EUR REV MED PHARMACOL SCI
2025; 29: 470-480

CBCT-BASED LONGITUDINAL ASSESSMENT OF MUSCLE LOSS IN OROPHARYNGEAL CANCER PATIENTS UNDERGOING RADIOCHEMOTHERAPY

F. FIORICA[1,2], M. COELI[1], G. CONDARELLI[1], S. TOMASI[1], U. TEBANO[1], G. MON[1], J. GIULIANI[3], M. GABBANI[1], T. SAVA[3], S. DE ROSSI[4], G. TONOLI[4], A. CASIRATI[5], R. CACCIALANZA[5,6], P. PEDRAZZOLI[7]

• • •

[1]Radiation Oncology and Nuclear Medicine Unit, AULSS 9 Scaligera, Verona, Italy
[2]Department of Clinical Oncology, ULSS 9 Scaligera, Verona, Italy
[3]Medical Oncology Unit, AULSS 9 Scaligera, Verona, Italy
[4]ENT Unit, AULSS 9 Scaligera, Verona, Italy
[5]Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[6]Department of Oncology and Hematology-Oncology, University of Milan, Milan, Italy
[7]Medical Oncology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

CORRESPONDING AUTHOR
Francesco Fiorica, MD; e-mail: francesco.fiorica@aulss9.veneto.it

ABSTRACT – ***Objective:*** Oropharyngeal cancer and its treatment often lead to sarcopenia, which is linked to increased toxicity, reduced response to therapy, and worse survival. Traditional weight-based metrics may fail to detect this muscle loss. This study investigates the feasibility of using cone-beam computed tomography (CBCT) to monitor sarcopenia longitudinally in patients undergoing radiochemotherapy.

Materials and Methods: A retrospective analysis was conducted on 15 patients with locally advanced, inoperable oropharyngeal cancer who maintained stable body weight during treatment. All patients received intensity-modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT), with daily cone-beam computed tomography (CBCT) for image guidance. Skeletal muscle area and density at the C3 vertebral level were measured weekly. A calibration phantom corrected CBCT Hounsfield Unit (HU) values. Longitudinal changes were assessed using linear mixed-effects models (LMMs), and correlations between skeletal muscle index (SMI) and body mass index (BMI) were evaluate.

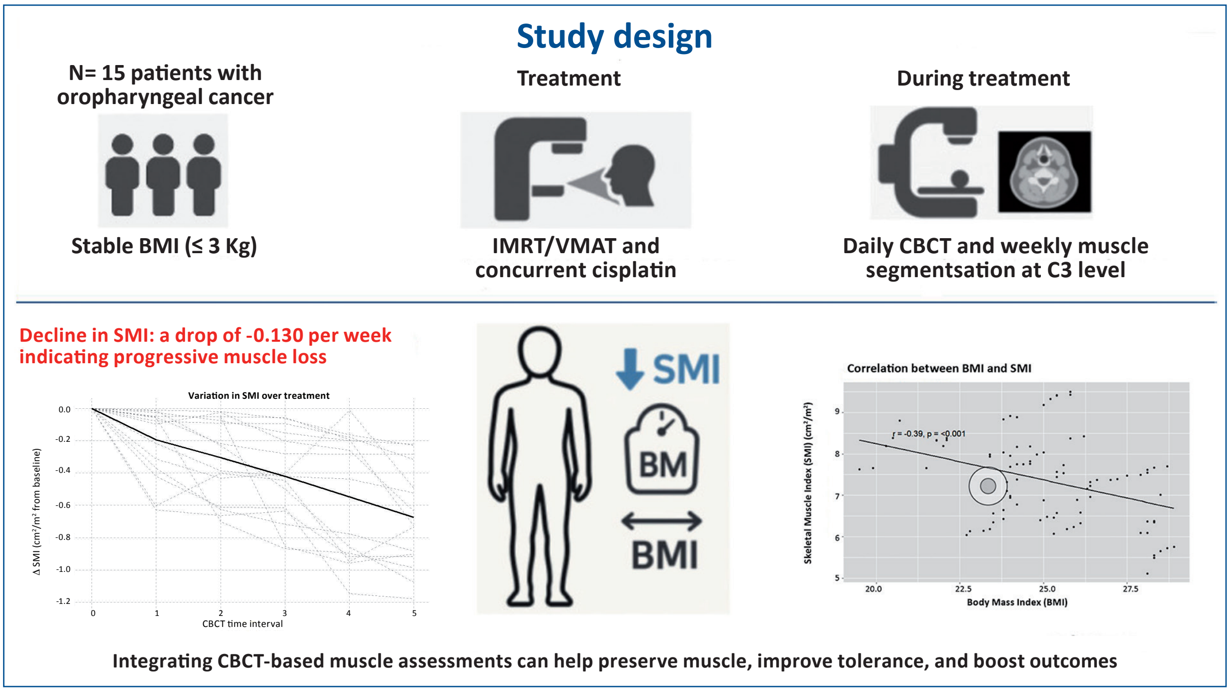
Results: A significant weekly decline in SMI ($p = 0.037$) was observed, particularly after week 3, despite stable BMI. The muscle area decreased progressively while the HU values remained stable. A moderate inverse correlation was found between SMI and BMI ($r = -0.39$, $p < 0.001$), indicating that BMI is an inadequate measure for reflecting muscle loss.

Conclusions: CBCT allows non-invasive, real-time monitoring of sarcopenia during treatment. Integrating CBCT-based body composition analysis into clinical practice could enable earlier detection and intervention, potentially improving treatment tolerance and outcomes. Larger studies and improved segmentation techniques are needed to validate and optimize this approach.

KEYWORDS: Cone-Beam CT (CBCT), Body composition, Radiochemotherapy monitoring, Skeletal muscle index (SMI), Sarcopenia.

INTRODUCTION

Oropharyngeal cancer, particularly in its locally advanced stages, presents a major challenge due to the combined impact of the disease and treatment on body composition, leading to muscle loss and sarcopenia[1]. While radiochemotherapy remains the standard approach for non-surgical



Graphical Abstract. Reanalysis of CBCT scans in oropharyngeal cancer patients undergoing radiochemotherapy offers added value beyond patient positioning. Weekly imaging at the C3 vertebral level allows longitudinal monitoring of SMI, revealing progressive sarcopenia even in patients with stable BMI. This underscores the potential of CBCT as a dual-purpose tool—enhancing both treatment accuracy and nutritional assessment—for early intervention and personalized care.

candidates[2], its effects on muscle deterioration and overall body composition remain insufficiently explored. Diagnostic CT at the L3 level is the reference standard for body-composition assessment; however, cervical (C3) measures appeared to correlate with L3[3].

Radiotherapy allows for precise targeting of the tumor while minimizing damage to surrounding healthy tissues[4]. Concomitant chemotherapy, typically platinum-based, acts as a radiosensitizer, improving the efficacy of radiation therapy[5,6]. Intensity-Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) provide highly conformal dose distributions, thereby reducing radiation exposure to critical structures[7]. Image-guided radiotherapy enhances treatment accuracy by incorporating daily imaging, such as cone-beam computed tomography (CBCT), ensuring proper patient positioning and tumor localization throughout the treatment course[8]. CBCT images are systematically stored in record and verify software, such as MOSAIQ Elekta, allowing for easy retrieval and post-treatment analysis.

During treatment for oropharyngeal carcinoma, muscle loss and sarcopenia are associated with decreased treatment tolerance, prolonged recovery times, and poorer overall survival[9-12]. A scoping review highlighted that sarcopenia is associated with increased treatment toxicity, reduced response to therapy, and poorer overall survival in HNC patients[13]. However, there are currently few tools available in outpatient oncology settings to effectively monitor nutritional status. Most assessments rely primarily on serial weight measurements and/or BMI evaluations, which may not provide a comprehensive picture of muscle depletion and sarcopenia[14]. Early identification of these changes could lead to modifications in supportive care strategies for these patients, improving treatment tolerance and clinical outcomes. Previous studies[15] have highlighted that sarcopenia can occur even without significant weight loss, suggesting that traditional weight-based assessments may not be sufficient for detecting clinically relevant changes in muscle mass. Martin et al[16] (2013) highlighted that skeletal muscle depletion can be present across all BMI categories, indicating that weight stability does not necessarily equate to preserved muscle mass. Consequently, relying solely on weight or BMI may lead to an underestimation of muscle depletion, emphasizing the need for more sensitive and specific imaging-based assessments. CBCTs routinely acquired can be used for longitudinal monitoring of body composition, providing clinicians with timely signals of treatment-related sarcopenia without the need for additional imaging sessions.

Beyond the catabolic effects of the tumor itself, radiation and chemotherapy may independently contribute to muscle atrophy through systemic inflammation, oxidative stress, and direct metabolic disruptions, further complicating the assessment of nutritional decline.

A key uncertainty remains whether these changes are primarily driven by reduced caloric intake due to treatment-related toxicities or if the treatment directly contributes to alterations in body composition through mechanisms, such as systemic inflammation, metabolic alterations, and direct muscle catabolism[17-19]. Radiation-induced muscle degradation and chemotherapy-related toxicity may exacerbate catabolic pathways, leading to accelerated muscle loss, which is also independent of caloric intake.

Disentangling the effects of malnutrition from direct treatment-induced muscle loss is crucial for tailoring supportive interventions, including targeted nutritional strategies and physical rehabilitation programs, to mitigate sarcopenia and improve patient outcomes. Understanding the relative contributions of malnutrition and treatment-induced muscle loss is crucial for developing personalized interventions to enhance clinical outcomes.

This study aims to evaluate whether CBCT, a tool already integrated into routine IGRT workflows, can be leveraged beyond its conventional role in patient positioning to assess longitudinal changes in body composition. We hypothesized that serial CBCT would detect a measurable, week-on-week decline in cervical paraspinal muscle metrics (SMI/area) during radiochemotherapy – even in patients with stable BMI – thus enabling earlier, targeted supportive care.

PATIENTS AND METHODS

Between November 1, 2018, and December 31, 2024, 169 inoperable oropharyngeal cancer records were retrieved from our Record & Verify database. Patients with distant metastases (28/169, 16.9%) were excluded from the analysis. Consequently, 47/169 (27.8%) patients received palliative RT and/or systemic therapy. Finally, 15 patients who maintained a stable weight with a deviation of no more than three kilograms during treatment were included in this retrospective analysis. All 15 patients had locally advanced disease (stage III-IV), with a Karnofsky performance status (KPS) of ≥70, hemoglobin of ≥10 g/dL, total leukocyte count of ≥4,000/mm³, platelet count of≥100,000/mm³, creatinine clearance of ≥60 mL/minute, and regular liver function tests.

This study was an exploratory, single-center, retrospective feasibility analysis. The sample size (n=15) reflects stringent eligibility criteria (weight stability during treatment and availability of serial CBCTs) to ensure protocol uniformity and high-quality longitudinal data. Given the hypothesis-generating aim, no a priori power calculation was performed.

All patients were treated with the IMRT or VMAT technique, delivered using a VERSA HD (Elekta, Stockholm, Sweden) linear accelerator, with simultaneous integrated boost (SIB) in 33 fractions of 2.12 Gy to the high-risk volume and 1.65 Gy to the low-risk volume for a total dose of 69.96 Gy and 54.45 Gy, respectively. The radiotherapy treatment was delivered using image-guided radiotherapy (IGRT), which involved daily cone-beam computed tomography (CBCT) scans to ensure precise tumor targeting and adaptive treatment adjustments. Twelve patients (80%) received concurrent cisplatin-based systemic treatment. All patients were monitored weekly in an outpatient setting with weight checks and nutritional counseling, and oral nutritional supplements (ONS) were prescribed to all.

Methods to obtain body composition

CT imaging enables the precise quantification of body composition by distinguishing between muscle and adipose tissue based on their radio-density, measured in Hounsfield Units (HU). Muscle tissue, subcutaneous fat, and visceral fat exhibit distinct HU ranges – skeletal muscle: -29 to +150 HU, subcutaneous fat: -190 to -30 HU, visceral fat: -190 to -30 HU. A common approach in body composition analysis is the selection of a single axial slice at a standardized anatomical location[20]. The third lumbar vertebra (L3) is the most widely used landmark in oncology due to its strong correlation with whole-body muscle and fat mass. However, muscle quantification is often performed at the C3 vertebral level in patients with head and neck cancer, as it strongly correlates with L3 measures. This correlation suggests that cervical-level assessments can serve as a valid surrogate for whole-body composition analysis, enabling body composition assessment without the need for additional dedicated imaging[3,21].

CBCT images (a volume reconstructed from 2D projections) lack a direct and consistent HU-to-density mapping compared with conventional CT due to scatter artifacts and a limited field of view. To correct HU values in CBCT-based images, we acquired a calibration phantom, the Gammex Tissue Characterization Phantom model 467 (Gammex, Middleton, WI, USA). This device was used to build a site-specific HU-to-physical-density calibration curve for our CT simulator and kV-CBCT workflows, supporting dose calculation and interpretation of tissue thresholds. The phantom, consisting of a 33 cm diameter Solid Water disk, is characterized by 2.8 cm diameter holes that can hold interchangeable rods made of different materials with a specific physical density[22]. Sixteen

Table I. Comparison of phantom insert physical densities and Hounsfield Unit (HU) values in CT and CBCT imaging.

Physical density g/cm^3	CT NUMBER CT simulator	CT NUMBER kV-CBCT
0.000	0	0
0.300	298	577
0.460	455	732
0.941	905	1,060
0.980	951	1,156
1.000	996	1,188
1.017	998	1,230
1.053	1,024	1,231
1.087	1,063	1,270
1.144	1,208	1,527
1.143	1,204	1,590
1.334	1,428	1,809
1.560	1,776	2,285
1.824	2,178	2,841
4.590	4,069	4,095

rods were inserted: LN-300 Lung, LN-450 Lung, AP6 Adipose, BR-12 Average Breast, Water Plug, four CT Solid Water rods, BRN-SR2 Brain, LV1 Liver, IB Inner Bone, B200 Bone Mineral, CB2 Resin – 30% $CaCO_3$, CB2 Resin – 50% $CaCO_3$, and SB3 Cortical Bone.

To achieve the purpose of this work, we scanned this phantom on the one hand with a CT simulator (SOMATOM Definition AS by Siemens, Forchheim, Germany) and on the other hand with the Elekta XVI (version 5.0.7.1) kilovoltage Cone-Beam CT (kV-CBCT) system mounted on the Versa HD linear accelerator (Elekta, Stockholm, Sweden) (Figure 1a). Both are located in the Radiation Oncology and Nuclear Medicine Section of the Department of Clinical Oncology of the AULSS 9 Scaligera, Verona. The phantom was acquired using head and neck scan protocols for CT and kV-CBCT, with a slice thickness of 3 mm and a kilovoltage of 100 kV. Table I lists the 16 physical densities corresponding to the Hounsfield Units in CT and CBCT, which generate the two curves in Figure 1b.

Table II summarizes CBCT acquisition and reconstruction parameters. CBCT acquisition was performed as part of standard clinical IGRT procedures using the Versa HD (Elekta) linear accelerator. As planned during the initial CT simulation, CBCT scanning was conducted in the treatment position with a thermoplastic mask for immobilization.

All CBCT images stored in the MOSAIQ (Elekta, Stockholm, Sweden) record and verify system are retrieved and sent to the MIM software (Cleveland, OH, USA). One image per week was analysed[23]. The total cervical paraspinal muscle area at the C3 level[3] was identified using an HU threshold with commercial software. Thresholds on CBCT (183-430) were derived from the site-specific phantom-based calibration and correspond to the classical CT range of −29 to +150 HU for skeletal muscle.

Area and attenuation (HU) were summarised for all 15 patients across weekly CBCTs (Table III). Increased intramuscular lipid content is reflected by lower attenuation (in Hounsfield units, or HU) and a reduced muscle area.

Statistical analysis

A comprehensive statistical analysis was conducted to evaluate changes in muscle composition over time in patients undergoing radiochemotherapy. Descriptive analysis was performed for continuous variables, including the Skeletal Muscle Index (SMI), muscle area, and muscle density (HU attenuation). Mean ± standard deviation (SD), median, and interquartile range (IQR), as well as the range (minimum-maximum values), were reported to provide a broader understanding of the variability in muscle measurements.

To analyze longitudinal muscle changes and trends over time, repeated weekly CBCT-derived measurements of muscle area and density were assessed using linear mixed-effects models (LMMs), which accounted for intra-patient correlations over multiple time points. This model treated time as a fixed effect, while patient ID was considered a random effect to control for individual variability. Additionally, post-hoc pairwise comparisons were conducted using Bonferroni correction to adjust for multiple comparisons across weekly time points and to identify signif-

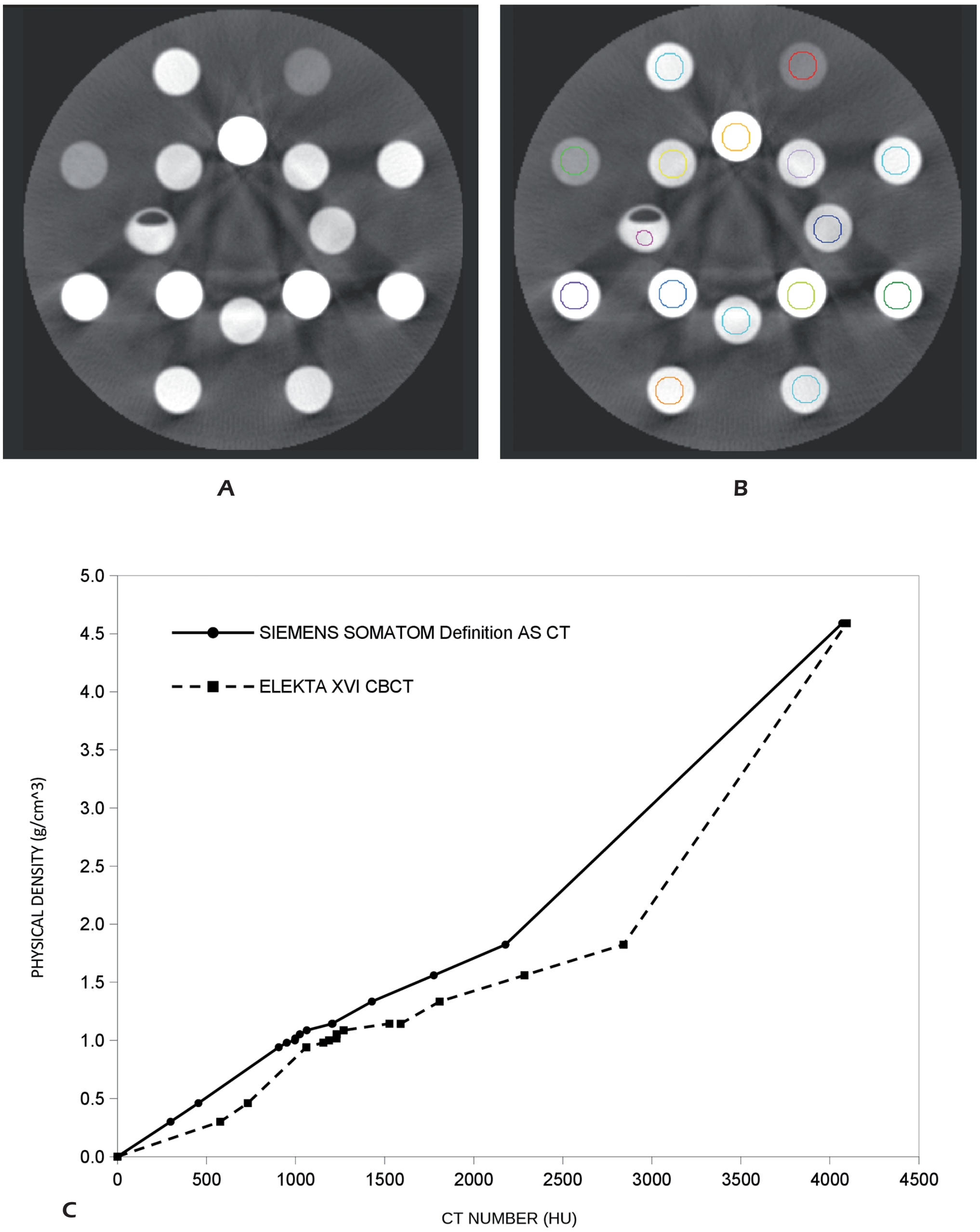


Figure 1. **A**, CBCT phantom acquisition; (**B**) selection of regions of interest (ROIs) on the phantom inserts; (**C**) calibration curves for CT and CBCT based on the measured HU values of different materials.

icant changes between different weeks. LMMs were selected over traditional repeated-measures ANOVA due to their ability to handle missing data points, control for intra-patient variability, and model individual trajectories over time.

Statistical tests were applied, depending on the data distribution, to compare the changes in muscle composition between Week 1 and Week 6. Paired *t*-tests were used for normally distributed data. At the same time, Wilcoxon signed-rank tests were applied for non-normally distributed data to ensure a robust assessment of significant differences over time. Effect sizes were calculated to quantify the magnitude of the observed differences, using Cohen's d for *t*-tests and rank-biserial correlation for Wilcoxon tests. A *p*-value of <0.05 was considered statistically significant for all analyses, ensuring that meaningful trends and differences were identified with high confidence.

To mitigate small-sample bias, we pre-specified the SMI slope over time as the primary endpoint and used linear mixed-effects models with patient-level random effects. Post-hoc contrasts were adjusted conservatively, and we report effect sizes with 95% confidence intervals in addition to *p*-values.

Table II. Parameters of CBCT acquisition.

CBCT mode	Head and Neck S20
Start acquisition angle (°)	25
Stop acquisition angle (°)	180
Reconstructed volume	512 × 512
kV collimator	S20
kV filter	F0
kV	100
Nominal mA per frame	10
Nominal ms per frame	10
Frames	183

CBCT: cone-beam computed tomography.

All statistical analyses were conducted using R software, which provided a flexible and powerful platform for performing mixed-effects modeling, hypothesis testing, and post-hoc adjustments. These rigorous statistical methods enabled an in-depth evaluation of muscle loss dynamics, revealing significant patterns of muscle depletion and underscoring the need for proactive clinical interventions to mitigate sarcopenia in patients with cancer.

RESULTS

Over the six-week radiochemotherapy course, a significant decline in SMI was observed, confirming progressive muscle depletion. While muscle area and weight exhibited steady reductions, mean HU values showed a non-significant downward trend, likely due to limitations in software-based segmentation. Table III presents the mean, standard deviation, and ranges of the Skeletal Muscle Index (SMI), muscle area, muscle density (HU values), weight, and body mass index (BMI) for all weekly CBCT assessments**.** Despite the small cohort size, the within-patient trend was

Table III. Characteristics of CBCT extrapolated parameters.

	Mean_HU	Muscle_Area_cm²	SMI	Weight_kg	BMI
Mean	225.25	1,972.64	7.37	67.05	25.03
Std	9.11	272.77	1.03	6.28	2.28
Min	208.0	1,309.9	5.12	50.0	19.5
25%	217.57	1,787.2	6.47	63.0	23.8
50%	228.75	1,986.95	7.46	67.25	25.05
75%	233.07	2,136.67	8.04	72.0	26.4
Max	239.4	2,432.8	9.5	78.0	28.9

SMI: Skeletal Muscle Index; BMI: Body Mass Index.

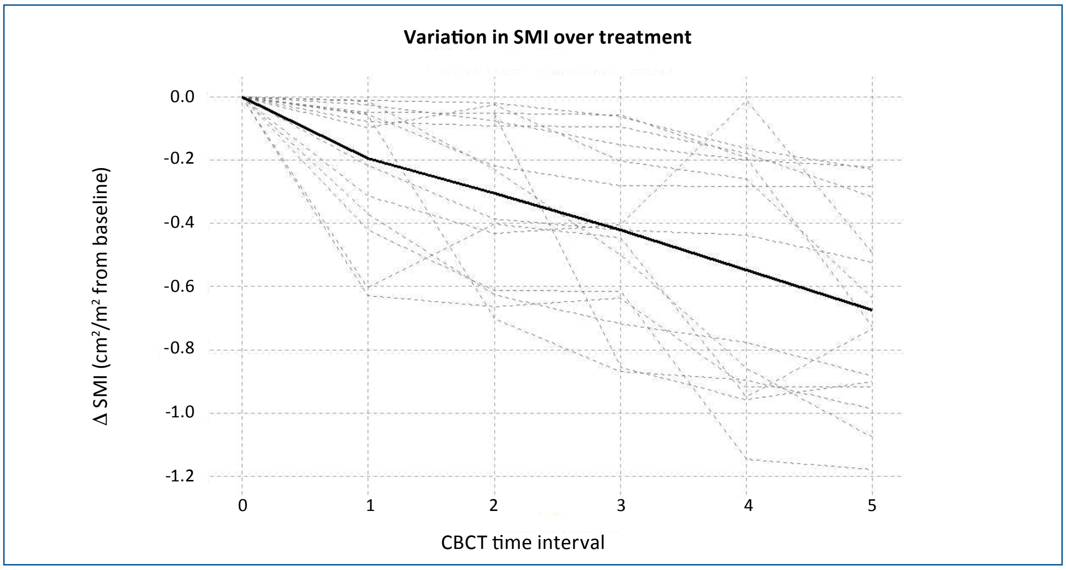


Figure 2. Individual trajectories and mean trend of the variation in Skeletal Muscle Index (SMI) over five CBCT time intervals during treatment. Each grey dashed line represents the SMI change of a single patient, while the bold black line indicates the mean variation across the cohort. The consistent downward trend illustrates a progressive reduction in skeletal muscle mass during therapy.

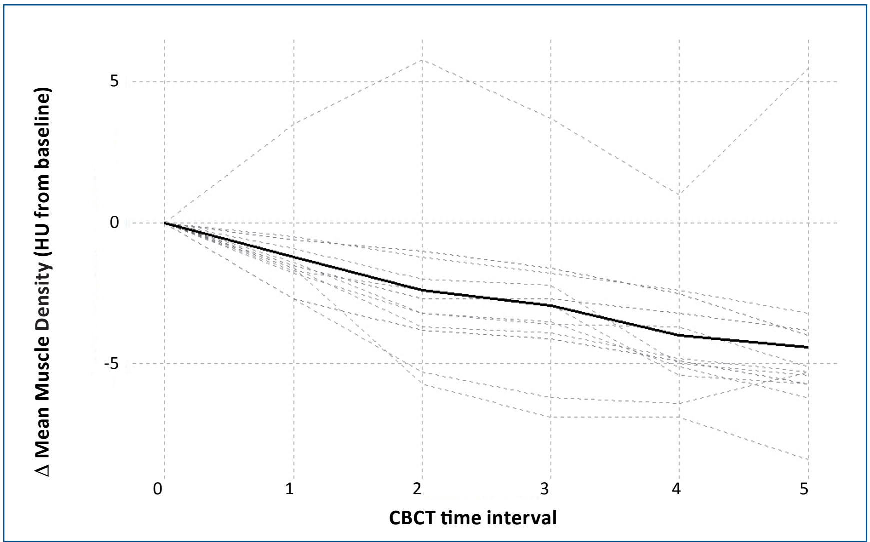


Figure 3. Individual trajectories and mean trend of variation in Mean Hounsfield Unit (HU) values across five CBCT time intervals during treatment. Each dashed grey line represents the change in muscle density for a single patient, while the thick black line indicates the average variation across all patients. The observed decline in mean HU values reflects a progressive reduction in skeletal muscle quality during radiotherapy.

directionally consistent across time points, and no single observation unduly influenced the overall effect (Figure 2).

The study analyzed longitudinal changes in the skeletal muscle index (SMI) of radiotherapy patients, including muscle area, muscle density (HU values), weight, and BMI. It revealed a progressive decline in SMI and muscle density, indicative of muscle depletion over time. A consistent decline in SMI was observed throughout the treatment course. The average SMI decreased progressively, highlighting treatment-induced muscle loss (Figure 2). Similarly, as measured by mean HU values, muscle density declined over time, suggesting increased intramuscular fat infiltration (Figure 3). These findings reinforce the impact of radiochemotherapy on muscle quality and overall body composition.

Linear mixed-effects models (LMMs) were used to account for intra-patient correlations across weekly CBCT assessments, enabling the assessment of muscle changes over time. Time (week) was included as a fixed effect, while patient grouping was treated as a random effect to account for

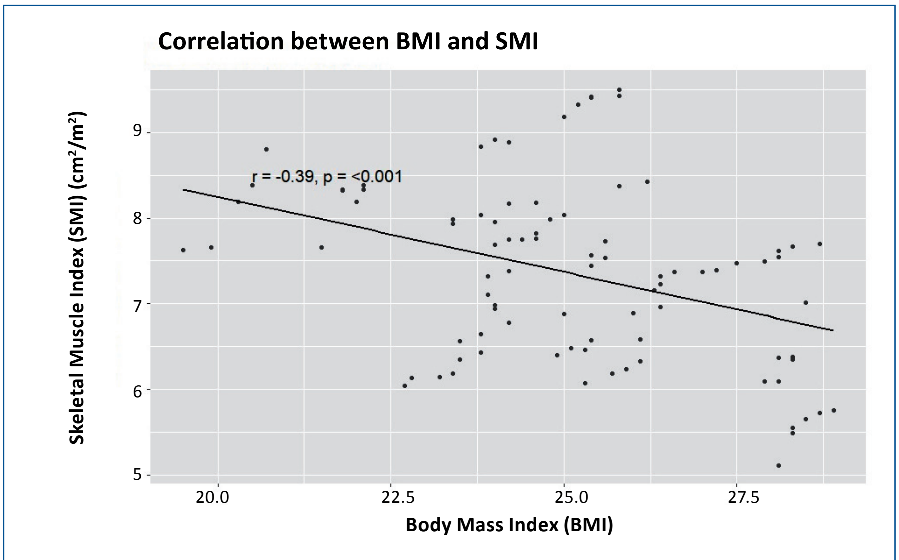


Figure 4. Scatter plot showing the correlation between Body Mass Index (BMI) and Skeletal Muscle Index (SMI) at baseline. Each dot represents an individual patient. A moderate negative correlation was observed ($r = -0.39$, $p < 0.001$), suggesting that higher BMI is associated with lower skeletal muscle index values.

inter-individual variability. The analysis revealed a significant decline in SMI over time, indicating progressive muscle depletion during radiotherapy. The intercept (baseline SMI) was 7.692 ($p < 0.001$), representing the initial muscle index before treatment initiation. With each additional treatment week, SMI decreased significantly by -0.130 ($p = 0.037$), confirming a steady decline in muscle mass throughout therapy. This finding underscores the catabolic impact of radiochemotherapy, emphasizing the need for early and intensive nutritional and supportive interventions. The most pronounced decline occurred after week 3, indicating accelerated muscle loss during the mid-to-late phase of radiotherapy.

Muscle density (HU) exhibited a different trend. The baseline means HU value was 227.455 ($p < 0.001$), but the weekly decline of -0.883 per week was not statistically significant ($p = 0.113$). This finding suggests that while muscle loss is consistent and measurable through SMI, changes in muscle quality (fat infiltration) are more variable, considering that areas with lipids are generally excluded from the definition of muscle. A moderate negative correlation ($r = -0.39$, $p < 0.001$) was found between SMI and BMI (Figure 4). This finding suggests that patients experienced muscle depletion, even though their BMI did not decrease proportionally, possibly due to the retention of fat. This finding underscores the limitations of BMI as a sole indicator of nutritional status in oncology patients, highlighting the importance of direct assessments of muscle composition using CBCT.

DISCUSSION

The results of this study confirm the significant impact of radiochemotherapy on skeletal muscle mass, as evidenced by the progressive decline in the Skeletal Muscle Index (SMI) throughout the treatment course. This muscle loss is particularly concerning given its established association with increased treatment-related toxicities, impaired functional status, and poorer survival outcomes in oncology patients. By utilizing cone-beam computed tomography (CBCT) for longitudinal muscle monitoring, we gain a valuable, non-invasive tool for detecting early signs of sarcopenia and implementing timely interventions to mitigate its effects[24,25].

Compared with conventional diagnostic CT (L3 as reference, with C3 correlates in head-and-neck settings), CBCT is already acquired daily for image-guided radiotherapy (IGRT), enabling high-frequency, treatment-course tracking without the need for additional imaging sessions or radiation beyond standard IGRT. Since CBCT covers a smaller area and is more prone to artifacts, HU values are less reliable; area-based trends, such as SMI, are usually preferable. Evidence on CBCT for longitudinal muscle quantification is limited. In head and neck cancer, a feasibility study[21] reported excellent inter-observer reliability for C3 muscle area on CBCT and a strong correlation with CT measurements, supporting CBCT as an alternative for on-treatment monitoring. Our findings are directionally consistent and extend prior evidence by quantifying weekly SMI trajectories on routine IGRT CBCT under a site-specific HU calibration and by proposing a pragmatic pathway to trigger nutritional/rehabilitative interventions based on CBCT-derived trends.

A key finding of this study is the statistically significant decrease in SMI over time, confirming that muscle atrophy is a progressive and measurable consequence of radiochemotherapy. In linear mixed-effects models with patient-level random intercepts, SMI declined by 0.13 cm^2/m^2/week ($p = 0.037$). Each additional treatment week resulted in a significant reduction in muscle area, supporting the hypothesis that muscle loss accelerates during therapy due to the metabolic burden of cancer, treatment-induced catabolism, and reduced oral intake caused by mucositis and dysphagia. This observation aligns with a prior study[26] demonstrating that sarcopenia in head and neck cancer patients is driven by a complex interplay of systemic inflammation, increased energy demands, and physical inactivity. The loss of skeletal muscle mass contributes to treatment intolerance, increased hospitalizations, and worse oncologic outcomes, making it a critical factor to monitor during therapy[27].

Interestingly, while the Mean HU values (indicative of muscle density and quality) also exhibited a downward trend, this reduction was not statistically significant. A plausible explanation for this finding lies in the threshold-based segmentation method used in CBCT analysis. Since the software identifies muscle tissue by applying fixed HU thresholds, the inner regions of the muscle that fall below the lower HU limit – often corresponding to areas of intramuscular fat infiltration – are partially excluded from the segmented volume. Consequently, the analysis primarily captures the denser muscle core, while overlooking the lower-density regions. This selective inclusion may lead to an underestimation of the actual decline in Mean HU values, even when qualitative muscle degradation is occurring. In other words, the observed discrepancy between the significant reduction in muscle area and the non-significant change in Mean HU may stem from the methodological filtering of low-density voxels within the muscle. In addition, residual HU variability inherent to CBCT can blunt sensitivity to small density shifts, despite phantom-based calibration. Future pipelines that quantify intramuscular fat explicitly (beyond thresholding) may improve CBCT's responsiveness to quality changes. This hypothesis suggests that while Mean HU remains a critical parameter for assessing muscle quality, its sensitivity may be limited when using CBCT-based thresholding techniques rather than direct delineation methods. Accordingly, area-based trends remain the preferred CBCT metric, while density estimates require harmonized calibration and validation against diagnostic CT.

Another crucial finding is the moderate negative correlation ($r = -0.39$, $p < 0.001$) between SMI and BMI, indicating that muscle loss does not necessarily lead to a proportional reduction in BMI. This finding suggests that BMI remains relatively stable in some patients despite significant muscle loss, likely due to the retention or redistribution of fat. Cancer patients undergoing treatment often experience shifts in body composition, where muscle mass declines but fat stores remain unchanged or even increase due to metabolic adaptations, inflammation, and decreased physical activity. This phenomenon underscores the limitations of BMI as a nutritional marker in oncology patients, reinforcing the need for direct assessments of muscle composition *via* CBCT or CT imaging. BMI alone fails to differentiate between fat and lean mass, which may lead to an underestimation of sarcopenia risk in patients who maintain their weight but suffer from progressive muscle depletion.

The clinical implications of these findings are substantial, emphasizing the necessity of integrating routine CBCT-based muscle monitoring into standard oncologic care. Identifying early signs of muscle loss allows for timely nutritional and rehabilitative interventions, potentially preventing excessive sarcopenia-related complications. Patients with declining SMI values may benefit from tailored nutritional strategies, including high-protein diets, oral nutritional supplements, or even enteral feeding when necessary. Moreover, given the impact of sarcopenia on treatment tolerance and overall prognosis, early detection could enable treatment modifications or supportive interventions to improve patient outcomes. Using CBCT as a real-time, non-invasive monitoring tool provides an opportunity for adaptive interventions without additional imaging sessions or radiation exposure.

Predefined alert thresholds (e.g., a relative SMI drop defined by local policy) can standardize referrals and escalation pathways. When trending weekly CBCT-derived SMI at C3, two actions can follow:

– Alert: SMI drop ≥ 3% from baseline or a negative slope sustained for two consecutive weeks → dietitian review (within 72 h); optimize energy (≈ 25-30 kcal/kg/day) and protein (≥ 1.2-1.5 g/kg/day); start oral nutritional supplements; adjust textures for mucositis/dysphagia.
– Escalate: SMI drop ≥ 5% or a persistently steep decline → multidisciplinary review and consider enteral support (NG/PEG) if oral intake remains < 60% of requirements for > 7 days. Reassess after 7 days; step down once SMI stabilizes.

We acknowledge the relatively small sample size (n = 15) and the single-center design, which limit external generalizability; use of one CBCT platform with a local HU-calibration workflow and inclusion of weight-stable patients may also reduce applicability to other head-and-neck subsites, vendors, or patients with overt weight loss/cachexia, and the feasibility, hypothesis-generating nature of the study further limits external generalizability.

Future research should validate CBCT-derived muscle assessments in larger, extensive, multi-center cohorts and explore the integration of functional outcomes (such as handgrip strength and mobility tests) to provide a more comprehensive evaluation of sarcopenia. Additionally, investigating alternative segmentation techniques that account for intramuscular fat content may enhance the sensitivity of CBCT in detecting changes in muscle quality. Given that sarcopenia has been linked to higher chemotherapy toxicity, increased treatment interruptions, and worse survival, refining methods for its early detection remains a crucial area of research. Harmonized CBCT acquisition and HU-calibration protocols, along with automated segmentation that quantifies intramuscular fat, should be prioritized, and trajectories linked to clinically meaningful endpoints.

CONCLUSIONS

This study highlights the detrimental impact of radiochemotherapy on muscle mass in patients with oropharyngeal cancer. It underscores the limitations of relying solely on BMI as a nutritional marker. The significant decline in SMI observed over the treatment course reinforces the importance of proactive monitoring. In contrast, the lack of a statistically significant reduction in Mean HU values may be attributed to software-based segmentation limitations rather than an absence of muscle quality deterioration. By integrating CBCT-based muscle assessments into clinical practice, radiation oncologists can implement targeted interventions to preserve muscle mass, enhance treatment tolerance, and improve patient outcomes. As a hypothesis-generating, single-center study with a small cohort, these findings warrant validation in larger, multi-center cohorts with harmonized CBCT calibration and advanced segmentation approaches.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

Francesco Fiorica: Conceptualization, methodology, supervision, manuscript writing, and editing.
Manuela Coeli, Giorgia Condarelli, Silvia Tomasi, Giovanna Mon: Data collection, statistical analysis.
Umberto Tebano, Milena Gabbani: CBCT image processing and segmentation.
Jacopo Giuliani, Teodoro Sava, Milena Gabbani: Clinical patient management, nutritional monitoring.
Stefano De Rossi, Giovanni Tonoli: Patient recruitment.
Amanda Casirati, Riccardo Caccialanza: Nutritional interpretation.
Paolo Pedrazzoli: Oncological oversight and manuscript revision.
All authors have read and approved the final manuscript.

Funding

This research received no external funding.

Ethics Approval

This study was conducted as a secondary retrospective analysis of anonymized clinical and imaging data from patients previously enrolled in an ethically approved observational protocol entitled *"Clinical observational study: analysis and quantification of inflammatory cytokines released after radiotherapy (with or without chemotherapy) as potential prognostic markers"* (Comitato Etico per la Sperimentazione Clinica delle Province di Verona e Rovigo, protocol No. 2199CESC, approved June 12, 2019). The secondary use of these anonymized data was consistent with the objectives of the original approved protocol and, in accordance with national and institutional regulations, did not require additional ethical review, and the study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Informed Consent

Informed consent had already been obtained from all participants at the time of the initial study. All data used for this analysis were anonymized in accordance with ethical and legal standards.

ORCID ID

Francesco Fiorica: 0000-0002-9404-3655
Jacopo Giuliani: 0000-0003-4096-2514
Amanda Casirati: 0000-0002-6005-5068
Riccardo Caccialanza: 0000-0002-9379-3569
Paolo Pedrazzoli: 0000-0002-9419-7160

REFERENCES

1) Fuggle N, Shaw S, Dennison E, Cooper C. Sarcopenia. Best Pract Res Clin Rheumatol 2017; 31: 218-242.
2) De Felice F, Cattaneo CG, Franco P. Radiotherapy and Systemic Therapies: Focus on Head and Neck Cancer. Cancers (Basel) 2023; 15: 4232.
3) Zopfs D, Pinto Dos Santos D, Kottlors J, Reimer RP, Lennartz S, Kloeckner R, Schlaak M, Theurich S, Kabbasch C, Schlamann M, Große Hokamp N. Two-dimensional CT measurements enable assessment of body composition on head and neck CT. Eur Radiol 2022; 32: 6427-6434.
4) Marta GN, Silva V, de Andrade Carvalho H, de Arruda FF, Hanna SA, Gadia R, da Silva JLF, Correa SFM, Abreu CE, Riera R. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiother Oncol 2014; 110: 9-15.
5) Sharma A, Kumar M, Bhasker S, Thakar A, Pramanik R, Biswas A, Kumar A, Sikka K, Singh AC, Mallick S, Kumar R, Deo SVS, Kakkar A, Baghmar S, Sehrawat A, Sethi P, Kumar A, Seth S, Upadhyay AD, Thulkar S. An open-label, noninferiority phase III RCT of weekly versus three weekly cisplatin and radical radiotherapy in locally advanced head and neck squamous cell carcinoma (ConCERT trial). JCO 2022; 40: 6004-6004.
6) Buciuman N, Marcu LG. Dosimetric justification for the use of volumetric modulated arc therapy in head and neck cancer—A systematic review of the literature. Laryngoscope Investig Otolaryngol 2021; 6: 999-1007.
7) Kiyota N, Tahara M, Mizusawa J, Kodaira T, Fuji H, Yamazaki T, Mitani H, Iwae S, Fujimoto Y, Onozawa Y, Hani N, Ogawa T, Hara H, Monden N, Shimura E, Minami S, Fuji T, Tanaka K, Homma A, Yoshimoto S, Oridate N, Omori K, Ueda T, Okami K, Ota I, Shiga K, Sugasawa M, Asakage T, Saito Y, Murono S, Nishimura Y, Nakamura K, Hayashi R. Weekly Cisplatin Plus Radiation for Postoperative Head and Neck Cancer (JCOG1008): A Multicenter, Noninferiority, Phase II/III Randomized Controlled Trial. J Clin Oncol 2022; 40: 1980-1990.
8) Kilburn JM, Soike MH, Lucas JT, Ayala-Peacock D, Blackstock W, Isom S, Kearns WT, Hison WH, Miller AA, Petty WJ, Munley MT, Urbanic JJ. Image guided radiotherapy may result in improved local control in locally advanced lung cancer patients. Pract Radiat Oncol 2016; 6: e73-80.
9) Löser A, Avanesov M, Thieme A, Gargioni E, Baehr A, Hintelmann K, Tribius S, Krull A, Peterson C. Nutritional Status Impacts Quality of Life in Head and Neck Cancer Patients Undergoing (Chemo)Radiotherapy: Results from the Prospective HEADNUT Trial. Nutr Cancer 2022; 74: 2887-2895.
10) Zeidler J, Kutschan S, Dorfler J, Buntzel J, Huebner J. Impact of nutrition counseling on nutrition status in patients with head and neck cancer undergoing radio- or radiochemotherapy: a systematic review. Eur Arch Otorhinolaryngol 2024; 281: 2195-2209.
11) Grossberg AJ, Chamchod S, Fuller CD, Mohamed ASR, Heukelom J, Eichelberger H, Kanton ME, Hutchenson KA, Gunn GB, Garden AS, Frank S, Phan J, Beadle B, Skinner HD, Morrison WH, Rosenthal DI. Association of Body Composition With Survival and Locoregional Control of Radiotherapy-Treated Head and Neck Squamous Cell Carcinoma. JAMA Oncol 2016; 2: 782-789.
12) Cardellini S, Deantoni CL, Paccagnella M, Casirati A, Pontara A, Marinosci A, Tresoldi M, Giordano L, Chiara A, Dell'Oca I, Di Muzio NG, Caccialanza R, Mirabile A. The impact of nutritional intervention on quality of life and outcomes in patients with head and neck cancers

undergoing chemoradiation. Front Oncol 2024; 14: 1475930.

13) Jovanovic N, Chinnery T, Mattonen SA, Palma DA, Doyle PC, Theurer JA. Sarcopenia in head and neck cancer: A scoping review. PLoS One 2022; 17: e0278135.
14) Baxi SS, Schwitzer E, Jones LW. A review of weight loss and sarcopenia in patients with head and neck cancer treated with chemoradiation. Cancers Head Neck 2016; 1: 9.
15) Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, Compher C, Correia I, Higashiguchi T, Holst M, Jensen GL, Malone A, Muscaritoli M, Nyulasi I, Pirlich M, Rothenberg E, Schindler K, Schneider SM, de van der Schueren MA, Sieber C, Valentini L, Yu JC, Van Gossum A, Singer P. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr 2017; 36: 49-64.
16) Martin L, Birdsell L, MacDonald N, Reiman T, Clandin MT, McCargar LJ, Murphy R, Ghosh S, Sawyer MB, Baracos VE. Cancer Cachexia in the Age of Obesity: Skeletal Muscle Depletion Is a Powerful Prognostic Factor, Independent of Body Mass Index. J Clin Oncol 2013; 31: 1539-1547.
17) Rosa-Caldwell ME, Fix DK, Washington TA, Greene NP. Muscle alterations in the development and progression of cancer-induced muscle atrophy: a review. J Appl Physiol 2020; 128: 25-41.
18) Kiprian D, Czarkowska-Paczek B, Wyczalkowska-Tomasik A, Fuksiewicz M, Kotowicz B, Paczek L. Radiotherapy and radiochemotherapy increase serum levels of pro-inflammatory interleukin-6 and C-reactive protein in patients with head and neck cancers. Transl Cancer Res 2018; 7: 41-47.
19) Rübe CE, Wilfert F, Uthe D, Schmid KW, Knoop R, Willich N, Schuck A, Rube C. Modulation of radiation-induced tumour necrosis factor α (TNF-α) expression in the lung tissue by pentoxifylline. Radiother Oncol 2002; 64: 177-187.
20) Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008; 33: 997-1006.
21) Huang W, Tan P, Zhang H, Li Z, Lin H, Wu Y, Du Q, Wu Q, Cheng J, Liang Y, Pan Y. Skeletal Muscle Mass Measurement Using Cone-Beam Computed Tomography in Patients With Head and Neck Cancer. Front Oncol 2022; 12: 902966.
22) Constantinou C, Harrington JC, DeWerd LA. An electron density calibration phantom for CT-based treatment planning computers. Med Phys 1992; 19: 325-327.
23) Coeli M, Muraro M, Tebano U, Napoli G, Luca N, Grigolato D, Gabbani M, Rinaldi G, Falconieri F, Salgarello G, Mon G, Fiorica F. The automatized workflow of a radiation oncology department: a complete integration of the oncology information system MOSAIQ with hospital information system. WCRJ 2022; 9: e2248.
24) Cereda E, Cappello S, Colombo S, Klersy C, Imarisio I, Turri A, Caraccia M, Borioli V, Monaco T, Bernazzo M, Pedrazzoli P, Corbella F, Caccialanza R. Nutritional counseling with or without systematic use of oral nutritional supplements in head and neck cancer patients undergoing radiotherapy. Radiother Oncol 2018; 126: 81-88.
25) Caccialanza R, Cereda E, Klersy C, Nardi M, Masi S, Crotti S, Cappello S, Caisutti V, Brovia C, Lobascio F, Formisano E, Colombo S, Filippi AR, Bonzano E, Comoli P, CAtenacci L, Alberti A, Musella V, Ferrari A, Imarisio I, Tancredi R, Monaco T, Ghi MG, Bossi P, Pedrazzoli P. The efficacy of immunonutrition in improving tolerance to chemoradiotherapy in patients with head and neck cancer, receiving nutritional counseling: study protocol of a randomized, open-label, parallel group, bicentric pilot study. Ther Adv Med Oncol 2021; 13: 17588359211025872.
26) Endo K, Ichinose M, Kobayashi E, Ueno T, Hirai N, Nakanishi Y, Kondo S, Yoshizaki T. Head and Neck Cancer and Sarcopenia: An Integrative Clinical and Functional Review. Cancers (Basel) 2024; 16: 3460.
27) Ganju RG, Morse R, Hoover A, TenNapel M, Lominska CE. The impact of sarcopenia on tolerance of radiation and outcome in patients with head and neck cancer receiving chemoradiation. Radiother Oncol 2019; 137: 117-124.