and fat mass (FM) were calculated from regression equations [8].

Statistical analysis

To compare baseline and end of treatment values between groups, t-test (taking into account homogeneity of variances) and Chi-square tests were reported. Stratification was done according to the median. A linear regression model was used to assess the clinical predictors of muscle and adipose tissue loss over time. In multiple regression analyses, adjustments were made for tumour site, nutrition impact symptoms at baseline, ABW and severe toxicity. The statistical package used was SPSS v.23 (Chicago, USA) and R v.3.5.

Results

Forty patients were included, mainly male ($n = 38$, 95%) with a mean overall age of 56.8 years (SD 7.92), with oropharynx cancer ($n = 19$; 47.5%,) and stage IVb ($n = 21$; 52.5%). Nutrition impact symptoms were present in $n = 18$ (45%) patients: odynophagia in 15 (37.5%), dysphagia in 13 (32.5%) (five patients with grade 3 requiring tube feeding) and 5 (12.5%) patients with anorexia. Two or more symptoms were present in 14 patients (77.8%). ABW was used to calculate nutrient requirements in $n = 16$ (40%) patients.

During cancer treatment, the population overall lost weight, muscle and fat (Table 1). On average, patients lost 7.9 kg (range -31.30 to $+9.20$) of body weight during treatment corresponding to 2.1 kg (range -7.95 to $+3.02$) of estimated SMM and 4.6 kg of estimated FM (range -28.32 to $+9.95$). Patients with BMI ≥ 25 kg/m^2, i.e., patients with ABW calculated, lost more weight ($p < 0.0001$), muscle ($p = 0.004$) and fat ($p < 0.0001$) than those patients with BMI < 25.

A comparative table of patients who gained/maintained and those who lost SMM and FM are presented in Table 2. Patients who lost muscle mass during the treatment also lost adipose tissue ($p = 0.003$), BMI ($p < 0.001$) and weight ($p < 0.001$) developing malnutrition ($p = 0.029$) according to the PG-SGA. Sarcopenia was more prevalent after oncological treatment (from 45 to 75% after treatment; $p = 0.041$). Those patients who had lost more FM throughout the oncological treatment were those who had more adipose tissue at the beginning of the treatment ($p < 0.001$).

A complete tumour response was achieved in 29 (72.5%) at the end of treatment. Well-nourished patients were more likely to have a complete final response (OR = 7.00; $p = 0.038$) than severely malnourished patients.

In univariate regression analysis, only the adjustment of the nutritional support according to ABW in patients with BMI ≥ 25kg/m^2 was associated with muscle mass loss ($p < 0.001$). Fat loss also associated with nutrition support based on ABW ($p = 0.002$) and the presence of severe treatment toxicity ($p = 0.008$). ABW was also an independent predictor of muscle loss ($p = 0.001$) in the multivariable regression analysis including covariates adjustments were made for

Table 1 Nutritional and body composition parameters at baseline and at study endpoint (*n* = 40 patients).

	Time course			
	Baseline[a]	Three months post-treatment[b]	*p* value*	Δ Overall
Time between assessments (days)		202.0 (12.3)		
Time between CT scans (days)		223.6 (31.2)		
Weight (kg)	74.6 (14.4)	66.8 (11.8)	<0.001	−7.9 (6.9)
BMI (kg/m^2)	25.0 (4.5)	23.0 (3.3)	<0.001	−1.9 (2.3)
Serum Albumin (g/L)	43.3 (4.5)	43.3 (4.7)	0.397	−0.03 (5.2)
SMI (cm^2/m^2)	−4.2 (5.2)	51.5 (9.4)	47.3 (7.7)	<0.001
SMA (cm^2)	149.2 (30.1)	136.7 (22.9)	<0.001	−12.5 (15.3)
TATI (cm^2/m^2)	91.8 (56.3)	69.6 (38.3)	0.001	−22.2 (38.9)
TATA (cm^2)	270.1 (175.4)	203.0 (115.3)	0.001	−67.1 (113.4)
Est SMM (kg)	26.9 (5.0)	24.8 (3.8)	<0.001	−2.1 (2.5)
Est FM (kg)	22.5 (11.9)	17.9 (7.8)	0.001	−4.6 (7.7)
Sarcopenia	23 (57.5)	29 (72.5)	0.083	
Sarcopenic obese (BMI ≥ 25 kg/m^2)	3 (7.5)	4 (10)	0.655	
PG-SGA			0.024	
Well nourished (A)	25 (62.5)	13 (32.5)		
Moderately malnourished (B)	8 (20)	20 (50)		
Severe malnourished (C)	7 (17.5)	7 (17.5)		
Nutritional support			NA	
Dietetic counselling	25 (62.5)	9 (22.5)		
Oral supplements	10 (25)	19 (47.5)		
Tube feeding	5 (12.5)	6 (15)		
No support	0	6 (15)		

Values are expressed as mean ± standard deviation (SD) or (%). Time course comprises treatment naïve until the evaluation of the tumour response according to RECIST criteria. Patients lost weight, muscle and fat mass during the course of treatment. Malnutrition according to PG-SGA exacerbates along the treatment.

BMI body mass index, *SMI* skeletal muscle index, *SMA* skeletal muscle area, *TATI* total adipose tissue index, *TATA* total adipose tissue area, *Est SMM* estimated skeletal muscle mass, *Est FM* estimated fat mass.

Nutritional status according patient-generated subjective global assessment (PG-SGA) classified as A: well nourished, B: moderately malnourished and C: severe malnourished.

*Paired *t*-test for continuous data and McNemar for categorical data.

[a]Baseline defined as treatment naïve.

[b]End of treatment defined as 3 months after finishing the whole treatment.

tumour site (*p* = 0.066), nutrition impact symptoms (*p* = 0.087) and severe toxicity during the induction chemotherapy (*p* = 0.875). Fat loss was associated with the use of ABW to set nutrition targets (*p* = 0.007), tumour site (*p* = 0.053) and of nutrition impact symptoms at baseline (*p* = 0.052).

Discussion

Our data underline the importance of including body composition assessment in HNC patients during treatment. We use CT to reveal that intensive nutrition support according to guidelines results in maintenance of muscle/FM in only about a half of patients. Tissue losses are associated with four main factors: tumour site, nutrition impact symptoms at baseline, severe treatment toxicity and the use of ABW to set nutrition targets in overweight/obese patients. The extended practice of ABW-based nutritional support for obese patients exacerbates the fat loss. Although originally the use of ABW was designed for renal disease [3] and critically ill patients to prevent overfeeding [10], its use has been expanding to other clinical settings.

Body composition analysis in HNC patients who receive radical treatment is useful to monitor whether nutritional support is sufficient to maintain muscle and FM. There are no nutritional guidelines for obese cancer patients with specific approaches to calculation of nutritional requirements, and the implications of weight reduction during treatment with curative intent in obese patients is unclear. Nutrition targets based on ABW, a strategy commonly used

Table 2 Characteristics of patients who maintained muscle and fat mass during head and neck cancer treatment.

	Muscle stable/gain (n = 20)			Muscle loss (n = 20)			p value muscle stable vs. loss		p value Δ muscle stable vs. loss
	Pre-treatment	Post- treatment	p value	Pre- treatment	Post-treatment	p value	Pre-treatment	Post-treatment	Overall
SMI (cm²/m²)	47.22 (7.94)	47.0 (8.0)	0.781	55.80 (8.92)	47.66 (7.65)	**<0.001**	**0.003**	0.791	**<0.001**
TATI (cm²/m²)	77.34 (38.72)	63.97 (32.93)	0.118	106.24 (67.51)	75.20 (43.10)	**0.003**	0.107	0.361	0.154
BMI (kg/m²)	23.63 (3.79)	22.78 (3.23)	0.077	26.28 (4.87)	23.24 (3.36)	**<0.001**	0.063	0.657	**0.002**
Serum albumin (g/L)	42.4 (4.91)	42.94 (5.42)	0.789	43.80 (3.38)	43.63 (3.96)	0.656	0.315	0.678	0.640
Weight (kg)	71.0 (12.50)	65.34 (10.53)	**0.003**	78.18 (15.60)	68.18 (13.09)	**<0.001**	0.121	0.454	**0.003**
Sarcopenia (yes)	14 (70%)	14 (70%)	1	9 (45%)	15 (75%)	**0.041**	0.201	1	NA
PG-SGA			0.086			**0.029**	1.000	0.134	NA
Well nourished (A)	12 (60%)	7 (35%)		13 (65%)	6 (30%)				
Moderately malnourished (B)	4 (20%)	12 (60%)		4 (20%)	8 (40%)				
Severely malnourished (C)	4 (20%)	1 (5%)		3 (15%)	6 (30%)				
Nutritional support			NA			NA	**0.033**	0.549	NA
Dietetic counselling	12 (60%)	5 (25%)		13 (65%)	4 (20%)				
Oral supplements	3 (15%)	10 (50%)		7 (35%)	9 (45%)				
Tube feeding	5 (25%)	3 (15%)		0 (0%)	3 (15%)				
No support	0 (0%)	2 (10%)		0 (0%)	4 (20%)				

	Fat stable/gain (n = 20)			Fat loss (n = 20)			p value fat stable vs. loss		p value Δ fat stable vs. loss
	Pre-treatment	Post- treatment	p value	Pre- treatment	Post-treatment	p value	Pre-treatment	Post-treatment	Overall
SMI (cm²/m²)	49.50 (8.12)	47.10 (7.82)	**0.026**	53.53 (10.33)	47.56 (7.84)	**<0.001**	0.179	0.853	**0.029**
TATI (cm²/m²)	58.85 (38.67)	67.66 (39.11)	0.096	124.73 (52.16)	71.51 (38.35)	**<0.001**	**<0.001**	0.755	**<0.001**
BMI (kg/m²)	22.73 (3.18)	22.26 (3.34)	0.249	27.13 (4.62)	23.75 (3.08)	**<0.001**	**0.001**	0.151	**<0.001**
Serum albumin (g/L)	43.90 (4.90)	45.66 (2.98)	0.402	42.38 (3.34)	41.08 (4.94)	0.353	0.230	**0.003**	0.210
Weight (kg)	67.70 (9.36)	63.57 (9.77)	**0.002**	80.13 (18.10)	69.96 (13.01)	**<0.001**	**0.002**	0.088	**<0.001**
Sarcopenia (yes)	14 (70)	14 (70)	1	9 (45)	15 (75)	**0.041**	0.201	1.000	NA
PG-SGA			0.139			NA	0.815	1.000	NA
Well nourished (A)	13 (65%)	7 (35%)		12 (60)	6 (30)				
Moderately malnourished (B)	3 (15)	10 (50)		5 (25)	10 (50)				
Severely malnourished (C)	4 (20)	3 (15)		3 (15)	4 (20)				
Nutritional support			NA			NA	0.810	0.377	NA
Dietetic counselling	13 (65)	3 (15)		12 (60)	6 (30)				
Oral supplements	4 (20)	10 (50)		6 (30)	9 (45)				
Tube feeding	3 (15)	3 (15)		2 (10)	1 (5)				
No support	0	4 (20)		0	2 (10)				

Values are expressed as mean ± standard deviation (SD) or (%). As stratification for muscle and fat loss and gain/maintain was done according to the median so both groups have same number of patients. However, some patients that lost muscle or fat might fall into the stable/gain group.

BMI body mass index, *SMI* skeletal muscle index, *SM area* skeletal muscle area, *TATI* total adipose tissue index, *TAT area* total adipose tissue area, *PG-SGA* Patient-Generated Subjective Global Assessment,

NA not applicable.

These are the statistically significant values.

in heavier patients, would appear to be insufficient, based on large tissue losses.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Original article

Assessing dynamic change in muscle during treatment of patients with cancer: Precision testing standards

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SUMMARY

Background: Computed tomography images acquired during routine cancer care provide an opportunity to determine body composition with accuracy and precision. Quantification of skeletal muscle is of interest owing to its association with clinical outcomes. However, the standards of precision testing considered mandatory in other areas of radiology are lacking from the literature in this area. We aim to describe the change in skeletal muscle over time at different anatomical levels using the precision error.
Methods: Thirty-eight male patients with squamous cell carcinoma of the head and neck were evaluated at two time points encompassing their treatment plan. Precision testing consisted of analyzing the cross-sectional area (CSA) of the skeletal muscle and total adipose tissue of 76 CT studies (38 images at baseline repeated twice and 38 follow-up images repeated twice) measured by a skilled observer. The % coefficient of variation (%CV), the root-mean-square standard deviation (RMS SD) and the corresponding 95% least significant change (LSC) were calculated for four anatomical levels: upper arm, thigh, chest and abdomen.
Results: The median time between scans was 223.6 (SD 31.2) days. Precision error (% CV) for total skeletal muscle cross sectional area was 0.86% for upper arm, 0.26% for thigh, 0.39% for chest and 0.63% for abdomen. The corresponding LSC values in upper arm, thigh, chest and abdomen were 2.4%, 0.7%, 1.1% and 1.8%, respectively.
Based on the LSC for RMS SD, patients were classified in two categories according to muscle cross-sectional area: stable (i.e within LSC value) or gained and loss. To compare the four anatomical levels, the proportion of patients with muscle loss exceeding the LSC value was 74.3% for arm, 86.2% for thigh, 82.9% for chest and 76.3% for abdomen. For these same anatomic regions, the mean muscle loss for those patients classified below the LSC was 14.6% (SD 9.3), 13.4% (SD 7.8), 11.9% (SD 6.5) and 11.6% (SD 5.5), respectively. Only the loss of muscle area was significantly higher in thigh (p = 0.023), using L3 as the reference level.
Conclusions: We recommend the uniform use of a standard precision test when reporting muscle change over time. LSC values vary from 0.7 to 2.4% depending on anatomic site; with the lowest precision error to detect change in the thigh.

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Based on this analysis, muscle wasting appears to be systemic and while present in limbs and trunk is significantly higher in the thigh than in the chest, abdomen or upper arm.

1. Introduction

Quantification of skeletal muscle is of clinical interest as it relates to physical functioning, nutritional status, treatment tolerance and prognosis [1—3]. With the advent of image-based assessment of muscle and adipose tissue in CT images acquired during routine care, quantitative and specific measures have become accessible. To date more than 600 publications report the impact of muscle and adipose tissue in relation to oncological outcomes such as survival, surgical complications or chemotherapy toxicity [2,4—7]. Whether the studies include single time or repeated quantification of muscle, reporting on the repeatability of the measures is generally weak. In some studies, no measure of repeatability is included. In others, intra-observer (and inter-observer) coefficient of variability is mentioned however we could find none stating that they conformed to a radiological standard for precision testing.

The International Society for Clinical Densitometry (ISCD) has established the specific requirements to standardized practice and reporting in patients for both diagnosis and longitudinal measurements of body composition using Dual-energy X-ray Absorptiometry (DXA) [8]. In bone densitometry, it is mandatory to perform precision studies at regular intervals and for accreditation, each individual observer is required to achieve a minimum acceptable precision. The least significant change (LSC) value is a key performance metric for repeated measures over time. LSC is the least amount of change that can be considered statistically significant and is calculated based on the precision error [9,10]. For a change between two images to be considered statistically significant it must exceed the value for LSC since there is some statistical uncertainty in the magnitude of the measured variation [9]. In the radiological determination of body composition repeated measurements, the LSC value is the accepted standardized metric of variability both in research and in clinical practice [8,11,12] While measures of skeletal muscle in oncology patients have become widespread in research, these have not fallen in line with the precision criteria mentioned above and in addition to low standards of precision testing, we could find no instance of LSC value reported.

There are many outstanding research questions related to cancer-associated muscle wasting. Through a radiological lens, we are just beginning to learn the tissue-specific changes associated with cancer and treatment types [13]. It is unresolved as to whether the muscle loss experienced by patients with cancer occurs uniformly throughout the body. A current convention is to measure skeletal muscle in the abdomen and much of the literature concerns muscle measures in single images landmarked at the 3rd lumbar vertebra (L3). This practice was adopted because oncologic images are rarely of the whole body and a single image in the lumbar region is highly correlated with the whole-body organ volumes (i.e for muscle and adipose tissue) [14].

While a significant proportion of the literature on CT-body composition in patients with cancer has been focused on L3 for the reasons mentioned above, it has not yet been established whether the lumbar region is actually representative of muscle loss over time. The factors thought to be involved in cancer-associated muscle wasting are in large part systemic (e.g. reduced nutrition, tumor and inflammation-derived catabolic effector molecules),

however localized effects could also occur. In animal models of cancer oxidative fiber type muscles show reduced levels of atrophy relative to glycolytic ones [15], suggesting inherent susceptibility at the tissue level. Reduced physical activity causes muscle loss, and muscles of the lower limb show a larger degree of loss than muscles of the trunk or upper limb during bed rest [16,17]. We do not know yet exactly how specific cancer treatments affect the muscle over time and how modifying treatments such as exercise, nutritional support or hormone therapy can interfere with these changes. Thus, it is uncertain to what extent the loss of muscle mass in cancer patients is systemic or localized.

The first requirement to answer this question is CT images that cover the whole body or a large proportion of it. Even though oncologic images, generated in routine diagnosis and follow up, makes the evaluation of body composition clinically accessible, these are usually limited to abdominal, pelvic or thoracic studies, according to the primary site of disease and regions of suspected metastases. In clinical routine, PET-CT studies are intended to discover occult metastases, wherever they might lie, and represent the most extensive cancer imaging studies as they include the entire body with the exception of lower leg and feet. Patient populations followed by PET-CT include a variety of tumor sites, including cancers of the head and neck. We and others have previously reported on lumbar muscle and fat loss over time in patients with cancers of the head and neck [7,18]; these patients tend to be rather catabolic, with often considerable losses of fat and muscle over the course of treatments.

Based on the foregoing, we aim to describe the change in skeletal muscle over time at different anatomical sites (upper arm, thigh, chest and abdomen) using the precision error to be able to identify significant change in muscle over time correctly. A secondary analysis focused on the variation of total fat.

2. Methods

2.1. Population and study design

In this retrospective study, we evaluated thirty-eight male patients (n = 38) with locally advanced squamous cell carcinoma of the head and neck treated with curative intent treatment based on induction chemotherapy followed by chemo-radiotherapy (CRT) or radiotherapy (RT) plus cetuximab according to local guidelines [19]. This cohort has been described in detail previously [18]. Patients were consecutively selected from January 2010 to December 2017. Eligibility criteria included pathologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx or nasopharynx with no history of recurrent disease. Only patients with staging positron emission tomography-computed tomography (PET/CT) scan available as part of their pre-treatment diagnosis procedure (within a month before initiation of treatment) and at the evaluation response after treatment (three months of finishing RT) were included.

Clinical data were recorded at baseline and three months after the end of treatment coinciding with evaluation of the tumour response according to RECIST criteria, version 1.1 [20]. These data included age, sex, primary tumor site, treatment scheme and response, height, current weight and body mass index (BMI). Cross-

sectional area (CSA) of total muscle and total adipose tissue were determined for each anatomical level.

The study was approved by the Hospital Universitari de Bellvitge Ethics Committee for Clinical Research (PR365/18). All patients provided written informed consent.

2.2. Image analysis

A PET/CT study was performed at the time of the diagnosis (baseline) and 3 months after finishing RT (post-treatment) and were used for the image analysis (i.e., an overall span of 7–8 months). PET/CT scan was used to analyze lumbar and thoracic images (L3 and T4), upper arm and thigh. For image analysis, standardized landmarks at different levels were selected by choosing the most comparable image between baseline and post-treatment scans of each patient. Images were obtained from the axial cross-sectional CT component of the whole-body PET/CT scans.

The 3rd lumbar (L3) vertebra was chosen on the axial cross-section CT component of the whole-body PET/CT scans as the reference point to calculate the muscle cross-sectional area (CSA), based on previous reports with this level [14,21,22]. In the thorax, the reference landmark was the 4th thoracic vertebra (T4), as this level is representative of the different muscular structures contained in the area (pectoral muscles, external intercostal, serratus anterior, teres major, subcapularis, infraspinatus, rhomboid major, erector spinae and trapezius) and has been analyzed in previous publications [23,24]. At L3 and T4, the landmarks selected were those showing the entire vertebral arc and the transverse and spinous processes. The upper arm landmark was 11.25 mm above the acromioclavicular joint in the left upper limb (arms raised) and included bicep brachii, coracobrachialis, deltoid and triceps brachii muscles. However, in some cases, these images were difficult to assess properly due to the different positioning of the arms in the baseline and post-treatment PET/CT of the same patient. Thigh images were also included in the analysis. Images from the left lower limb were 11.25 mm below the lesser trochanter of the femur including rectus femoris, sartorius, vastus intermedius, vastus lateralis, adductor, gracilis, gluteus maximus, biceps femoris and semitendinous muscles.

From the original dataset of 40 patients (Fig. 1), two women were excluded in order to analyze a homogeneous group of men. Moreover, we rejected 3 patients' images acquired for T4 and upper arm due to patient's position (arms were raised at baseline and lowered after treatment and no space between arms and the body to identify both CSA of T4 and upper arm). One patient was dismissed at the thigh level due to patient's position.

Initially, we also selected the 3rd cervical vertebra (C3) as it was suggested by Swartz JE et al. to be a landmark for head and neck cancer patients with images confined to the head and neck [25]. However, 25 out of 38 (65.8%) of the patients at C3 level were rejected due to the differences in the position of the neck and the limitation of the anatomical changes in tumor size or lymph nodes after treatment. Since so many patients were excluded, the number available did not meet ISCD recommendations for a minimum of 30 subjects for a precision test, we decided to rule out this level for the purpose of this study.

Precision testing was based on CSA values of the anatomic skeletal muscles listed above, as well as adipose tissue in the selected anatomical regions. The Hounsfield Unit (HU) range is a standardized element of the annotation and this is standardized in the literature [21] to maintain uniformity of pixel identification within each given anatomical structure. The HU range from −29 to +150 HU using SliceOmatic© software (v5.0 Rev 8, Tomovision, Magog, Canada). Predetermined Hounsfield unit (HU) thresholds

for total adipose tissue (TAT) was −50 to −190 HU [14,26,27]. Total adipose tissue CSA was determined in cm^2 for L3, T4, thigh and upper arm.

Values were obtained by a single observer (IA) blinded to the patients' data. An independent expert on anatomical radiology was consulted regarding all anatomical questions.

For the PET/CT studies, images were acquired either in a Discovery ST or in a Discovery IQ scanner (GE Healthcare, Waukesha, WI), according to standard recommendations for oncologic purposes [28]. Scanning protocol included a torso imaging (from the skull base to mid-thigh), with arms raised above the head, when possible, plus a dedicated head and neck acquisition, performed immediately after the torso images. In all cases the CT sequence of the PET/CT was a helical, low-dose, non-contrast enhanced CT, applying 120 kV and modulated intensity, and with a slice thickness of 3.75 mm. Baseline and post-treatment examinations of the same patient were performed at the same PET/CT scanner.

2.3. Precision test

Precision describes the ability of a quantitative measurement technique to reproduce the same numerical result when repeatedly performed in an identical manner i.e consistent CSA of muscle values on repeated measurements of the same patient over a period of time when real change would not be expected to occur, to monitor small variations in serial measurements [29]. Precision error was measured analysing twice 76 images (38 images at baseline repeated twice and 38 follow-up images repeated twice) previously selected [9,10]. Precision error was calculated by the percentage coefficient of variation (%CV) and by the root-mean-square standard deviation (RMS SD) with the least significant change (LSC) for %CV and for RMS SD at four anatomical levels: upper arm, thigh, chest and abdomen for monitoring muscle and fat changes. RMS SD is the ISCD-recommended form for expression precision error [29]. The precision test was performed via repeated measurements by the same observer (IA) using the same image.

The observer (IA) has extended experience in body composition analysis using imaging techniques. Analysed images were reviewed by an expert on anatomical radiology who was also blind to the data.

2.4. Statistical analysis

Sample size was calculated based on previously established methodology described in the White Paper of the ISCD when performing a precision test (i.e 30 images measured in duplicate or 15 images measured in triplicate) [29]. Precision and the chosen confidence interval (CI) for precision error determines the LSC for skeletal muscle, which represents a statistically significant change in the patient's muscle and not simply owing to random errors in the measurements. The assessment of the precision error was carried out by referring to the ISCD recommendation [9,29]. The precision error was calculated as RMS SD of a set of measurements in cm^2. The %CV was calculated as the RMS SD divided by the mean and expressed as a percentage.

Once the precision error of the measurements is known, the magnitude of the change in muscle at the different anatomical levels that indicates real biologic change can be determined by the LSC [9]. The 95% confidence LSC was defined for each RMS-SD and RMS-CV precision error estimate by multiplying by 2.77 [29].

Pearson correlation coefficient was used to study the association of muscle and fat loss between all different anatomical levels. Statistical significance was set at a probability level ≤0.05. The statistical package used to treat the data and perform the statistical analysis was R software version 3.5.
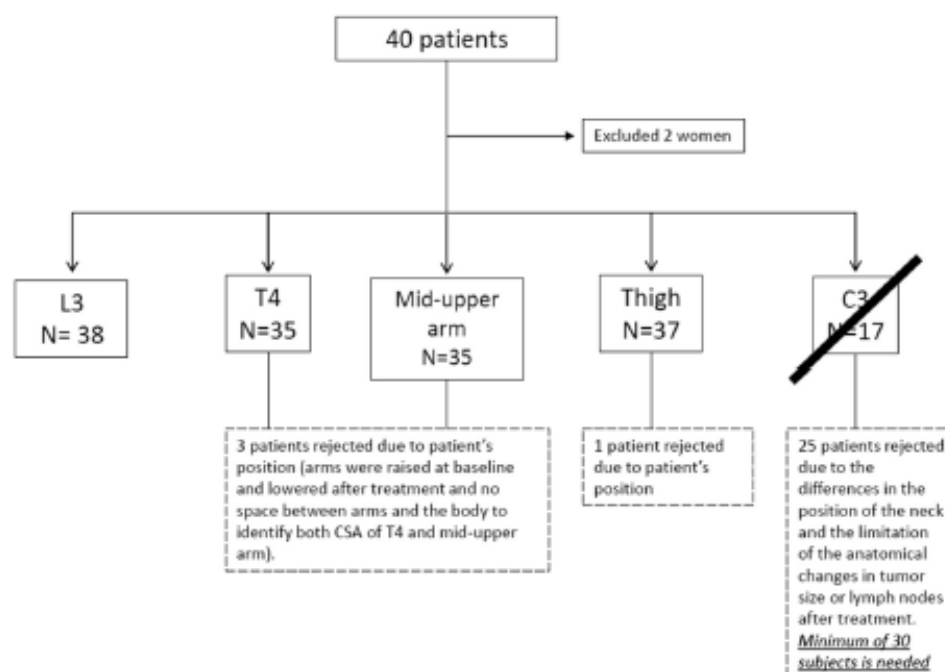
Fig. 1. Flow chart.

3. Results

3.1. Clinical data

The clinical profiles of patients are presented in Table 1. All were male and the mean age was 56.5 (SD 7.1) years. The mean scan interval was 223.6 (SD 31.2) days. The mean overall percentage weight loss was −7.7% (SD 7.6) during treatment.

3.2. Precision test

We evaluated the precision error for each CSA at the four anatomical levels. After analyzing 76 images twice, the precision error and the LSC of muscle and adipose tissue measurements at the four anatomical levels are presented in Table 2.

Precision errors defined as %CV (RMS SD) for total skeletal muscle CSA were 0.86% (0.66 cm^2) for upper arm, 0.26% (0.33 cm^2) for thigh, 0.39% (0.76 cm^2) for thoracic level and 0.63% (0.92 cm^2) for abdominal level (Table 2). The corresponding LSC (LSC $_{RMS\ SD}$) values in upper arm, thigh, T4 and L3 were 2.4% (1.8 cm^2), 0.7% (0.9 cm^2), 1.1% (2.1 cm^2) and 1.8% (2.6 cm^2), respectively.

Precision errors were also calculated for total fat CSA according to %CV and RMS SD and the corresponding LSC (Table 2). The precision error was 1.49% for upper arm, 4.73% for thigh, 6.53% for T4 and 1.37% for L3. The LSC $_{%CV}$ for upper arm was 4.1%, 13.1% for thigh, 18.1% for T4 and 3.8% for L3.

3.3. Muscle loss over time

Most of the patients had lost a significant amount of muscle after the treatment. Based on the LSC according to RMS SD recommended by the ISCD for expression precision error, patients were classified in 2 categories according to the change in muscle

CSA: patients with stable/gain or loss of muscle. In order to compare the four regions (Table 3), 26 out of 35 patients (74.3%) lost muscle CSA more than the LSC value in the arm region, 86.5% (32 out of 37) loss muscle in the thigh, 82.9% (29 out of 35) in the thoracic and 76.3% (29 out of 38) in the abdominal region. The mean muscle loss was 14.6% (SD9.3), 13.4% (SD7.8), 11.9% (SD6.5) and 11.6% (SD5.5), respectively for arm, thigh, T4 and L3. Figure 2 shows the relationship of muscle loss between all different anatomical levels. The sites that capture the most patients classified as loss of muscle were the thigh and L3 which covered 74.3% of those patients classified in the category of loss of muscle. Patients with BMI ≥25 kg/m^2 at diagnosis lost almost five times more muscle than those with BMI <25 kg/m^2 (4.9 vs 23.7 cm^2; p < 0.0001).

Using L3 at the reference landmark, we analyzed those patients with muscle loss in both L3 and another anatomical level. Thus, we observed that there were no statistical differences between the muscle loss in L3 and T4 or the mid-upper arm (p = 0.50 and p = 0.73, respectively). However, patients lost significantly more muscle in the thigh than at any part of the body (p = 0.02). No other statistically differences were observed in any other paired landmarks.

3.4. Fat loss over time

Total adipose CSA loss at all anatomical levels was substantial (Table 3). Using the LSC value, patients classified as having loss of adipose tissue greater than −34.4% (SD20.0) of fat at L3, −27.3% (SD13.5) at T4, −19.8% (SD11.5) in thigh and −32.0% (SD15.8) in the upper arm. There were no statistical differences in adipose tissue loss between any anatomical levels using L3 as the reference landmark. When looking at the loss of adipose tissue according to BMI, there was significantly greater depletion in overweight and obese patients (23.9 vs 131.5 cm^2; p = 0.006) comparing with patients with BMI <25 kg/m^2.

44

Table 1
Characteristics of patients.

	Baseline (n = 38)[a]	End of treatment (n = 38)[a]	P value
Weight (kg)	72.9 (16.6)	67.0 (11.8)	<0.001
BMI (kg/m²)	25.1 (4.5)	23.1 (3.3)	<0.001
	N (%) patients	N (%) patients	
BMI classifications (kg/m²)			
Underweight (<18.5)	2 (5.3)	4 (10.5)	
Normal weight (18.5–24.9)	21 (55.3)	27 (71.1)	
Overweight (25.0–29.9)	11 (28.9)	7 (18.4)	
Obese (>30.0)	4 (10.5)	–	
	Baseline	End of treatment	
For L3	**n = 38**	**n = 38**	
SMA (cm²)	150.5 (28.1)	138.1 (21.2)	<0.001
SMI (cm²/m²)	52.0 (8.7)	47.9 (7.1)	<0.001
TATA (cm²)	272.3 (176.2)	205.7 (115.1)	0.001
TATI (cm²/m²)	92.6 (56.2)	70.6 (38.3)	0.002
For T4	**n = 35**	**n = 35**	
SMA (cm²)	193.0 (29.8)	173.7 (22.3)	<0.001
SMI (cm²/m²)	66.8 (8.8)	60.3 (7.7)	<0.001
TATA (cm²)	144.0 (78.4)	122.1 (56.6)	0.006
TATI (cm²/m²)	49.3 (25.1)	41.8 (18.1)	0.003
For upper arm	**n = 35**	**n = 35**	
SMA (cm²)	78.3 (15.0)	71.4 (14.5)	0.002
SMI (cm²/m²)	27.1 (4.5)	24.8 (5.3)	0.004
TATA (cm²)	31.4 (22.4)	26.8 (17.5)	0.026
TATI (cm²/m²)	10.6 (6.9)	9.2 (5.5)	0.079
For thigh	**n = 37**	**n = 37**	
SMA (cm²)	135.9 (23.5)	119.9 (16.9)	<0.001
SMI (cm²/m²)	46.8 (6.5)	41.4 (5.2)	<0.001
TATA (cm²)	93.7 (49.0)	85.6 (36.8)	0.055
TATI (cm²/m²)	31.9 (15.2)	28.7 (12.2)	0.013

SMA, skeletal muscle area; TATA: total adipose tissue area; BMI, body mass index.
[a] Data are means ± standard deviation (SD).

4. Discussion

This is the first study to present a precision test according to the LSC using CT images to discriminate biological change from measurement error and evaluate the changes of muscle over time simultaneously in four different anatomical levels. Within a pre-specified and well-characterized understanding of the measurement error, we have determined that muscle loss in this patient population is systemic in the sense that every muscle group and every muscle level is implicated. However, the muscle loss from the lower limbs is significantly greater than other levels. In the discussion, we will describe the methodological and physiological findings in two separate sections.

4.1. Methodological considerations

Use of CT for the assessment of body composition in cancer patients is increasingly more common, not only using the diagnostic image as a predictor biomarker but also evaluating the

changes over time using a specific landmark [4,5]. As in longitudinal studies using DXA for bone density or body composition assessment, changes over time should first establish the precision of the measurements [8,29]. Our precision findings are very consistent with the precision demonstrated in DXA measurements [8] of bone, lean and soft tissue whole body and regional compartments. In CT studies measurements are made on a single slice; therefore, although CT measures have a good precision for muscle, our precision test specifically for fat is poor compare with same precision test for DXA shown in other studies [30–32]. So, it is important to bear in mind that we are looking at precision test for cross-sectional area in specific anatomical levels in CT images while DXA measures whole body compartments. It would be interesting to compare our results with other precision studies performed for CT imaging. Nevertheless, intra-observer and inter-observer precision have been reported in other studies. Intra-observer reliability of CSA imaging is usually reported with good agreement between repeated measurements using CT images [33,34] although precision error associated with patient positioning and slice selection using CT imaging increase up to 2.5% in the same individual. A recent study investigate the intra- and interobserver variability in skeletal muscle measurements of three experienced radiologists using computed tomography images [34]. Intra-observer variability was low reporting data between 1.57% and 2.89% for a single slice while comparison between radiologists showed that the measurement variability reduced as the fraction of repeat measurement taken at the same slice increased. Anatomic variations and technical issues may both contributed to variability among experts.

Our precision at the different anatomical levels varies from 0.7 to 2.4%. Interestingly, the best precision is observed in the thigh; thus, this level could be considered when looking to detect small changes over time. Intervention studies assessing physical function could benefit in evaluating changes that occur during the course of the intervention.

4.2. Physiological considerations

The dynamics of muscle changing is given by known or unknown determinants of this change over time. Animal studies have shown us that there are certain muscle types more prone for muscle wasting. Studies in mice reported results comparing fast contracting muscles with slow contractors with different fiber type [35]. These studies revealed that fast fibers are more susceptible in cachexia and other acute catabolic states [35,36], so the type of fiber within the muscle is a factor for muscle wasting. In humans, the majority of muscles are mixed fiber types and the investigations are focused on muscle groups with a mixture of fiber types. In our study we did not examine specific fiber type or specific muscles, our purpose was to evaluate an aggregate effect on groups of muscles which were likely to be representative of the overall muscularity and four different levels. In spite of selecting a population with similar clinical features and treatment, our findings show an important inter-individual

Table 2
Precision error and least significant change (LSC) of the cross-sectional area (CSA) for **muscle** (cm²) and **adipose tissue** (cm²).

	Total muscle area				Total adipose tissue area			
	Precision		LSC (95% CI)		Precision		LSC (95% CI)	
	RMS SD	% CV	LSC $_{RMS\ SD}$	LSC $_{\%\ CV}$	RMS SD	% CV	LSC $_{RMS\ SD}$	LSC $_{\%\ CV}$
Upper Arm (n = 35)	0.66	0.86	1.8	2.4	1.49	6.0	4.1	16.6
Thigh (n = 37)	0.33	0.26	0.9	0.7	4.73	2.21	13.1	6.1
T4 (n = 35)	0.76	0.39	2.1	1.1	6.51	3.63	18.0	10.0
L3 (n = 38)	0.92	0.63	2.6	1.8	1.37	2.21	3.8	6.1

RMS SD, root-mean-square error standard deviation; %CV, % coefficient of variability; LSC, least significant change; LSC $_{RMS\ SD}$, least significant change for the for the root-mean-square deviation; LSC $_{\%CV}$, least significant change for the for the root-mean-square percent coefficient of variation.

45

Table 3
Muscle and fat change over time according to least significant change (LSC) value.

| | All | Muscle area | | | | | Adipose tissue area | | | | |
| | | Maintained within the LSC value or gained | | Loss ($>LSC_{RMS\ SD}$) | | | Maintained within the LSC value or gained | | Loss ($>LSC_{RMS\ SD}$) | | |
	N	N (%)	Mean (SD)	N (%)	Mean (SD)	p-value	N (%)	Mean (SD)	N (%)	Mean (SD)	P-value
Upper arm	35	9 (25.7)	11.7 (9.9)	26 (74.3)	−14.6 (9.3)	0.73	15 (42.9)	41.9 (41.7)	20 (57.1)	−32.0 (15.8)	0.31
Thigh	37	5 (13.5)	5.9 (5.7)	32 (86.5)	−13.4 (7.8)	**0.02**	14 (37.7)	14.3 (9.6)	23 (62.3)	−19.8 (11.5)	0.51
T4	35	6 (17.1)	3.0 (0.8)	29 (82.9)	−11.9 (6.5)	0.50	13 (37.1)	19.7 (33.1)	22 (62.9)	−27.3 (13.5)	0.33
L3[a]	38	9 (23.7)	4.2 (3.5)	29 (76.3)	−11.6 (5.5)		10 (26.3)	48.5 (72.6)	28 (73.7)	−34.4 (20.0)	

LSC, least significant change; LSC$_{RMS\ SD}$, least significant change for the for the root-mean-square deviation.
Values statistically significant are marked in bold.
[a] Used as the reference landmark to measure the loss.

variability as muscle changes range from positive to very negative. We have a well-powered sample, with precise measurements comparing different anatomical levels within individuals. Patients with higher BMI lost more muscle mass as well as adipose tissue than those with lower BMI. As we observed in a previous publication [18], patients with higher baseline BMI had greater muscle loss (≥25 vs <25 kg/m^2, p < 0.001). In obese patients where muscle loss is not readily visible, imaging allows us to quantify these changes over time with sensitivity and specificity. Higher BMI at diagnosis does not protect against muscle wasting. Currently there are no nutrition clinical practice guidelines for obese cancer patients on weight management (or body composition management); therefore, nutritional intervention is just as necessary as for patients with lower BMI in the same clinical situation.

Based on our findings, muscle wasting appears to be systemic although with stronger effect in the thigh. We do not have any data at this time to explain the cause of this outcome. However, the signals causing muscle wasting in a patient with cancer may be presumed to be mostly systemic in nature. Blood borne factors such as inflammatory cytokines would reach all muscles, and the effect of decreased food intake would be expected to impact all muscles [37,38]. A local effect could be potentially explained by changes in a specific region such as the activity used of the lower limbs

[16,17,39]. In the future, a reduction in activity in the lower limbs might be detected by the use of actigraphy or other methods used in different parts of the body studied along with the changes over time in the muscle mass.

Our study has some limitations that should be noted. The main one is that was a single observer study, the precision error is unique to this observer and comparisons with other observers will be needed to establish what can reasonably expected in this type of studies. Moreover, precision error calculated for bone densitometry involves patient's positioning and operator-related factor. Since CT studies entail high doses of radiation (DXA~0.003 mSv versus CT~12 mSv), we have reviewed the images available as part of each patient's routine clinical procedure, so repeated scanning as not performed. Another important limitation is that we have evaluated only male patients since head and neck cancer incidence in Southern Europe is more frequent in men but adipose tissue and muscle loss may differ in males and females. Moreover, the retrospective design of the study is also a limitation.

In conclusion, we recommend the uniform use of a standard precision test when analyzing changes over time in muscle with CT images. Significant loss of muscle and fat occurred in head and neck cancer patients during radiotherapy-based treatment. Based on our results, the rate for muscle loss is higher in the lower limbs than in the chest, abdomen or upper limbs. Further studies should investigate causes of regional muscle loss in this group of patients and whether specific interventions may attenuate or restore this loss during treatment. Moreover, additional studies are needed to understand whether similar patterns of loss are also occurring in women.

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Statement of authorship

LA, LM, RM, VB contributed to the conceptualization of the study and methodology. LA, MS and ARGT participated in the software with the validation of ASLL and MC. The formal analysis was performed by NP. MT, RM and LA contributed to the investigation and resources. LA prepared the original draft. RM and VB supervised the study. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
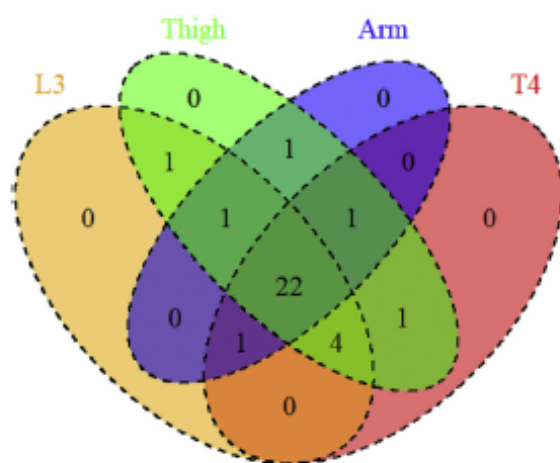
Fig. 2. Relationship of muscle loss between the four anatomical levels: L3, thigh, upper-arm and T4. This Venn diagram represents the distribution of patients depending on muscle loss at the different anatomical levels. A total of 35 patients are included in this diagram with the four measurements. 22 patients lost muscle in all levels, 4 patients lost in thigh, T4 and L3; one patient lost in thigh and T4; one patient lost in upper-arm and thigh; one patient lost in L3, upper-arm and thigh; one patient lost in upper-arm, T4 and thigh and one patient lost in upper-arm, T4 and L3.

46

Acknowledgements

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ARTICLE 4

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Predictive Value of Skeletal Muscle Mass in Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma Patients Treated With Immune Checkpoint Inhibitors

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Background: Reduced muscle mass has been associated with increased treatment complications in several tumor types. We evaluated the impact of skeletal muscle index (SMI) on prognosis and immune-related adverse events (IrAEs) in a cohort of recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) treated with immune checkpoints inhibitors (ICI).

Methods: A single-institutional, retrospective study was performed including 61 consecutive patients of R/M HNSCC diagnosed between July 2015 and December 2018. SMI was quantified using a CT scan at L3 to evaluate body composition. Median baseline SMI was used to dichotomize patients in low and high SMI. Kaplan-Meier estimations were used to detect overall survival (OS) and progression-free survival (PFS). Toxicity was recorded using Common Terminology Criteria for Adverse Event v4.3.

Results: Patients were 52 men (85.2%) with mean of age 57.7 years (SD 9.62), mainly oral cavity (n = 21; 34.4%). Low SMI was an independent factor for OS in the univariate (HR, 2.06; 95% CI, 1.14–3.73, p = 0.017) and multivariate Cox analyses (HR, 2.99; 95% CI, 1.29–6.94; p = 0.011). PFS was also reduced in patients with low SMI (PFS HR, 1.84; 95% CI, 1.08–3.12; p = 0.025). IrAEs occurred in 29 (47.5%) patients. There was no association between low SMI and IrAEs at any grade (OR, 0.56; 95% CI, 0.20–1.54; p = 0.261). However, grades 3 to 4 IrAEs were developed in seven patients of whom three had low SMI.

49

Conclusions: Low SMI before ICI treatment in R/M HNSCC patients had a negative impact on OS and PFS. Further prospective research is needed to confirm the role of body composition as a predictive biomarker in ICI treatment.

Keywords: head and neck (H&N) cancer, body composition, muscle mass, immune checkpoint inhibitors, sarcopenia, immune-related adverse events (irAE)

INTRODUCTION

Among patients with head and neck squamous cell carcinoma (HNSCC), between 5% and 10% are diagnosed with metastatic disease. Additionally, despite aggressive multimodal strategies, about 60% of patients treated with radical intention for a locally advanced disease will eventually recur (1). Until the introduction of immunotherapy agents, the median survival was 10.1 months, with an 82% rate of grades 3 to 4 adverse events using the historic standard first-line EXTREME (combining platinum and 5-fluorouracil (5-FU) and cetuximab) (2). Patients with progressive disease after platinum-based chemotherapy have a poor prognosis with a 1-year survival under 5% (3). Hereby, there is an urgent need for improved therapy in the recurrent and metastatic (R/M) population.

Targeting the programmed cell death (ligand)-1 (PD-(L)1) pathway has shown significant activity, and improved overall survival (OS) in patients with previously treated R/M HNSCC, associated with fewer grades 3 or 4 toxicities than standard therapy (4, 5). These results have led to approval of two anti-PD1 agents (pembrolizumab and nivolumab) as second-line treatment for patients with R/M HNSCC who experience disease progression on or after a platinum-based therapy (6, 7). More recently, pembrolizumab has been approved in the first-line setting, alone or in combination with chemotherapy (8). Despite improving the results compared with older strategies, approximately 70% of patients do not benefit from immune checkpoint inhibitors (ICI) as they have progression as the best response, enhancing the need for predictive biomarkers (6, 8).

Patients with R/M HNSCC are at an increased nutritional risk, and malnutrition has been shown to be an independent indicator of prognosis in cancer patients (9). The nutritional deterioration of HNSCC patients is often present from diagnosis and worsens throughout onco-specific treatments (10). This deterioration does not only occur exclusively at the expense of weight alone but also because the loss of muscle mass has been shown to associate with prognosis and complications (10, 11).

Sarcopenia, defined as a reduced skeletal muscle mass that reduce muscle function, is noted in geriatric populations (12). Reduced muscle mass is also prominent in patients at any age with different chronic diseases, including cancer. This is also termed sarcopenia, and it is typically classified in relation to the risk of disease-specific outcomes, such as mortality, surgical complications, or cancer treatment (13). Sarcopenia has been reported to have a significant impact on both OS and complications in cancer patients undergoing onco-specific treatment and/or surgery (14). These results have also been described in head and neck cancer patients (15–18). Although some studies have revealed that low muscle mass may also have a role in the oncological outcomes in patients with melanoma (19, 20) or lung cancer (21, 22) treated with ICI, as far as we know, there are no current studies evaluating the impact of low muscle mass in R/M HNSCC undergoing these therapies.

We aim to evaluate the muscle mass as a predictive biomarker of OS and progression-free survival (PFS) in patients diagnosed with R/M HNSCC treated with ICI. A secondary analysis focused on the association of muscle mass on the onset of immune-related adverse events (IrAES).

MATERIALS AND METHODS

Population and Study Design

This longitudinal retrospective single-center study was approved by the local ethics committee for clinical research (PR302/18). All patients provided written informed consent. Patients diagnosed with R/M HNSCC treated with ICI, regardless of treatment line, from July 2015 and December 2018 at the Catalan Institute of Oncology, were evaluated. Patients were eligible if they had R/M HNSCC and were treated with ICI including anti-PD1 or anti-PDL1 alone or in combination with other ICI (such as anti-CTLA4) or chemotherapy and had a staging full-body computed tomography (CT) scan as part of their pre-treatment procedure (within 10 days prior to the introduction of ICI) and at evaluation of tumor response according to RECIST criteria, version 1.1 (23).

Clinical data included age, sex, smoking status, alcohol consumption, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), TNM on Cancer (7th edition) (24), primary tumor site, treatment line for R/M disease, type of recurrence prior ICI, and response. Those patients, who had received the last dose of platinum 6 months before of initiation of ICI, were classified as platinum-refractory. Additional information regarding IrAEs according to the CTCAE version 4.3 2009 (25) and vital status were also collected from medical records.

Nutritional data were collected at baseline (before starting treatment). These data included body mass index (BMI calculated as [(weight (kg)/height (m)^2)], serum albumin levels, and type of nutritional intervention if any.

Image Analysis

All treatment images were selected by a trained researcher to ensure they correspond to the same vertebra landmarks to allow a proper comparison of body composition. Values were obtained by a single observer blinded to the patients' data.

Images were accessed from the axial cross-sectional CT as all patients had an abdominal CT scan as part of their routine care. The third lumbar (L3) vertebra was chosen on the axial cross-section CT component of the full-body CT scans as the reference point, based on previous reports with this level to calculate the skeletal muscle index (SMI) (26, 27) using SliceOmatic© software (v5.0 Rev 8, Tomovision, Montreal, Quebec, Canada). Regional analysis at L3 strongly predicted whole-body fat and fat-free mass (r=0.86-0.94; p < 0.001) (26). Muscle cross-sectional area (CSA) was quantified within a Hounsfield unit (HU) range from -29 to +150HU and then normalized for height to report as SMI (cm²/m²). Sarcopenia was defined according to Martin L et al. (28) using specific SMI cut points for advanced cancer patients. CSA of adipose tissue were determined using tissue-specific HU range defined at this level (29).

Statistical Analysis

To define cohort characteristics, categorical variables were presented as the number of cases and percentages, whereas continuous variables were presented as the mean and standard deviation (SD) or median and interquartile range (IQR). Median baseline SMI was used to dichotomize patients in two groups: low SMI (patients with baseline SMI lower than median baseline SMI) or high SMI (patients with baseline SMI equal or higher than median baseline SMI).

It was planned to test for the effect of baseline SMI on survival. Time between treatment initiation and disease progression or death from any cause (PFS) and time between treatment initiation and death from any cause (OS) was assessed using the Kaplan-Meier estimator. One-year OS rate and 1-year PFS rate were also analyzed. The Cox proportional hazards model was used to perform univariate and multivariate survival analyses, which are reported as the hazard ratio (HR) and 95% confidence interval. Covariates with a p-value lower than 0.1 in the univariate model were included in the multivariate models. The proportionality of risks in the Cox model was verified using the Schoenfeld residuals.

To evaluate the effect of baseline variables in the development of toxicity, logistic regression models were used. Odds ratios and their corresponding 95% confidence intervals were derived from both univariate and multivariate models.

Statistical significance was set at a probability level ≤0.05. The statistical package used to treat the data and perform the statistical analysis was R software version 3.5.

RESULTS

Patient Characteristics

Table 1 shows baseline demographic and clinical characteristics of the 61 patients included in the analysis. Most patients were male (n = 52, 85.2%) with a mean age of 57.7 years (SD 9.62). Tumor location was mainly oral cavity (n = 21; 34.4%). Most of patients recurred with locoregional plus metastatic disease (n = 28; 45.9%). Four (6.5%) patients

received ICI as the first treatment and 59% (n = 36) were platinum refractory.

At baseline, the mean BMI was 23.8 kg/m² (SD 4.56); underweight (BMI ≤18.5) was present in 9 (14.8%) patients and 26 (42.6%) were overweight (BMI ≥25) or obese (BMI ≥30). Median SMI was 42.0 cm²/m² (IQR 37.5; 48.6) and was used to classify patients between high and low SMI. Nutritional support was required in 34 (55.7%) patients, 15 (44.1%) of them needed a tube feeding. Two thirds (n=41, 67.2%) of the patients were sarcopenic according to previously published cut points (30) and three of them were also obese (**Table 1S, Supporting Information**).

Significant differences were identified for patients with low vs high SMI in mean age (p = 0.035), baseline weight (p < 0.001), BMI (P < 0.001), and total adipose tissue (p = 0.003). Patients with high SMI were older, heavier, and with higher BMI. No other significant differences between patients with low and high SMI at baseline were found.

Effects of SMI in Overall Survival (OS) and Progression Free Survival (PFS)

Median follow-up time was 9 months (range, 3.6–21.3). Up to a third of patients (n=16; 26.2%) were alive at last follow-up. The median time to death was 4.3 months (range, 2.3–10.9). **Table 2** summarized univariate and multivariate analyses of OS, PFS, 1-year survival, and 1-year PFS.

Patients with low SMI had shorter OS (HR, 2.06; 95% CI, 1.14–3.73; p = 0.017) (**Figure 1**) and 1-year OS rate (HR, 2.64; 95% CI, 1.33–5.23; p = 0.005) in the univariate analysis. Low SMI was also associated with global PFS (global PFS HR, 1.84; 95% CI, 1.08–3.12; p = 0.025, and 1-year PFS rate HR, 1.83; 95% CI, 1.01–3.23; p = 0.036) among other factors such as age (PFS HR, 0.96; 95% CI, 0.94–0.99; p = 0.002), baseline albumin (PFS HR, 0.95; 95% CI, 0.91–0.99; p = 0.027), platinum-refractory (PFS HR, 3.04; 95% CI, 1.67–5.56; p = <0.001), and any number of prior lines for R/M disease (PFS HR, 1.94; 95% CI, 1.09–3.46; p = 0.025). The association was maintained at 1-year PFS, although the number of prior lines showed only a trend (PFS HR, 1.71; 95% CI, 0.93–3.16; p = 0.084). One-year PFS showed a clear association with age (PFS HR, 0.97; 95% CI, 0.94–1.00; p = 0.036), serum albumin (PFS HR, 0.94; 95% CI, 0.90–0.99; p = 0.025), low SMI (PFS HR, 2.53; 95% CI, 1.19–5.37; p = 0.015), and patients who received platinum within 6 months prior to ICI (PFS HR, 3.57; 95% CI, 1.50–8.51; p = 0.004).

The multivariate analyses adjusted for serum albumin, baseline SMI, and platinum-refractory confirmed low SMI as an independent predictor for OS (HR, 2.19; 95% CI, 1.19–4.05; p = 0.012) and 1-year survival (HR, 2.79; 95% CI, 1.37–5.67; p = 0.005) adjusting this analysis also for age. Type of recurrence prior ICI initiation and BMI were not included in the multivariate analysis because it did not show association for survival or PFS in the univariate analysis.

Similar results were found using previously published cut points for sarcopenia (28) for OS but not for PFS. These results showed that sarcopenia was an independent factor for OS (HR, 2.06; 95% CI, 1.01–4.23; p = 0.048) after adjusting by the same covariates than the analysis performed for low SMI. This analysis

TABLE 1 | Patient baseline characteristics (overall and according to low vs high skeletal muscle index) (SMI) (n=61).

	Overall (n=61)	Low SMI (n=30)	High SMI (n=31)	p-overall
Age, years				
Mean (SD)	57.7 (9.62)	55.1 (9.93)	60.3 (8.73)	0.035
Median (range)	59.0 (23-78)	55.9 (23-70)	61.3 (35-78)	0.753
Male, n (%)	52 (85.2)	24 (80.0)	28 (90.3)	0.301
Smoking status, n (%)				0.394
Current	28 (45.9)	16 (53.3)	12 (38.7)	
Former*	26 (42.6)	12 (40.0)	14 (45.2)	
Never	7 (11.5)	2 (6.7)	5 (16.1)	
Alcohol consumption*, n (%)				
Yes	36 (59.0)	19 (63.3)	17 (54.8)	0.699
Location, n (%)				0.283
Oral cavity	21 (34.4)	11 (36.7)	10 (32.3)	
Hypopharynx	8 (13.1)	5 (16.7)	3 (9.7)	
Larynx	19 (31.3)	6 (20.0)	13 (41.9)	
Oropharynx**	13 (21.3)	8 (26.7)	5 (16.1)	
Type of recurrence				0.700
Locoregional	23 (37.7)	10 (33.3)	13 (41.9)	
Distance	10 (16.4)	6 (20.0)	4 (12.9)	
Locoregional + distance	28 (45.9)	14 (46.7)	14 (45.2)	
Line of therapy, n (%)				0.865
First	22 (36.1)	10 (33.3)	12 (38.7)	
Second or above	39 (63.9)	20 (66.7)	19 (61.3)	
Type of ICI therapy, n (%)				0.786
AntiPD1	8 (13.1)	5 (16.7)	3 (9.7)	
AntiPD1+virus	1 (1.64)	0 (0.0)	1 (3.3)	
AntiPD1 + chemotherapy	3 (4.92)	2 (6.7)	1 (3.2)	
AntiPDL1	12 (19.7)	5 (16.7)	7 (22.6)	
AntiPDL1+antiCTLA4	22 (36.1)	11 (36.7)	11 (35.5)	
AntiPDL1+IOA	15 (24.6)	9 (29.0)	6 (20.0)	
ECOG-PS, n (%)				0.363
0	1 (1.64)	0 (0.0)	1 (3.2)	
1	58 (95.1)	30 (100)	28 (90.3)	
2	2 (3.28)	0 (0.0)	2 (6.5)	
Platinum within 6 months of ICI,n (%)	36 (59.0)	18 (60.0)	18 (58.1)	1.000
Weight, kg				
Mean (SD)	67.3 (15.0)	59.5 (10.9)	74.9 (14.7)	<0.001
Median [Q1; Q3]	65.2 [54.3;79.0]	58.8 [51.0;65.6]	77.5 [64.3;84.5]	<0.001
BMI, kg/m^2				
Mean (SD)	23.8 (4.56)	21.3 (3.33)	26.2 (4.32)	<0.001
Median (range)	23.6 (15.8-34.7)	21.7 (15.8-27.6)	26.8 (17.7-34.6)	<0.001
BMI categorized, kg/m^2				0.001
Underweight (<18.5)	9 (14.8)	7 (23.3)	2 (6.5)	
Normal (18.5 – 25)	26 (42.6)	17 (56.7)	9 (29.0)	
Overweight /obese (>25)	26 (42.6)	6 (20.0)	20 (64.5)	
Albumin, g/L				
Mean (SD)	42.9 (60.3)	43.0 (3.24)	42.9 (7.86)	0.933
Median [Q1; Q3]	44.0 [41.0;46.0]	43.0 [41.0;45.0]	44.0 [42.0;46.5]	0.302
SMI, cm^2/m^2				
Mean (SD)	43.6 (7.75)	37.2 (3.14)	49.8 (5.44)	<0.001
Median [Q1; Q3]	42.0 [37.5;48.6]	37.5 [35.2;39.6]	48.6 [46.1;53.0]	<0.001
TATI, cm^2/m^2				
Mean (SD)	91.4 (53.3)	71.7 (44.5)	111 (54.7)	0.003
Median [Q1; Q3]	98.8 [49.4;118]	70.8 [31.5;101]	112 [82.0;148]	0.004

*Ex-smoker defined as no cigarettes for more than 6 months before diagnosis.

*Alcohol consumption defined as sustained heavy drinker (≥4 drinks per week in women and ≥5 drinks per week in men). Includes active and former drinkers.

ICI, immune checkpoint inhibitor; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BMI, body mass index; SMI, skeletal muscle index; TATI, total adipose tissue index; IOA, immuno-oncology agent.

**3 of them HPV-related.

is provided as **Supplementary Information** (**Table 2S** and **Figure 1S**).

We sought to determine whether different BMIs were associated with any of the abovementioned outcomes.

There were no statistically significant differences in OS and PFS, when examining overweight or obese patients (BMI ≥ 25 kg/m^2) compared with patients with normal BMI.

52

TABLE 2 | Univariate and multivariate analysis examining OS, one-year survival, global PFS and one-year PFS in association with skeletal muscle index (SMI) (n=61).

Univariate analysis	SURVIVAL						PROGRESION FREE SURVIVAL					
	Overall survival			1-year survival			Global PFS			1-year PFS		
	HR	95% IC	P value	HR	95% IC	P value	HR	95% IC	P value	HR	95% IC	P value
BMI	0.97	0.91;1.04	0.432	0.96	0.89;1.03	0.232	0.96	0.91;1.02	0.237	0.96	0.90;1.03	0.235
Age	0.98	0.96;1.01	0.177	0.98	0.95;1.00	0.077	0.96	0.94;0.99	0.002	0.96	0.94;0.99	0.002
Serum albumin	0.97	0.93;1.00	0.056	0.97	0.93;1.01	0.112	0.95	0.91;0.99	0.027	0.95	0.90;0.99	0.024
Low skeletal muscle index	2.06	1.14;3.73	0.017	2.64	1.33;5.23	0.005	1.84	1.08;3.12	0.025	1.83	1.01;3.23	0.036
Platinum-refractory	1.76	0.94;3.28	0.075	1.85	0.91;3.78	0.089	3.04	1.67;5.56	<0.001	2.95	1.57;5.55	0.001
Type of recurrence												
Distance	0.86	0.35;2.11	0.748	0.77	0.28;2.15	0.625	0.80	0.36;1.77	0.582	0.71	0.28;1.78	0.466
Locorregional + distance	1.16	0.61;2.22	0.651	1.08	0.53;2.19	0.830	1.03	0.58;1.83	0.929	1.11	0.61;2.02	0.736
Line of therapy 2 or above	1.26	0.68;2.34	0.470	1.21	0.60;2.41	0.596	1.94	1.09;3.46	0.025	1.71	0.93;3.16	0.084
Multivariate analysis*	**HR**	**95% IC**	**P value**	**HR**	**95% IC**	**P value**	**HR**	**95% IC**	**P value**	**HR**	**95% IC**	**P value**
Age				0.99	0.96;1.02	0.359	#	#	#	0.97	0.94;1.00	0.025
Serum albumin	0.96	0.93;1.00	0.052	0.96	0.93;1.00	0.082	#	#	#	0.94	0.90;0.99	0.016
Low skeletal muscle index	2.19	1.19;4.05	0.012	2.79	1.37;5.67	0.005	#	#	#	1.90	1.04;3.48	0.037
Platinum-refractory	1.74	0.92;3.30	0.090	1.73	0.84;3.56	0.138	#	#	#	3.31	1.40;7.83	0.006
Line of therapy 2 or above							#	#	#	0.68	0.30;1.53	0.349

OS, overall survival; PFS, progression free survival; BMI, body mass index; ICI, immune checkpoint inhibitors; Type of recurrence includes locorregional disease, distance disease and locorregional+distance disease; Line of therapy includes first vs second or above lines.
*Adjusted for the covariates with p-value <0.1 in the univariate analysis.
#Multivariate models for global PFS were not computed due to the small numbers of patients in the no-event group.

Treatment Toxicity

IrAEs occurred in 29 (47.5%) patients mainly in those treated with anti-PDL1 plus IOA (n = 15; 80%) and treated with anti-PD1 plus chemotherapy (n = 2; 66.7%). Thyroiditis, skin, and liver alterations were the most common IrAEs, and the vast majority was grade 1 or grade 2. Only seven patients developed grade 3 or above toxicity, three of them with low SMI.

There was no association with low SMI and IrAEs of any grade (OR, 0.56; 95% CI, 0.20–1.54; p = 0.261).

Different factors were examined to determine their effect in the development of IrAEs. Patients with BMI ≤18.5 kg/m^2 (OR, 0.09; 95% CI, 0.00–0.63; p = 0.012), the presence of distance metastasis (OR, 4.93; 95% CI, 1.01–30.4, p = 0.048), and those patients platinum-refractory (OR, 0.33; 95% CI, 0.11–0.94, p = 0.037) were associated with toxicity of any grade. In the multivariate analysis, only being refractory to platinum (OR, 2.88; 95% CI, 1.05–8.98, p = 0.050) was a predictive factor of IrAEs occurrence. The presence of distant metastasis was not included in the multivariate analysis because only three patients with distant metastasis did not develop IrAEs.

DISCUSSION

Immunotherapy is significantly changing the therapeutic landscape for R/M HNSCC (4, 5). Its clinical efficacy varied among HNSCC patients, and there is a lack of accurate and effective predictive biomarkers. Low SMI is frequently encountered in HNSCC patients (10, 16). However, whether low SMI can be used as a predictive biomarker for ICI remains unknown, and the clinical data regarding the association between SMI and ICI efficacy are quite limited. To the best of our knowledge, this is the first study to assess the association between SMI and clinical outcomes of R/M HNSCC patients undergoing ICI therapy.

In our study, low SMI was confirmed to be an independent factor for reduced OS and 1-year survival after adjusting the model for relevant factors associated with clinical outcomes in HNSCC. These findings are in agreement with other studies performed in melanoma and lung cancer (19, 31). We did not assess mortality specific for cancer as only two patients died from another cause different from the primary cancer. Important variables such as age, serum albumin, refractoriness to platinum or the number of lines of therapy prior to ICI therapy are well-known predictive factors. However, body composition is often overlooked in clinical practice. BMI is not a good indicator of body composition as elevated BMI may hide a distribution of low muscle mass increasing the risk for adverse outcomes (19, 32). Moreover, muscle has been shown to be one of the strongest parameters associated with mortality in cancer patients (33) even when weight and BMI are included in the analysis.

There are numerous cut points values published for sarcopenia although none of them is yet definitive. Some of these cut points used OS as the outcome according to the SMI (27, 30). We have chosen Martin et al. (30) as their population is a large sample with advanced stage and includes all BMIs. Moreover, these cut points have been used in many previous publications, so readers can compare our results. As our cohort is a slightly distinct population, we also chose the median L3 SMI cut point to evaluate SMI as a predictive biomarker in R/M HNSCC.

Although the mechanism by which reduced SMI has a negative effect on the clinical efficacy of ICI remains unclear. New evidence shows that skeletal muscle cells, as an endocrine organ, may secrete specific cytokines that regulate immunity.

53

FIGURE 1 | Kaplan-Meier survival curves according to baseline SMI. **(A)** Overall survival. **(B)** Progression Free Survival.
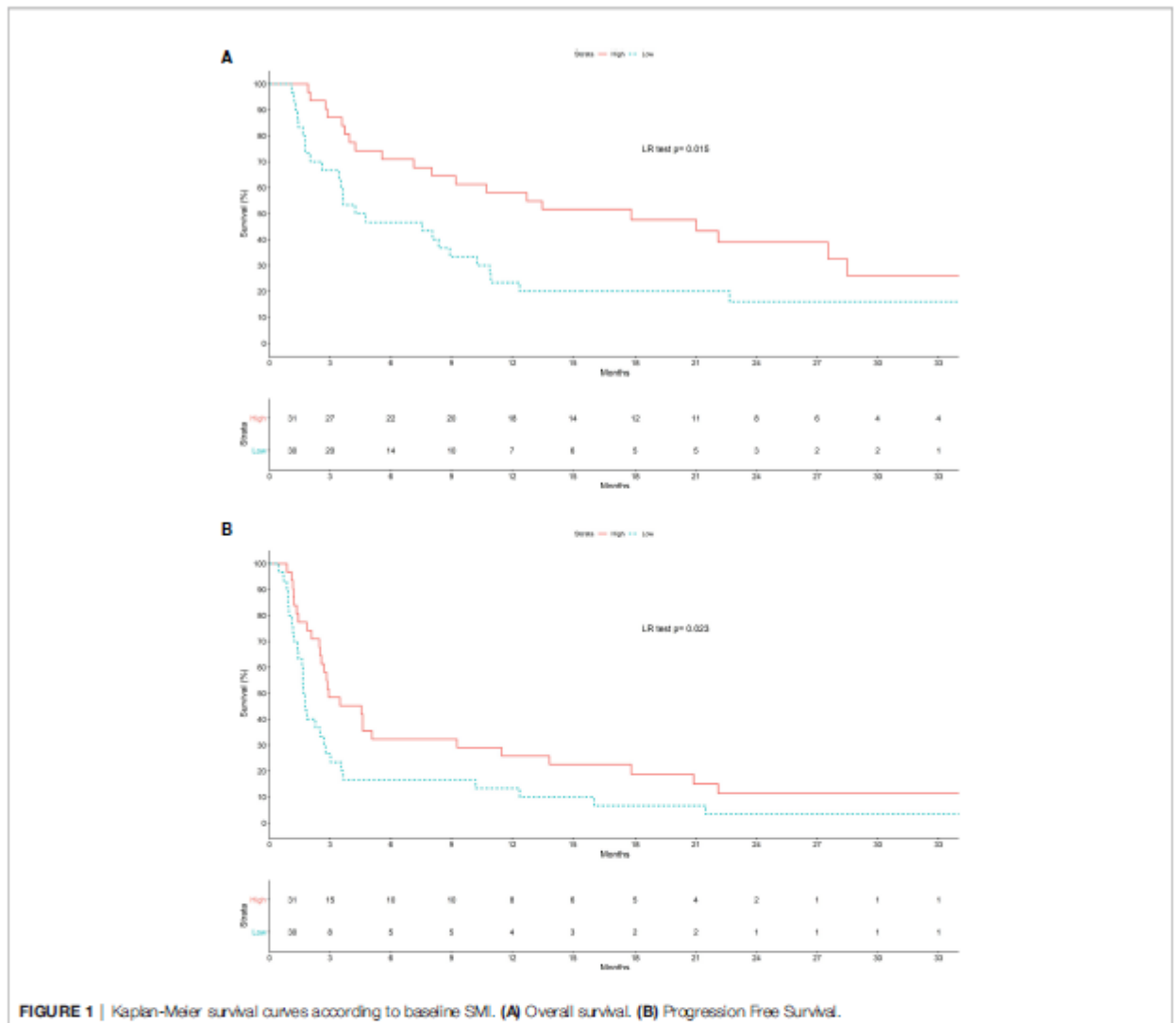
These myokines are involved in modulating the immune response (34). Thus, a reduction in muscle mass may have a deleterious effect on the anti-tumor response mediated by the immune system, following in immunosuppression (35). A decrease in myokines due to the loss of muscle mass could suppress tumor response to ICI, resulting in the immune escape of tumor cells (36, 37). Inflammation also plays an important role in the loss of muscle mass (38). All these factors may contribute to the impairment of the antitumor immune response to ICI in HNSCC.

We did not find any statistically significant associations between BMI and clinical outcomes to ICI. Young et al. (19) identified trends toward worse outcomes in patients with high BMI and low muscle mass in patients with melanoma treated with anti-PD1. However, we included only six patients with BMI ≥ 25 kg/m^2 and low SMI.

Compared with traditional treatments (chemotherapy or radiotherapy), the incidence of toxicity in HNSCC patients treated with ICI has been reduced. We explored the effect of low SMI on the incidence of adverse event related to ICI in HNSCC patients, finding that low SMI was not significantly associated with the incidence of IrAEs. Evidence suggests that the incidence of IrAEs of any grade is associated with improved clinical outcomes (39). Unfortunately, subgroups analysis could not be further performed because of insufficient data.

Our study has some limitations that should be addressed. The main ones are the retrospective design of the study and the limited number of patients. Moreover, the CT imaging analysis was limited by the data availability; indeed, the acquisition protocol was planned according to the presence of previous examination. Finally, we did not take into account the type of ICI therapy alone or in combination.

54

In conclusion, our finding shows that baseline SMI is an independent factor for survival R/M HNSCC treated with ICI. SMI is not associated with the onset of IrAEs. Further prospective research is needed to confirm the role of body composition as a predictive biomarker in ICI treatment and how SMI can affect drug-specific and organ-specific adverse events caused by ICI in HNSCC patients.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: IDIBELL repository (http://diposit.ub.edu/dspace/handle/2445/172899).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hospital Universitari de Bellvitge Ethics Committee for Clinical Research (PR302/18). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FUNDING

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.699668/full#supplementary-material

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55

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56

SUPPLEMENTARY MATERIAL

Supplementary material (Article 4)

frontiers

Supplementary Material

1   Supplementary Figures and Tables

Table 1S. Patient baseline characteristics (overall and according to the presence of sarcopenia) (n=61)

	Overall (n=61)	Sarcopenia (n=41)	No sarcopenia (n=20)	p-overall
Age, years				
Mean (SD)	57.7 (9.62)	57.2 (9.94)	58.7 (9.10)	0.561
Median (range)	59.0 (23-78)	59.0 (23-70)	59.5 (35-78)	0.753
Male, n (%)	52 (85.2)	35 (85.4)	17 (85.0)	1.000
Smoking status, n (%)				0.180
Current	28 (45.9)	22 (53.7)	6 (30.0)	
Former*	26 (42.6)	14 (34.1)	12 (60.0)	
Never	7 (11.5)	5 (12.2)	2 (10.0)	
Location, n (%)				0.556
Oral cavity	21 (34.4)	14 (34.1)	7 (35.0)	
Hypopharynx	8 (13.1)	7 (17.1)	1 (5.0)	
Larynx	19 (31.3)	11 (26.8)	8 (40.0)	
Oropharynx**	13 (21.3)	9 (22.0)	4 (20.0)	
Type of recurrence				0.254
Locoregional	23 (37.7)	14 (34.1)	9 (45.0)	
Distance	10 (16.4)	9 (22.0)	1 (5.0)	
Locoregional + distance	28 (45.9)	18 (43.9)	10 (50.0)	
Line of therapy, n (%)				0.871
First	22 (36.1)	14 (34.1)	8 (40.0)	
Second or above	39 (63.9)	27 (65.9)	12 (60.0)	
Type of ICI therapy, n (%)				0.752
AntiPD1	8 (13.1)	6 (14.6)	2 (10.0)	
AntiPD1+virus	1 (1.64)	1 (2.4)	0 (0.0)	
AntiPD1 + chemotherapy	3 (4.92)	3 (7.3)	0 (0.0)	
AntiPDL1	12 (19.7)	9 (22.0)	3 (15.0)	
AntiPDL1+antiCTLA4	22 (36.1)	13 (31.7)	9 (45.0)	
AntiPDL1+IOA	15 (24.6)	9 (22.0)	6 (30.0)	
ECOG-PS, n (%)				0.032
0	1 (1.64)	0 (0)	1 (5.00)	
1	58 (95.1)	41 (100)	17 (85.0)	
2	2 (3.28)	0 (0)	2 (10.0)	
Platinum within 6 months of ICI,n (%)	36 (59.0)	25 (61.0)	11 (55.0)	0.866
Weight, kg				
Mean (SD)	67.3 (15.0)	66.2 (15.4)	69.5 (14.2)	0.413
Median [Q1; Q3]	65.2 [54.3;79.0]	62.9 [54.0;77.8]	72.2 [59.8;80.8]	0.303
BMI, kg/m²				
Mean (SD)	23.8 (4.56)	23.4 (4.73)	24.7 (4.16)	0.260
Median (range)	23.6 (15.8-34.7)	22.9 (15.8-34.7)	24.7 (17.7-32.1)	0.208
BMI categorized, kg/m²				0.869
Underweight (<18.5)	9 (14.8)	7 (17.1)	2 (10.0)	
Normal (18.5 – 25)	26 (42.6)	17 (41.5)	9 (45.0)	
Overweight /obese (>25)	26 (42.6)	17 (41.5)	9 (45.0)	
Albumin, g/L				
Mean (SD)	42.9 (60.3)	42.0 (6.87)	44.9 (3.23)	0.032
Median [Q1; Q3]	44.0 [41.0;46.0]	43.0 [41.0;45.0]	45.0 [42.0;47.2]	0.025
SMI, cm²/m²				
Mean (SD)	43.6 (7.75)	40.1 (5.79)	50.8 (6.17)	<0.001
Median [Q1; Q3]	42.0 [37.5;48.6]	39.0 [36.1;42.0]	48.8 [46.2;55.0]	<0.001
TATI, cm²/m²				
Mean (SD)	91.4 (53.3)	92.6 (54.9)	88.9 (51.1)	0.798
Median [Q1; Q3]	98.8 [49.4;118]	92.3 [49.9;138]	99.7 [56.1;112]	0.794

Ex-smoker defined as no cigarettes for more than 6 months before diagnosis

ICI, immune checkpoint inhibitor; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BMI, body mass index; SMI, skeletal muscle index; TATI, total adipose tissue index

** 3 of them HPV-related

Table 2S. Univariate and multivariate analysis examining OS, one-year survival, global PFS and one-year PFS in association with sarcopenia (n=61).

	SURVIVAL						PROGRESION FREE SURVIVAL					
	Overall survival			1-year survival			Global PFS			1-year PFS		
Univariate analysis	**HR**	**95% IC**	**P value**	**HR**	**95% IC**	**P value**	**HR**	**95% IC**	**P value**	**HR**	**95% IC**	**P value**
BMI	0.97	0.91;1.04	0.432	0.96	0.89;1.03	0.232	0.96	0.91;1.02	0.237	0.96	0.90;1.03	0.235
Age	0.98	0.96;1.01	0.177	0.98	0.95;1.00	0.077	0.96	0.94;0.99	0.002	0.96	0.94;0.99	0.002
Serum albumin	0.97	0.93;1.00	0.056	0.97	0.93;1.01	0.112	0.95	0.91;0.99	0.027	0.95	0.90;0.99	0.024
Sarcopenia	2.21	1.11;4.37	0.023	2.32	1.06;5.10	0.036	1.40	0.79;2.46	0.248	1.49	0.82;2.72	0.192
Platinum-refractory	1.76	0.94;3.28	0.075	1.85	0.91;3.78	0.089	3.04	1.67;5.56	<0.001	2.95	1.57;5.55	0.001
Type of recurrence												
Distance	0.86	0.35;2.11	0.748	0.77	0.28;2.15	0.625	0.80	0.36;1.77	0.582	0.71	0.28;1.78	0.466
Locorregional + distance	1.16	0.61;2.22	0.651	1.08	0.53;2.19	0.830	1.03	0.58;1.83	0.929	1.11	0.61;2.02	0.736
Line of therapy 2 or above	1.26	0.68;2.34	0.470	1.21	0.60;2.41	0.596	1.94	1.09;3.46	0.025	1.71	0.93;3.16	0.084
Multivariate analysis	**HR**	**95% IC**	**P value**	**HR**	**95% IC**	**P value**	**HR**	**95% IC**	**P value**	**HR**	**95% IC**	**P value**
BMI	1.20	0.45;3.19	0.717	1.40	0.51;3.85	0.517	#	#	#	1.08	0.44;2.64	0.861
Age	0.98	0.95;1.01	0.225	0.98	0.95;1.01	0.138	#	#	#	0.96	0.94;0.99	0.010
Serum albumin	0.97	0.94;1.01	0.179	0.97	0.93;1.02	0.226	#	#	#	0.95	0.90;1.00	0.044
Sarcopenia	2.06	1.01;4.23	0.048	2.05	0.90;4.67	0.087	#	#	#	1.50	0.78;2.87	0.222
Platinum-refractory	1.97	0.81;4.76	0.133	2.04	0.76;5.50	0.158	#	#	#	3.17	1.33;7.57	0.009
Line of therapy 2 or above	0.63	0.26;1.52	0.301	0.51	0.19;1.39	0.189	#	#	#	0.61	0.25;1.46	0.264

OS, overall survival; PFS, progression free survival; BMI, body mass index; SMI, skeletal muscle index; ICI: immune checkpoint inhibitors; Type of recurrence includes locorregional disease, distance disease and locorregional+distance disease; Line of therapy includes first vs second or above lines.
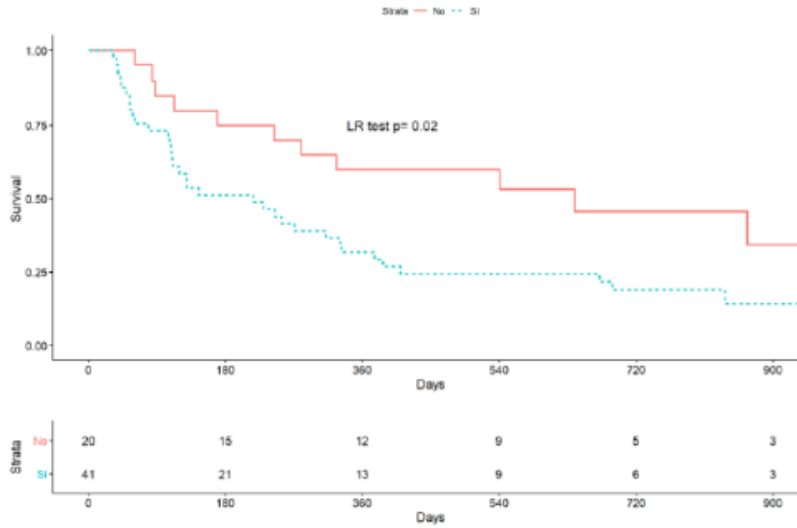
*Adjusted for age, serum albumin, baseline SMI, BMI, line of therapy and platinum-refractory.

Multivariate models for global PFS were not computed due to the small numbers of patients in the no-event group.
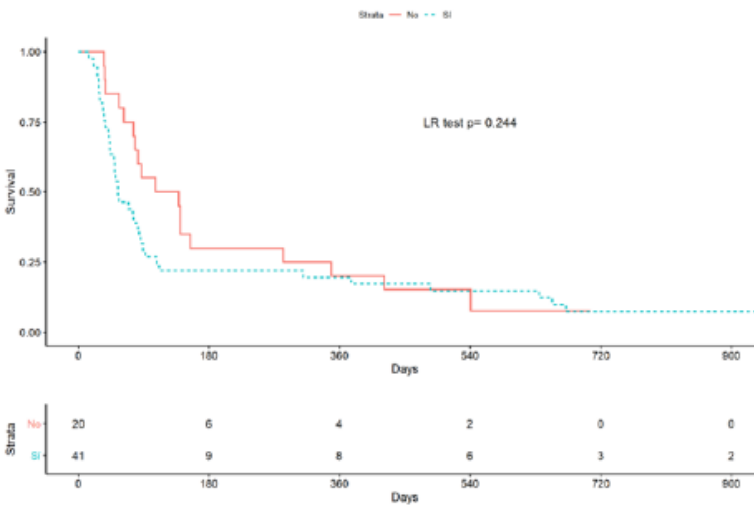
1.1 Supplementary Figures

Figure 1S. Kaplan-Meier survival curves according to sarcopenia. (A) Overall survival. (B) Progression Free Survival

(A)

(B)

6

GENERAL DISCUSSION

Which nutritional and body composition changes occur in patients with LA-HNSCC during the oncological treatment?

Induction chemotherapy phase: For the prospective study (article 1), 70% of our patients were well nourished at diagnosis and did not lose a significant amount of weight prior diagnosis. Similar results were found in the retrospective cohort (62.5%) (article 2). There were positive changes in body weight and energy intake during the induction chemotherapy phase. These results are in agreement with Silver HJ et al study [137]. The improvement of the symptoms that initially limited the oral intake may have contributed to these changes due to induction chemotherapy. In our study dysphagia and odynophagia were the most frequent symptoms that affected our patients at diagnosis. Only one patient remained with severe dysphagia after the induction chemotherapy. There was also an increase in fat free mass (FFM) measured by bioimpedance (BIA) despite a progressive deterioration in functionality according to the hand grip strength (HGS) (*Figure 1, thesis article 1*). Data in the literature described that muscle mass and functionality are two different concepts and both can have clinical benefits [138,139].

Concomitance treatment: Despite an intensive nutritional support along the oncological treatment, 75% of patients in the prospective cohort and 67.5% of the retrospective cohort was malnourished according to the PG-SGA three months after finishing the concomitance. Adherence to the nutritional treatment is usually complicated due to the acute toxicity. In our hospital nutritional support is integrated as part of the head and neck multidisciplinary unit and all patients are assessed in a multimodal supportive care [53,54] trying to optimize the best nutritional intervention according to the oncological treatment.

Once the concomitant radiation and systemic therapy started, all nutritional parameters (energy and protein intake, nutritional status, weight, BMI) and body composition compartments (FFM, SMI, TATI, estimated skeletal muscle mass (SMM), estimated fat mass (FM)) decreased in the same manner as is reported in the literature [5,137,140,141]. Garcia-Peris P et al [142] and Silver HJ et al [137] described an increase in the basal metabolic rate in HNC patients during treatment. Our patients, although maintaining a fair energy intake before and after treatment (before treatment was 2018.2 kcal/d (SD 358.5) and 1892.5 kcal/d (SD 620.2) after treatment), still failed to meet their nutritional requirements. We manage to maintain FFM and HGS up to one month after the concomitance in spite of a significant deterioration. Although patients did not follow a standardized exercise program, we emphasized the importance of the physical activity, and we provide them with small daily goals to incorporate in their daily life to increase physical activity. In our studies it becomes evident the nutritional and body composition depletion that occurs in these patients even at three months post treatment. It is essential to maintain a close monitoring to optimized nutritional support. A recent meta-analysis [143] analyzing exercise and nutrition interventions in patients with HNC during curative treatment based on radiotherapy found significant positive effects of nutrition and physical exercise intervention alone in favor of the treatment groups but no effects in studies with combined interventions were observed. However, the included studies were highly heterogenic both regarding measurements methods and the content of the interventions which may have affected the results of the meta-analysis.

Which clinical predictors are involved in muscle and adipose tissue loss during treatment in patients with LA-HNSCC during concomitance with chemo-radiotherapy?

Our data (article 2) underline the importance of including body composition assessment in HNC patients during treatment suggesting that intensive nutrition support according to guidelines only

benefits about a half of patients. Patients who lose more muscle and fat are more likely to have a higher BMI at baseline, therefore, the need for a high food intake should be considered. However, this could be challenging during this aggressive cancer treatment and the negative energy balance is indisputable evidenced especially by the large fat losses. Tissue losses are associated with four main factors: tumour site, nutrition impact symptoms at baseline, severe toxicity and the use of ABW to set nutrition targets in overweight/obese patients.

Weight loss has been described most commonly in patients with oropharynx and oral cavity[144] primary tumours and worse nutritional status[67,145] as they are more likely to have symptoms that interfere in the oral intake, hence the energy consumption is expected to be deficient. As induction chemotherapy can lead to severe toxicity affecting food intake, this might be another cause for tissue loss. Our results show that only ABW was an independent predictor of muscle loss in the multivariable regression analysis including covariates adjustments such as tumor site, nutrition impact symptoms and severe toxicity during the induction chemotherapy. Fat loss was also associated with the use of ABW to set nutrition targets, tumour site and of nutrition impact symptoms at baseline. The extended practice of ABW-based nutritional support for obese patients contributes to exacerbate the fat loss. Although originally the use of ABW was designed for renal disease [146] and critically ill patients to prevent overfeeding [147], its use has been expanding to other clinical settings. As there are no oncological or nutrition guidelines for obese cancer patients during treatment, the use of adjusted body weight-based nutritional support in obese patients is still a routine practice for nutrition professionals as it is a way of providing a realistic amount of nutrients in a group of patients that are already battling to eat.

There are no nutritional guidelines for obese cancer patients with specific approaches to calculate of nutritional requirements, and the implications of weight reduction during treatment with curative intent in obese patients are unclear. Moreover, about 42% of obese patients are also sarcopenic reducing further the overall survival for this group of patients [96,148].

Is our precision test able to discriminate biological changes from measurement error?

Our precision findings (article 3) are very consistent with those precision demonstrated in DXA measurements [102] of bone, lean and soft tissue whole body and regional compartments. In CT studies measurements are made on a single slice; therefore, although CT measures have a good precision for muscle, our precision test specifically for fat is poor compare with same precision test for DXA shown in other studies [149–151]. So, it is important to bear in mind that we are looking at precision test for cross-sectional area in specific anatomical levels in CT images while DXA measures whole body compartments. It would be interesting to compare our results with other precision studies perform for CT imaging. Nevertheless, intra-observer and inter-observer precision have been reported in other studies. Intra-observer reliability of CSA imaging is usually reported with good agreement between repeated measurements using CT images [152,153] although precision error associated with patient positioning and slice selection using CT imaging increase up to 2.5% in the same individual. The intra- and interobserver variability in skeletal muscle CSA measurements of three experienced radiologists using CT images [153] was recently reported. Intra-observer variability was low reporting data between 1.57% to 2.89% for a single slice while comparison between radiologists showed that the measurement variability reduced as the fraction of repeat measurement taken at the same slice increased. Anatomic variations and technical issues may both contributed to variability among experts.

Our precision at the different anatomical levels varies from 0.7 to 2.4% (*Table 2, thesis article 3*). Interestingly, the best precision is observed in the thigh; thus, this level could be considered when looking to detect small changes over time. Intervention studies assessing physical function could benefit in evaluating changes that occur during the course of the intervention.

We recommend the uniform use of a standard precision test when analyzing changes over time in muscle with CT images.

Are muscle and adipose tissue loss systemic?

The dynamics of muscle change has known and unknown determinants. Animal studies have shown us that there are certain muscle types more prone for muscle wasting. In mice fast fibers (versus slow fibers) are more susceptible to atrophy in cancer cachexia and other acute catabolic states [154,155]. In humans, the majority of muscles are mixed fiber types and the investigations are focus on muscle groups with a mixture of fiber types. In our study we do not examine fiber type or specific muscle, our purpose is to evaluate an aggregate effect on groups of muscles which are likely to be representative of the overall muscularity and four different levels.

In spite of selecting a population with similar clinical features and treatment, our findings show an important inter-individual variability as muscle changes range from gain to very substantial losses.

Based on our findings, muscle wasting appears to be systemic although with stronger effect in the thigh (Table 3). We do not have any data at this time to explain the cause of this difference. However, the signals causing muscle wasting in a patient with cancer may be presumed to be mostly systemic in nature. Blood borne factors such as inflammatory cytokines would reach all muscles, and the effect of decreased food intake would be expected to impact all muscles [156,157]. A local effect could be potentially explained by changes in a specific region such as the activity used of the lower limbs [106,107,158]. In the future, a reduction in activity in the lower limbs might be detected by the use of actigraphy or other methods used in different parts of the body studied along with the changes over time in the muscle mass.

Two important limitations from our results that must be taken into account. The main one is that as a single observer study, the precision error is unique to this observer and comparisons with other observers will be needed to establish what can reasonably expected in this type of studies. Another important limitation is that we have evaluated only male patients since head and neck cancer incidence in Southern Europe is higher in men but adipose tissue and muscle loss may differ in males and females.

Further studies should investigate causes of regional muscle loss in this group of patients and whether specific interventions may attenuate or restore this loss during treatment. Moreover, additional studies are needed to understand whether similar patterns of loss are also occurring in women.

Is muscle mass a good biomarker for survival in patients with R/M HNSCC treated with immunotherapy?

Immunotherapy is significantly changing the therapeutic landscape for R/M HNSCC [127,159127,159]. Its clinical efficacy varied among HNSCC patients and there is a lack of accurate and effective predictive biomarkers. Low SMI is frequently encountered in HNSCC patients [67,68]. However, whether low SMI can be used as a predictive biomarker for ICI remains unknown and the clinical data regarding the association between SMI and ICI efficacy is quite limited.

In our study (article 4) low SMI was confirmed to be an independent factor for reduced OS and one-year survival after adjusting the model for relevant factors associated with clinical outcomes in HNSCC (*Figure 1, thesis article 4*). These findings are in agreement with other studies performed in melanoma and lung cancer [134,160]. We did not assess mortality specific for cancer as only 2 patients died from another cause different from the primary cancer. Important variables such as age, serum albumin, refractoriness to platinum or the number of lines of therapy prior to ICI therapy are well-known predictive factors. However, body composition is often overlooked in clinical practice. BMI is not a good indicator of body composition as elevated BMI may hide a distribution of low muscle mass increasing the risk for adverse outcome [96,134]. Moreover, muscle has been shown to be one of the strongest parameters associated with mortality in cancer patients [97] even when weight and BMI are included in the analysis.

A recent meta-analysis [161] evaluating the prognostic factor of sarcopenia on clinical outcomes in patients with malignant neoplasms receiving ICI has included our findings in their analysis. The study included 19 studies with lung, gastrointestinal, melanoma, renal cell carcinoma, urothelial carcinoma, pancreatic cancer, soft tissue sarcoma and HNC patients. According to univariate and multivariate analyses, patients with sarcopenia at pre-immunotherapy had poorer progression free survival (PFS) and OS than those without. HRs and the corresponding 95% CI of PFS were 1.91(1.55–2.34, p <0.00001) and 1.46 (1.20–1.78, p =0.0001), respectively, and HRs and the corresponding 95% CI of OS were 1.78 (1.47–2.14, p <0.00001) and 1.73 (1.36–2.19, p <0.0001), respectively. Patients with sarcopenia showed poor PFS and OS during treatment. In addition, patients with sarcopenia had worse objective response rate (ORR) (OR 0.46, 95% CI 0.28–0.74, p = 0.001) and disease control rate (DCR) (OR 0.44, 95% CI 0.31–0.64, p<0.0001.

Although the mechanism by which reduced SMI has a negative effect on the clinical efficacy of ICI remains unclear. New evidence shows that skeletal muscle cells, as an endocrine organ, may secrete specific cytokines that regulate immunity. These myokines are involved in modulating the immune response [162]. Thus, a reduction in muscle mass may have a deleterious effect on the anti-tumor response mediated by the immune system, following in immunosuppression [163]. A decrease in myokines due to the loss of muscle mass could suppress tumor response to ICI, resulting in the immune escape of tumor cells [164,165]. Inflammation also plays an important role in the loss of muscle mass [166]. All these factors may contribute to the impairment of the antitumor immune response to ICI in HNSCC.

Is there any association between muscle mass and the occurrence of immunotherapy-related adverse effects in patients with R/M HNSCC?

Compared with traditional treatments (chemotherapy or radiotherapy), the incidence of toxicity in HNSCC patients treated with ICI has been reduced. We explored the effect of low SMI on the incidence of adverse event related to ICI in HNSCC patients, finding that low SMI was not significantly associated with the incidence of IrAEs (OR 0.56, 95%IC 0.20;1.54, p=0.261). IrAEs occurred in 29 (47.5%) patients mainly in those treated with antiPDL1 plus IOA (n=15; 80%) and treated with antiPD1 plus chemotherapy (n=2; 66.7%). Only seven patients developed grade 3 or above toxicity, three of them with low SMI. Evidence suggests that the incidence of IrAEs of any grade is associated with improved clinical outcomes [167]. Unfortunately, subgroups analysis could not be further performed due to insufficient data.

In the meta-analysis published by Li S et al [161] the incidence of irAEs of any grade and high-grade in patients with sarcopenia did not increase, OR and the corresponding 95% CI were 0.58(0.30–1.12, p = 0.10) and 0.46 (0.19–1.09, p = 0.08). Another meta-analysis performed in lung cancer [160] showed similar results. However, a few studies have reported the effect of sarcopenia on irAEs with an increase in the incidence [168,169]. Due to the small number of studies that report the incidence rate of irAEs according to sarcopenia, more data are needed.

METHODOLOGICAL CONSIDERATIONS

Limitations

- In the first article, despite having a prospective cohort of LA-HNSCC patients, body composition analysis could only be performed by BIA, so body composition results were made from predictive equations and not by direct measurements.
- The limited sample size in all cohorts and its retrospective design.
- The CT imaging analysis was limited by the data availability.
- There are inflammatory biomarkers such as CRP or functionality tests that have not been recorded.
- Systemic muscle loss was only evaluated in male patients since HNC incidence is higher in men in Southern Europe, but body composition changes may differ in males and females.
- The precision testing was performed by a single observer; therefore, comparisons with other observers will be needed.

Strengths

- The prospective design of the first cohort.
- All patients had nutritional assessment and follow-up with an intensive and individualized intervention by the same oncology dietitian, which unified the criteria for nutritional intervention.
- All images were analyzed by the same researcher and reviewed by the same radiologist or nuclear medicine physician.
- The same software has always been used and the analysis has always been performed in the same manner.
- The use of precision test to evaluate body composition changes over time
- The multidisciplinary effort and work to carry out every one of the studies and the involvement of all the services.

Future research directions related to the thesis topic

The projects associated to this thesis were not conceptually designed at once and that overall project has been evolving and extended in order to answer new generated hypothesis. The information generated by the project and presented in the thesis is of great importance.

However, there remain gaps of knowledge that deserve further research beyond the work here presented, and we are currently working on:

- A double blind randomized clinical trial conducted in LA-HNSCC with conservative treatment using a specific nutrient (i.e eicosapentaenoic acid; EPA) to minimize muscle loss during oncological treatment. This trial has already been completed and currently analyzing the results.

- A prospective study assessing body composition, nutritional characteristics, functionality and inflammatory biomarkers to evaluate the association between these parameters and oncological outcomes such as survival, recurrence and toxicity in patients with R/M HNSCC treated with immunotherapy; currently recruiting.

- A retrospective study evaluating the impact of body composition in oncology patients who have received immunotherapy or tyrosine kinase inhibitors (ITK) as part of compassionate drug use. The results will be part of a clinical score to assist in decision making for oncologists.

- In the same way that there is a personalized oncological treatment, we could consider personalized oncological nutrition based on body composition. That is to say, that the nutritional intervention should be based on the patient's body composition for the calculation of requirements taking into account their muscle mass and adipose tissue and their evolution, in order to improve tolerance to treatment and perhaps improve the prognosis in patients with radical intent and improve the relapse rate in patients with tumors related to obesity or the development of diseases related to overweight/obesity.

SUMMARY LIST OF CONCLUSIONS

- Despite an intensive nutritional support from diagnosis and throughout oncologic treatment in patients with locally advanced head and neck squamous cell carcinoma, nutritional status and body composition compartments deteriorate during treatment and thereafter.

- In patients with locally advanced head and neck squamous cell carcinoma, induction chemotherapy could help improve nutritional status by alleviating symptoms that limit intake.

- Body composition analysis using CT imaging in patients with head and neck cancer receiving radical treatment could be useful to monitor whether nutritional support is adequate to maintain muscle and adipose tissue. Setting nutritional goals based on the use of "adjusted body weight" for obese or overweight patients seems inappropriate given the large loss of muscle and adipose tissue reported.

- We strongly recommend the consistent use of a standard precision test when reporting muscle change over time. The value of the least significant change varies between 0.9 and 2.5% depending on the anatomical site; the greatest sensitivity for detecting change is in the thigh.

- Based on our analysis, muscle depletion appears to be systemic and, although it occurs in the limbs and trunk, it is significantly greater in the thigh than in the thorax, abdomen or arm.

- Baseline muscle mass prior to initiation of immunotherapy treatment is an independent factor for survival in patients with recurrent and/or metastatic head and neck squamous cell carcinoma treated with immunotherapy but is not associated with the occurrence of immunotherapy-related adverse effects.

SPECIFIC TASKS PERFORMED WITHIN THE STUDY

The PhD student (Lorena Arribas) has participated in the following tasks related to the studies:

- Design and preparation of protocols of the project.

- Design the database and collect the clinical and radiological information related to the patients included in the analysis.

- Preparation of grant application. Specifically, the PhD student (Lorena Arribas) was the Principal Investigator of the grant awarded of the project investigating the role of body composition with head and neck cancer patients treated with immune-checkpoints inhibitors.

- Participation in the coordination of some steps of the project.

- The student has learned to select, analyzed and interpreted the body images from CT and PET scans.

- The student was recruited all patients in the prospective study and done all the visits.

- The student performed two months stay, from July to August 2017 in the Cross Cancer Institute, University of Alberta, Edmonton, Canada within the group lead by Vickie E Baracos. During these two months the student learned to analysis body images and participated in several activities such as weekly meetings with all members of both sites (Cross Cancer Institute and University of Alberta) including students, lab staff and group leaders (Dr Baracos and Dr Mazurak) and participating directly in a paper about sarcopenic obesity. This paper has been described in the section "articles related to the PhD project": *Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy.*

- Participation in the field work of the project and preparation of all articles.

- Active intervention in the Head and Neck Multidisciplinary Team.

IMPLICATIONS IN CLINICAL PRACTICE

The results obtained in this thesis may have relevant clinical implications not only for nutrition professionals but also for the health care system.

The fact of confirming an improvement in the symptoms that limit oral intake after the induction chemotherapy in patients with LA-HNSCC should help nutrition professionals in the decision making for gastrostomy feeding tubes at diagnosis since, dysphagia and odynophagia are the main symptoms that deteriorate the nutritional status but could be improved quickly after the first cycle of induction chemotherapy. This may help to optimize the nutritional status prior the beginning of concomitance therapy.

Nowadays more than 85% of nutrition professionals worldwide use the ABW in obese patients for the calculation of nutritional requirements despite the lack of clinical evidence. The results shown in this thesis suggest that its use for calculating the requirements of obese or overweight oncology patients may be one of the main causes of nutritional deterioration so its use in oncology should be discouraged.

The calculation of the precision test in the analysis of body composition through imaging techniques should be the first step to standardize these measurements, especially for those studies analysis changes over time. The standardization will build more homogeneous studies in order to increase clinical evidence on the negative impact of the depletion of body tissues in oncological clinical outcomes.

It would be advisable that body composition measurements using imaging techniques to assess changes over time be performed at least at two anatomical levels. One of these measurements should include a distal measurement since it appears that the loss is greater in the lower limbs. Adding a measure of functionality centered on the lower limbs would be important.

Improving the clinical evidence regarding the impact of body composition in specific groups of oncology patients, may be beneficial for patients by improving their quality of life with more effective treatments reducing toxicity but also the health system by reducing additional costs.

PRIZES AWARDED DURING THE THESIS

- Award for the best oral communication at the CODINUCAT (Col.legi de Dietistes-Nutricionistes de Catalunya), Nov 2017: "Nutritional changes in patients with locally advanced head and neck cancer during treatment". **Arribas L**, Hurtós L, Taberna M, Peiró I, Vilajosana E, Lozano A, Vazquez S, Mesia R, Virgili N.

- FRESENIUS KABI / SENPE-FUNDACIÓN SENPE 2021 Award for "the best publication in the field of clinical nutrition for oncology patients": **Arribas L,** Sabaté-Llobera A, Taberna M, Pallarés N, Narro Marin A, Virgili N, Hurtós L, Peiró I, Vilajosana E, Lozano A, Baracos V, Mesia R. Adequacy of nutritional support using computed tomography (CT) in patients with head and neck cancer (HNC) during chemo-radiotherapy (CRT). Eur J Clin Nutr. 2021 Feb 10. doi: 10.1038/s41430-021-00863-z. Epub ahead of print. PMID: 33568807.

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OTHER ARTICLES RELATED TO THE PhD PROJECT

Article reference	Impact Factor	Journal rank in the category
Baracos VE & **Arribas L**. *Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy.* Ann Oncol 2018; 29 (suppls_2):ii1-ii9.	**32.976**	Oncology 7/242 Q1
Taberna M, Gil Moncayo F, Jané-Salas E, Antonio M, **Arribas L**, Vilajosana E, Peralvez Torres E, Mesía R. *The Multidisciplinary Team (MDT) approach and quality of care.* Front Oncol 2020 Mar 20;10:85	**6.244**	Oncology 61/325 Q2

♯ *Journal Citation Reports (Clarivate Analytics, 2021); "Q": Quartil*
*Equal contribution as senior author

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