https://doi.org/10.31925/farmacia.2025.6.10 **ORIGINAL ARTICLE**

NUTRITIONAL STATUS AND SALIVARY CYTOKINE DYNAMICS IN PATIENTS WITH HEAD AND NECK CANCERS UNDERGOING RADIOTHERAPY

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Abstract

This study evaluated the nutritional status and salivary inflammatory cytokines in patients with head and neck cancer (HNC) undergoing radiotherapy. Anthropometric parameters, NRS-2002 scores, and salivary IL-1β and IL-6 were assessed before and after treatment. BMI decreased significantly during therapy ($p = 5.16\times10^{-6}$), accompanied by a rise in nutritional risk, with NRS-2002 ≥ 3 increasing from 25.8% to 51.6%. Higher baseline NRS-2002 scores were significantly associated with subsequent percutaneous endoscopic gastrostomy placement ($p = 0.0007$). Salivary IL-1β increased significantly at treatment completion compared with baseline and controls, consistent with radiation-induced mucosal inflammation. IL-6 levels were significantly higher in patients than in healthy subjects at both time points ($p = 0.0142$ and $p = 0.00055$), but did not increase further during radiotherapy ($p = 0.0997$), which might suggest a predominantly tumour-driven chronic IL-6 activation. These findings indicate concurrent declines in nutritional status and dysregulation of inflammation during radiotherapy. Moreover, our results highlight the need for early, targeted nutritional strategies during radio/chemotherapy and support the exploration of anti-inflammatory or cytokine-modulating interventions as adjuncts to optimise therapeutic tolerance and outcomes.

Rezumat

Acest studiu a evaluat statusul nutrițional și citokinele pro-inflamatorii salivare la pacienți diagnosticați cu cancer de cap și gât supuși radioterapiei. Parametrii antropometrici, scorurile NRS-2002 și nivelurile salivare de IL-1β și IL-6 au fost determinate înainte și după tratament. A fost observată o scădere semnificativă a IMC pe parcursul terapiei ($p = 5.16\times10^{-6}$) și o creștere a riscului nutrițional, proporția pacienților cu NRS-2002 ≥ 3 crescând de la 25,8% la 51,6%. Scorurile NRS-2002 inițiale mai ridicate au fost asociate semnificativ cu necesitatea ulterioară de gastrostomie endoscopică percutană ($p = 0.0007$). Nivelul salivar al IL-1β a crescut semnificativ la finalul tratamentului comparativ cu momentul inițial și cu grupul de control, sugerând o inflamație accentuate a mucoasei indusă de iradiere. IL-6 a prezentat valori semnificativ mai mari la pacienți decât la voluntarii sănătoși în ambele momente ale determinării ($p = 0.0142$ și $p = 0.00055$), fără o creștere suplimentară pe parcursul radioterapiei ($p = 0.0997$), aspect ce sugerează o activare cronică a IL-6 predominant determinată de tumoare. Aceste rezultate indică o deteriorare concomitentă a statusului nutrițional și o disfuncție a răspunsului inflamator în timpul radioterapiei. De asemenea, este subliniată necesitatea unor intervenții nutriționale precoce și direcționate în cursul radio/chimioterapiei.

Keywords: head and neck cancer, radiotherapy, nutritional status, NRS-2002, salivary cytokines

Introduction

Head and neck cancers (HNC) are a heterogeneous group of malignant tumours that mainly affect the epithelium of the upper aerodigestive tract. These neoplasms are characterised by a high incidence and significant mortality and are often diagnosed at advanced stages when therapeutic options are limited [1, 2]. Because of the anatomical location and the complex functional role of the oropharyngeal region, treatment aims not only at tumour control, but also at preserving vital functions such as speech, chewing and swallowing [3].

In this context, radiotherapy, alone or in combination with chemotherapy, remains one of the main therapeutic strategies used in HNC [4]. Radiotherapy acts by inducing DNA damage in tumour cells, but irradiation

of healthy tissues in the oropharyngeal area produces inflammatory and degenerative damage to the mucosa, salivary glands and gustatory nerve endings, causing local inflammatory reactions and structural alterations that are clinically manifested by mucositis, xerostomia, dysgeusia and dysphagia [5, 6]. When combined with chemotherapy, the effects are amplified by cumulative systemic toxicity, with nausea, vomiting, fatigability and loss of appetite. These complications reduce oral feeding capacity and lead to decreased caloric and protein intake and the onset of nutritional imbalance [7].

Malnutrition is one of the most common and severe consequences of oncologic treatment in HNC. Rapid weight loss and muscle wasting, frequently associated with chronic inflammation and metabolic stress, define a catabolic profile that significantly impairs the ability to recover [8]. HNC patients with an inadequate nutritional status might present a reduced tolerance to treatment, an increased risk of infectious complications, delayed tissue healing and a higher rate of radiotherapy discontinuation [9].

Nutritional assessment is the systematic process of identifying, quantifying and monitoring nutritional risk and changes in body composition. Regular monitoring of these parameters enables early detection of nutritional decline and the implementation of appropriate interventions, such as diet therapy and enteral or parenteral support [10].

This study aimed to characterise the nutritional and inflammatory profile of patients with HNCs undergoing radiotherapy by analysing anthropometric parameters, the NRS-2002 score, and salivary levels of interleukin-1β and interleukin-6.

Materials and Methods

Study design and setting

This prospective, longitudinal study was conducted at the Amethyst Radiotherapy Clinic in Bucharest between August 2023 and April 2024 to assess the evolution of nutritional and inflammatory parameters in HNC patients undergoing radiotherapy.

The research protocol was approved by the Ethics Committee of the Amethyst Clinic, and all participants signed an informed consent. The research was conducted in accordance with the Declaration of Helsinki, with confidentiality and anonymity of patient data maintained.

Patients were assessed at two time points: before the initiation of radiotherapy (T0) and at its completion (T1). Each patient underwent periodic multidisciplinary assessments and continuous monitoring of their general status to identify and prevent adverse reactions and to adjust nutritional support.

Study population and selection criteria

Patients diagnosed with head and neck neoplasms, at various stages of localised or loco-regional disease, undergoing curative radiotherapy, were eligible for inclusion. Participants were selected based on clinical and functional criteria designed to ensure group homogeneity and the ability to complete the entire nutritional and biological monitoring protocol. A main inclusion criterion was a Karnofsky Performance Status (KPS) score > 70%. The KPS score is a clinical tool for assessing overall functional capacity, expressed as a percentage between 0 and 100, with 100% indicating a fully active patient and values below 50% reflecting dependence on care. A KPS score > 70% is suggestive of the patient's ability to perform daily activities without assistance [11]. In addition, a KPS score > 60% has been proposed as an indicator of eligibility for curative treatments and for inclusion in clinical trials [12].

In addition to functional status, only patients who completed the planned radiotherapy regimen in full, without interruptions, showed adequate compliance with weekly monitoring and nutritional assessments, consented to the collection of salivary biological samples at both stages of the study, and signed the informed consent form, expressing their agreement to the anonymous use of data for research purposes.

The exclusion criteria were: patients with poor functional status (KPS ≤ 70) or severe systemic conditions that could interfere with treatment tolerance, definitive interruption of radiotherapy for medical or non-medical reasons, inability to collect complete biological samples at one of the two study moments, presence of chronic inflammatory disease or active acute infection at the time of inclusion, as well as pharmacological treatments with immunomodulatory potential, such as corticosteroids, systemic doses of non-steroidal anti-inflammatory drugs or biological therapies.

The final selection of patients was made through a consecutive analysis of the medical records of individuals treated during the study period. Inclusion in the analysis was performed only after ensuring that all the above criteria were met.

Nutritional assessment

Nutritional assessment was performed before the initiation of radiotherapy (T0) and at the end of treatment (T1). Patients were monitored weekly to identify any changes during therapy. The nutritional assessment consisted of anthropometric measurements, validated nutritional screening tools and detailed clinical observations. The current body weight and height of each patient were measured, and their body mass index (BMI) was calculated. Weight loss during radiotherapy was classified into four grades (< 5%, 5 - 10%, 10 - 15% and > 15%) to define nutritional risk and decide when to initiate dietary intervention.

The Nutritional Risk Screening 2002 (NRS-2002) tool, developed and validated by the European Society for Clinical Nutrition and Metabolism (ESPEN),

was utilised to identify malnutrition risk early. This score consists of two components: nutritional status assessment (which takes into account weight loss, recent food intake and BMI) and disease severity, which reflects the metabolic impact of the underlying condition on energy requirements. An additional point is added to the score for patients aged > 70 years [13, 14]. The total score ranges from 0 to 7, and a score ≥ 3 indicates significant nutritional risk and requires active nutritional intervention [15]. The NRS-2002 is recommended for cancer patients, as it allows a standardised assessment that is comparable across centres and sensitive to rapid changes induced by treatments.

The clinical assessment included the analysis of symptoms with nutritional impact (nausea, vomiting, taste or smell disorders, dysphagia, odynophagia, xerostomia, mucositis, constipation or diarrhoea) and psychosocial factors that may influence food intake (anxiety, depression, social isolation). The dietary history was obtained through a nutritional interview and a 24-hour dietary survey.

Based on this information, individual energy requirements were calculated according to ESPEN guidelines [16]. Protein requirements were estimated at 1.2 - 2 g/kg body weight/day, and water requirements at approximately 30 mL/kg body weight/day, with adjustments for fever, dehydration, or comorbidities. Patients identified as having moderate or severe nutritional risk were included in a stepwise nutritional support protocol, individualised according to food intake and digestive tolerance. In cases where oral intake was insufficient (< 50 - 75% of estimated requirements), supplementation with high-calorie and high-protein oral nutritional supplements was recommended. For patients for whom oral intake became impossible or ineffective, the need for enteral nutrition was assessed and provided *via* a nasogastric tube or a percutaneous endoscopic gastrostomy (PEG). PEG is an enteral access method used in patients with severe dysphagia, in whom oral feeding no longer allows adequate intake, but digestive function is maintained [17]. According to the ESPEN guidelines, PEG placement is indicated when oral feeding is expected to be unsuccessful for >3-4 weeks or when weight loss exceeds 10% of initial weight [18].

Radiotherapy protocol and clinical monitoring

All patients included in the study underwent radical radiotherapy, in accordance with current standards of care for HNC. Radiotherapy was administered according to the attending physician's instructions, depending on the tumour location and individual anatomical characteristics.

For all patients included in the study, the total prescribed dose was 70 Gy, administered in 2 Gy fractions, 5 days a week, over 7 weeks.

During treatment, patients were clinically evaluated weekly, according to the institutional protocol, to identify acute adverse reactions early, adjust symptomatic management, and monitor nutritional status. During each visit, body weight, general clinical status, and updated NRS-2002 score were recorded, and patients were advised on dietary adaptation and hydration based on food tolerance.

Determination of inflammatory biomarkers

To determine inflammatory biomarkers, saliva samples were collected from all the patients included in this analysis at two time points: before the first radiotherapy session (T0) and at the end of the last session (T1). The samples were centrifuged to remove cellular debris and stored at −80°C until analysis.

IL-1β and IL-6 were measured using the Enzyme-Linked Immunosorbent Assay (ELISA) method with commercial kits (Cat. No.: E-EL-H0149 and E-EL-H6156, Elabscience). The determinations were performed according to the manufacturer's instructions, using the ThunderBolt® ELISA (Gold Standard Diagnostics, USA). The samples were allowed to defrost at ambient temperature, and subsequently, 200 µL were pipetted. Due to their high viscosity, certain samples required a 1:2 or 1:4 dilution with the Sample Diluent provided in the kit, which could have led to pipetting errors during analysis.

For IL-1β, the calibration curve was constructed by serial dilutions of the reference standard provided in the kit, according to the manufacturer's instructions. The standard was reconstituted to an initial concentration of 500 pg/mL and progressively diluted to obtain seven dilutions with concentrations ranging from 7.81 to 0 pg/mL (500, 250, 125, 62.5, 31.25, 15.63, 7.81, and 0 pg/mL). Similarly, for IL-6, the calibration curve was constructed according to the manufacturer's instructions, by serial dilutions of the reference standard reconstituted at an initial concentration of 100 pg/mL. Seven successive dilutions were prepared, yielding seven concentrations ranging from 1.56 to 100 pg/mL (100, 50, 25, 12.5, 6.25, 3.13, 1.56 and 0 pg/mL).

The optical density (OD) was measured at 450 ± 2 nm using a microplate reader. Absorption values were used to construct a standard curve by the four-parameter logistic (4-PL) method, and sample concentrations were determined by interpolation against this curve. The final results were expressed in pg/mL.

To distinguish between changes induced by cancer treatment and normal physiological variability, the results were compared with those of a group of healthy volunteers of similar age who were not subjected to immunomodulatory drug treatments and did not have acute or chronic inflammatory disease.

Statistical analysis

Statistical analyses were performed in R (R Foundation for Statistical Computing, version 4.5.1). Continuous variables were reported as median and interquartile range (Q1-Q3), and differences between more than two groups were tested nonparametrically with the Kruskal-Wallis test, followed, where necessary, by Dunn post-hoc comparisons with Bonferroni correction; for salivary cytokines, the normality of distributions was previously checked with the Shapiro-Wilk test. Associations between categorical variables were assessed with the χ^2 test (with Yates correction for 2×2 tables) or, in the presence of small expected frequencies/sparsity, with Fisher's exact test or χ^2 with simulated p-value (10,000 replicates). The significance threshold was set at $\alpha = 0.05$.

Results and Discussion

Malignant cells, tumour-associated fibroblasts, infiltrating macrophages and neutrophils, endothelium and platelets release a set of pro-inflammatory mediators. These signals support cell survival by inhibiting apoptosis, stimulate angiogenesis, invasion, and metastasis, and facilitate immune evasion by increasing PD-L1 expression and recruiting immunosuppressor cells (TAM, MDSC, Treg) [19]. Subsequently, circulating mediators induce a generalised catabolic state [20]. IL-6 stimulates the acute-phase hepatic response and hepcidin synthesis, generating inflammatory anaemia [21]. TNF-α and IL-1β modulate hypothalamic appetite centres, leading to anorexia and reduced intake [22]. In parallel, muscle proteolysis through the ubiquitin-proteasome system and autophagy, lipolysis and, in some patients, "browning" thermogenesis are activated, resulting in accelerated weight loss and sarcopenia [20].

Particularly for HNC, this inflammatory-catabolic picture is amplified by local and iatrogenic factors that reduce intake: dysphagia, odynophagia, trismus, xerostomia, mucositis and dysgeusia induced by malignant cells and radio/chemotherapy [23]. The result is a vicious cycle in which low intake overlaps with inflammatory catabolism, accelerating weight loss and sarcopenia. In practice, a spectrum from malnutrition to cancer-cachexia (usually defined as > 5% weight loss in 6 months or > 2% with BMI < 20 and/or sarcopenia) emerges, impacting treatment tolerance, toxicity and survival [24]. The magnitude of these phenomena varies inter-individually.

Radiotherapy, used for curative purposes in HNC, can induce complex molecular changes that contribute to the aggravation of tissue and metabolic reactions, thus complicating the clinical management of cancer patients [25]. Exposure of healthy tissues to ionising radiation generates intense oxidative stress through the formation of reactive oxygen and nitrogen species, which affect membrane lipids, proteins and cellular DNA. These lesions activate NF-κB-, MAPK- and p53-dependent signalling pathways, leading to increased expression of pro-inflammatory cytokines and endothelial adhesion molecules [26]. In the salivary glands, these processes promote acinar cell apoptosis and progressive fibrosis, leading to reduced salivary flow and an altered biochemical composition of the secretions [5].

Irradiation promotes the release of damage-associated molecular patterns (DAMPs), which stimulate macrophage and neutrophil recruitment and sustain chronic local inflammation [27]. At the same time, disruption of the epithelial barrier facilitates bacterial translocation and fungal colonisation, and can lead to mucositis, candidiasis, and taste perception disorders [28].

Therefore, the progressive deterioration of nutritional status in HNC patients could be a consequence of radiotherapy-induced changes in the mucosa and salivary glands [29]. Local inflammation, pain, xerostomia, and taste disorders can thus reduce food intake, while systemic inflammation can accelerate protein degradation and muscle loss. The imbalance between energy intake and consumption leads to malnutrition, sarcopenia and hypoproteinaemia, factors correlated with decreased treatment tolerance, increased risk of acute toxic reactions, delayed tissue healing processes and reduced therapeutic efficacy [30].

General characteristics

During the study period, a total of 159 patients with HNC were admitted to the clinic. Of these, only 31 met all inclusion criteria and were therefore included in this analysis. The average age was 58.94 ± 11.54 years, ranging from 33 to 83 years, and the initial body weight averaged 72.92 ± 15.81 kg.

The most common tumour site in the study group was the oropharynx (13 cases), followed by the larynx (8 cases) and the hypopharynx (4 cases). Oral cavity neoplasms were identified in 3 patients, and those with mixed laryngopharyngeal origin in 2 patients. Only one case was diagnosed with localisation in the salivary glands (Figure 1).

Most patients included in the study had a normal BMI at baseline (48%), while 29% were overweight, 13% were obese, and only 9.7% were underweight (Figure 2). Thus, it was observed that, before the initiation of radiotherapy, most patients had an apparently balanced nutritional status.

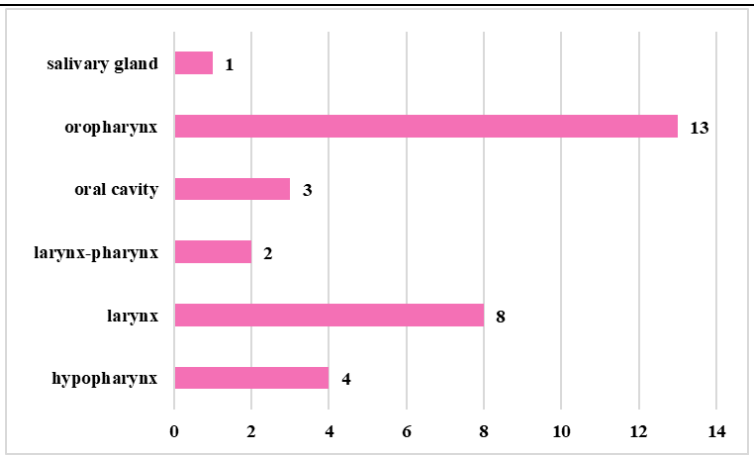


Figure 1.
Distribution of primary tumour locations in the study cohort

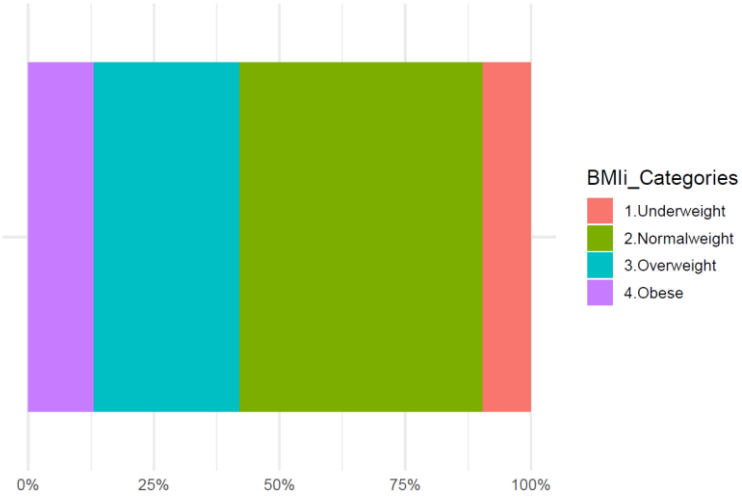


Figure 2.
Distribution of BMI categories before the initiation of radiotherapy

Changes in nutritional status during radiotherapy

BMI values decreased after completion of radiotherapy compared to baseline. A statistically significant reduction in BMI was observed ($p = 5.163 \times 10^{-6}$), highlighting the impact of treatment on patients' weight status (Figure 3).

The nutritional status of HNC patients can be substantially impacted by treatment, as evidenced by the decrease in BMI following radiotherapy. Even a moderate reduction in body weight may, in fact, suggest loss of muscle mass and protein reserves, with possible consequences on treatment tolerance, healing processes and clinical evolution [31].

Radiotherapy in the HNC region can cause damage to the oropharyngeal epithelium and salivary glands, associated with pain, dysphagia, xerostomia and dysgeusia, factors that can reduce food intake [25].

At the same time, repeated activation of inflammatory pathways promotes a catabolic state with amino acid mobilisation and increased use of energy substrates [32]. These processes may contribute to the loss of lean mass rather than fat mass, a phenomenon frequently reported in patients undergoing concomitant chemoradiotherapy [33].

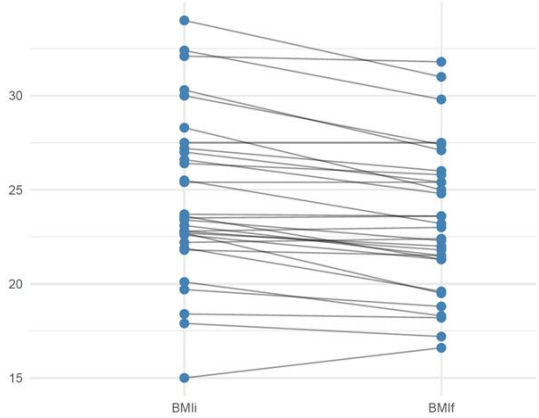


Figure 3.
Evolution of BMI before (BMIi) and after completion of radiotherapy (BMIf)

A study by Gjelstad *et al*. reported that at the conclusion of radiotherapy, 60% of patients experienced critical

weight loss, defined as a reduction of more than 5% from baseline. Yet, only 50% of these individuals received enteral nutrition therapy. It was found that 92% of patients were malnourished at the conclusion of treatment, with 71% remaining malnourished at follow-up [34]. In clinical practice, these observations underscore the importance of early nutritional risk assessment and the early initiation of nutritional support, whether oral, enteral, or parenteral, from the early stages of radiotherapy.

BMIf values varied across weight loss categories defined during radiotherapy. Median BMIs were slightly higher in the WLRT2 group than in WLRT1, while patients in the WLRT3 group had the lowest median BMI (Figure 4).

Thus, these results suggest that patients with a higher initial BMI were more likely to experience moderate weight loss. Even after weight loss, they still had a higher final BMI than those who initially had a normal BMI and lost less weight. In contrast, patients in WLRT3 had greater weight reduction and a significantly lower final BMI. It is important to note that the same proportion of weight loss does not have the same clinical significance for all patients: a 5 - 10% loss in an obese patient may seem acceptable, but may conceal a considerable loss of muscle mass, while a similar loss in a normal-weight patient may quickly lead to severe energy and protein depletion. In normal-weight or underweight patients, relative weight loss may be limited, but even a small reduction in body weight has important clinical consequences. In this category, decreases of less than 5% can lower BMI below safe thresholds, exposing the patient to the risk of protein-energy malnutrition and impacting treatment tolerance and tissue healing [35].

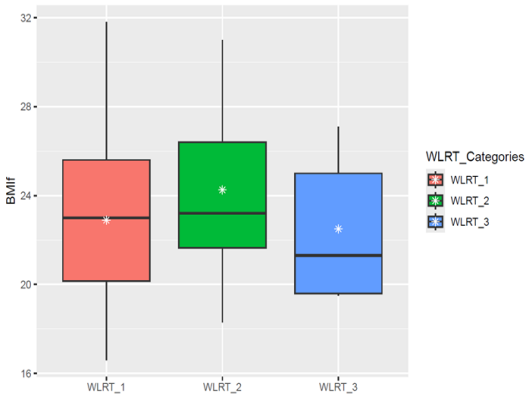


Figure 4.
Distribution of BMIf values according to weight loss categories during radiotherapy (WLRT)

Before radiotherapy, the proportion of patients with high nutritional risk (NRS score ≥ 3) was 25.8%. However, after treatment completion, it doubled to 51.6%, suggesting a substantial worsening of nutritional risk during treatment and supporting the need for serial monitoring and early nutritional interventions, especially in patients who were apparently stable at onset (Table I).

Table I
Distribution of NRS-2002 scores before and after radiotherapy (n = 31)

NRS-2002	Pre-radiotherapy (%)	Post-radiotherapy (%)
1	61.3	19.4
2	12.9	29.0
3	19.4	35.5
4	6.5	12.9
6	0.0	3.2

Similarly, Kono *et al*. reported that 30% of HNC patients experienced malnutrition prior to radiotherapy [36]. Moreover, Liu *et al*. indicated that the prevalence of malnutrition in HNC patients rises from 11.9% prior to treatment to 49.4% following radiotherapy or chemoradiotherapy. Patients at risk of malnutrition prior to therapy exhibited a lower survival rate compared to those at risk during treatment or those not at risk of malnutrition [37]. Malnutrition elevates the risk of infection, delays wound healing, impairs cardiac and pulmonary function, contributes to depression, causes muscle weakness, diminishes quality of life, increases post-operative complications, reduces the efficacy of chemotherapy and radiotherapy, and heightens mortality [38].

The age of the patients varied across the final NRS score categories, with no statistically significant differences between groups (Kruskal-Wallis test, p = 0.4). The median values were 60 years for NRS1, 55 years for NRS2, 60 years for NRS3, 72 years for NRS4, and 71 years for NRS6. There was a tendency towards older age among patients with higher NRS scores, corresponding to an increased nutritional risk (Figure 5).

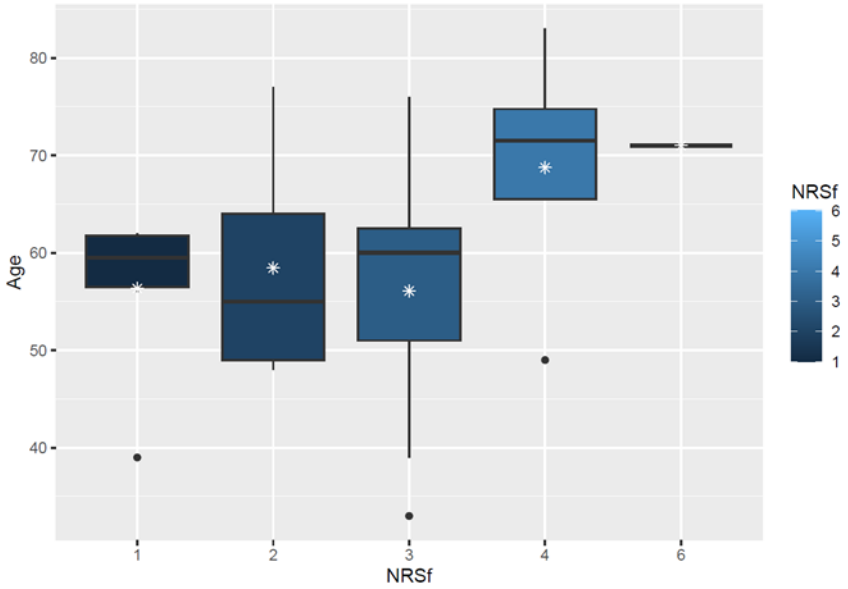


Figure 5.
Distribution of patient age according to the final NRS score at the end of radiotherapy

Correlations between clinical parameters, symptoms and treatment

Figure 6 shows a bubble plot with the initial nutritional risk score (NRSi) on the X-axis and the final score (NRSf) on the Y-axis. The colour of the dots indicates the weight-loss category, and their size indicates the age category, with older patients represented by larger bubbles. The points are concentrated in the NRSi 1-3 and NRSf 2-4 ranges. The WLRT1 category is the most common, covering most NRSi-NRSf combinations. The WLRT2 category occurs less frequently, especially in combinations with NRSf between 2 and 4, and WLRT3 is found mainly in combinations of low initial scores and moderate or high final scores (patients who went from an initial score of 1 to a final score of 3, from 3 to 4, or from 4 to 6). Bubbles corresponding to higher final scores (NRSf 4-6) tend to be larger, suggesting a higher proportion of elderly patients in these nutritional risk categories. In comparison, lower scores are associated with smaller bubbles.

Figure 7 shows the relationship between the initial nutritional risk score (NRSi, X-axis) and the final score (NRSf, Y-axis), analysed according to tumour location and patient age. A concentration of cases was observed in the NRSi 1-3 and NRSf 2-4 ranges, with low dispersion, suggesting that most patients had moderate initial and final nutritional scores. Patients with oropharyngeal tumours exhibit a wider range of values, from combinations with low initial scores and moderate final scores (1-2) to higher scores (3-4), indicating greater variability in the nutritional profile. Laryngeal and laryngopharyngeal tumours are predominantly located in the central area of the graph, corresponding to NRSi 2 and NRSf 2-4 ranges. In contrast, cases of oral cavity and salivary gland tumours are less numerous and are predominantly found in the lower area of the graph, associated with lower scores. There is also a tendency for older patients to be located in regions with higher final scores (NRSf 4-6). In comparison, younger patients are concentrated in areas with lower values for both indices.

In this study, an increase in nutritional risk scores during radiotherapy was observed, suggesting a gradual deterioration in nutritional status. Most patients presented with mild or moderate risk at baseline, but by the end of treatment, they had reached ranges corresponding to increased risk. Even weight losses of less than 5% were associated with increased risk scores, highlighting the sensitivity of this parameter in identifying early metabolic decline. Patients with losses of 5-10% generally showed a more pronounced worsening of nutritional risk, suggesting that moderate weight loss may have clinically relevant consequences for metabolic adaptation during radiotherapy. Patients who lost 10-15% of their weight showed a marked deterioration in nutritional status. Patients who initially appear stable at the onset of treatment may rapidly become susceptible to the metabolic stress induced by radiotherapy. It is plausible that, during treatment, the balance between anabolic and catabolic processes will progressively shift towards catabolism due to dysfunction of the neuroendocrine axis and increased resistance to insulin and leptin. This context leads to inefficient energy use and accelerated mobilisation of protein and lipid substrates [39]. Therefore, even in the absence of a significant initial nutritional risk, the accumulation of these metabolic disturbances could explain the steady nutritional decline observed during radiotherapy.

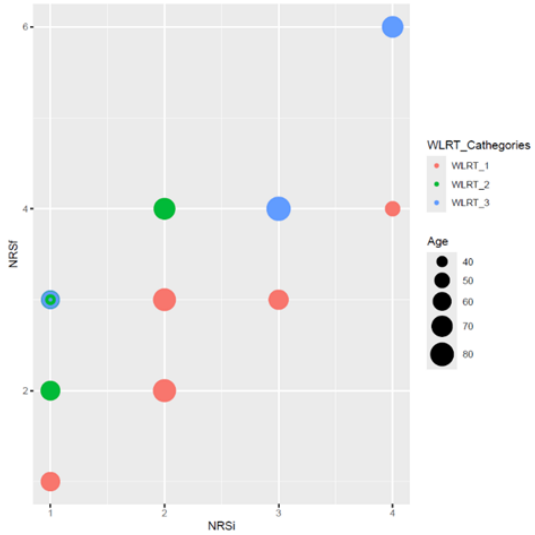


Figure 6.
Relationship between NRSi and NRSf, stratified by WLRT categories; dot size indicates age

At the same time, a higher proportion of elderly patients can be observed in the significant nutritional risk categories. This observation can be explained by the progressive reduction in anabolic capacity and metabolic plasticity with advancing age [40]. Elderly patients may often exhibit reduced muscle mass, a prolonged inflammatory response, and decreased sensitivity to insulin and leptin, which limit the efficiency of protein synthesis [41,42]. In this context, radiotherapy can act as an additional metabolic stress factor, accelerating the transition from moderate to severe nutritional risk.

Furthermore, patients with oropharyngeal tumours showed the most significant variability in nutritional risk scores, probably due to the clinical impact of dysphagia, extensive inflammation and local pain on nutrition. In contrast, patients with laryngeal or hypopharyngeal tumours had a more stable progression.

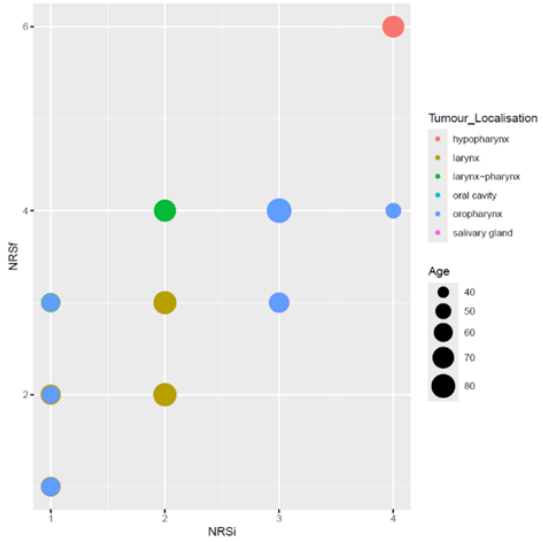
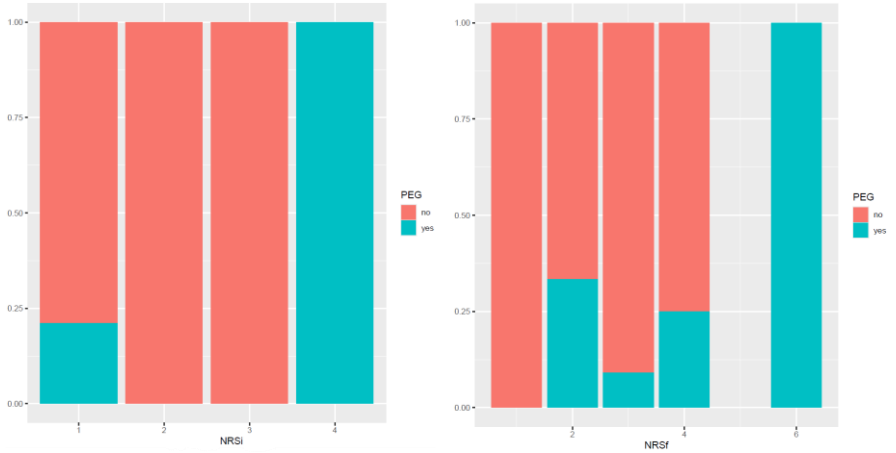


Figure 7.
Distribution of NRSi and NRSf scores according to tumour location and age

On the other hand, a statistically significant association was observed between the need for PEG placement and the initial NRS-2002 nutritional score (Fisher's Exact Test, $p = 0.0007$), suggesting that patients with higher nutritional risk (NRS ≥ 3) were significantly more likely to require PEG placement. In contrast, statistical significance was not maintained for the association between PEG and final NRS scores ($p > 0.05$) (Figure 8).



(a) (b)

Figure 8.
Association between the need for percutaneous endoscopic gastrostomy (PEG) and nutritional risk score (NRS-2002) in patients with HNC: (a) initial values (NRSi) and (b) values at the end of radiotherapy (NRSf)

The association between the need for PEG and the nutritional risk score at onset underscores the need for an initial nutritional assessment to identify vulnerable patients. The absence of a relationship

with the final score does not contradict this implication, as it is possible that the intervention may have mitigated the subsequent decline and, together with post-therapeutic variability and limited statistical power, reduced the contrast at the end. Additionally, corroborating these observations with the increase in NRS values at the end of treatment, even in patients who received PEG, could indicate that enteral intervention does not fully compensate for treatment-induced alterations in nutritional status. Furthermore, the NRS-2002 score presents a limitation in that it assesses overall nutritional risk, not just dietary intake. Thus, even when maintaining adequate caloric intake with PEG, parameters related to disease severity and treatment impact may lead to an increase in the total score. Besides, it is worth mentioning that there might be an indication bias, as physicians more often recommend PEG placement for patients assessed from the outset as having increased nutritional risk. Therefore, this observed association might reflect the initial clinical selection rather than an effect of the procedure itself. Consequently, these observations suggest that PEG is a necessary yet insufficient measure to prevent the exacerbation of nutritional risk during radiotherapy. Our findings support the need for prompt initiation of nutritional interventions and dynamic monitoring of metabolic status alongside clinical progression to enhance the management of oncology patients.

Among patients without PEG, the WLRT1 category was predominant, followed by WLRT2, and WLRT3 cases accounted for a much lower proportion. In contrast, among patients who required PEG placement, this distribution changed: the proportion in the WLRT2 and WLRT3 categories increased, while the frequency in WLRT1 decreased (Figure 9). This change in distribution could suggest a possible correlation between the severity of weight loss and the need for enteral support, with patients who needed PEG being more frequently associated with more advanced degrees of weight loss. However, the χ^2 test did not reveal a significant difference between the two groups ($p = 0.4$).

It is important to note that we observed a shift in the distribution towards weight loss of 5-10% and 10-15% in patients with a PEG tube. This could be explained by the fact that patients assessed at baseline as having a higher nutritional risk received a PEG tube after weight loss had already set in. Thus, early integration of the multidisciplinary team is important for objective assessment of swallowing and implementation of protocols to adapt nutritional support before significant weight loss occurs. Controlling toxicities that affect ingestion, such as pain, mucositis or xerostomia, along with standardising feeding tube care and hygiene, can help maintain adequate food intake.

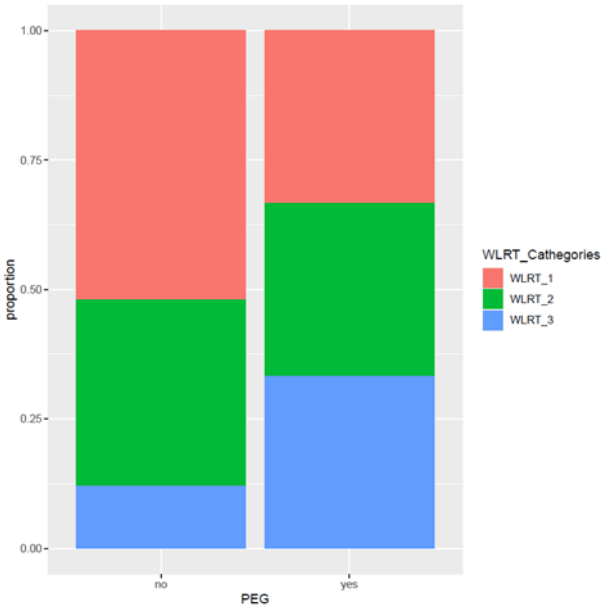


Figure 9.
Distribution of weight loss categories during radiotherapy (WLRT) according to the need for percutaneous endoscopic gastrostomy (PEG)

Figure 10 illustrates the distribution of patients according to the presence or absence of PEG and the incidence of specific oral complications. There is a slightly higher proportion of candidiasis cases among patients who required PEG than among those without PEG (50% versus 32%). However, the difference was not statistically significant (χ^2 test, $p = 0.6$). The incidence of ageusia was lower in patients with PEG than in those without (17% vs. 36%), but the difference did not reach statistical significance (χ^2 test, $p = 0.6$). In contrast, dysgeusia was significantly more common in patients without PEG (76%) than in those with PEG (33%), with the difference being statistically significant (χ^2 test, $p = 0.047$). This observation suggests a possible association between the need for PEG placement and a lower incidence of dysgeusia.

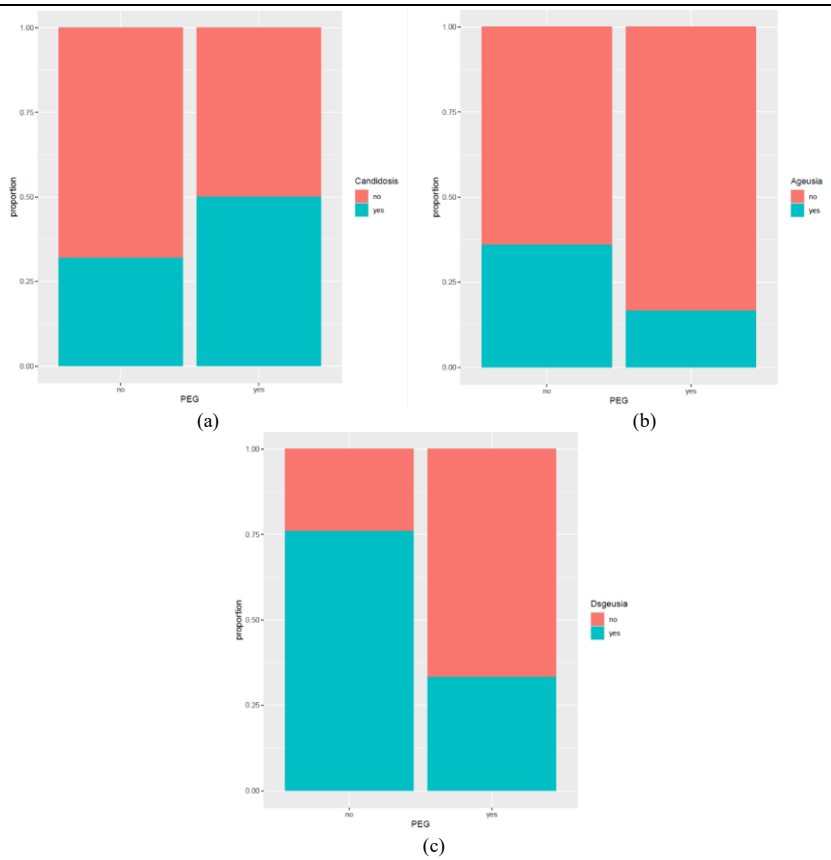


Figure 10.

Association between the use of percutaneous endoscopic gastrostomy (PEG) and the occurrence of oral candidiasis (a), ageusia (b) and dysgeusia (c) in patients with ENT cancers undergoing radiotherapy

The lower incidence of dysgeusia in patients with PEG can be explained by reduced or avoided oral intake after placement, which implies lower taste exposure and, implicitly, possible underreporting of taste disorders. It is also possible that patients with severe dysphagia were referred more quickly to enteral feeding, thus reducing contact with taste stimuli and the likelihood of perceiving or reporting taste changes.

Similarly, most patients with 5-10% and 10-15% weight loss underwent chemoradiotherapy, whereas those with <5% weight loss were registered in all groups. However, this variation did not reach statistical significance (Figure 11). This result could illustrate the cumulative effect of combined treatment, which increases requirements and the incidence of adverse reactions such as nausea, vomiting and anorexia. However, the variability in individual response suggests a heterogeneous effect.

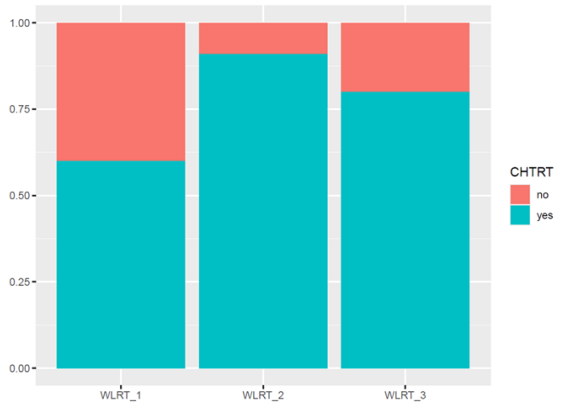


Figure 11.

Association between concomitant chemoradiotherapy (CHTRT) and weight loss categories during radiotherapy (WLRT)

The trend observed in this study aligns with a similar investigation by Berg et al., which included 47 HNC patients. The authors concluded that the group receiving radiotherapy and concomitant radio-chemotherapy experienced significant body weight loss during treatment and the initial phase of revalidation [43].

Candidiasis was more common in patients treated concomitantly with chemotherapy than in those who underwent radiotherapy alone, but the difference was not statistically significant (χ^2 with Yates correction, $p = 0.2$). The incidence of ageusia was similar between groups, with no statistically significant differences ($p > 0.9$). Dysgeusia was reported more frequently among patients receiving combination therapy than among those treated with radiotherapy alone, but the difference did not reach statistical significance ($p = 0.4$), suggesting only a trend toward a higher incidence of taste disorders with concomitant treatments (Figure 12).

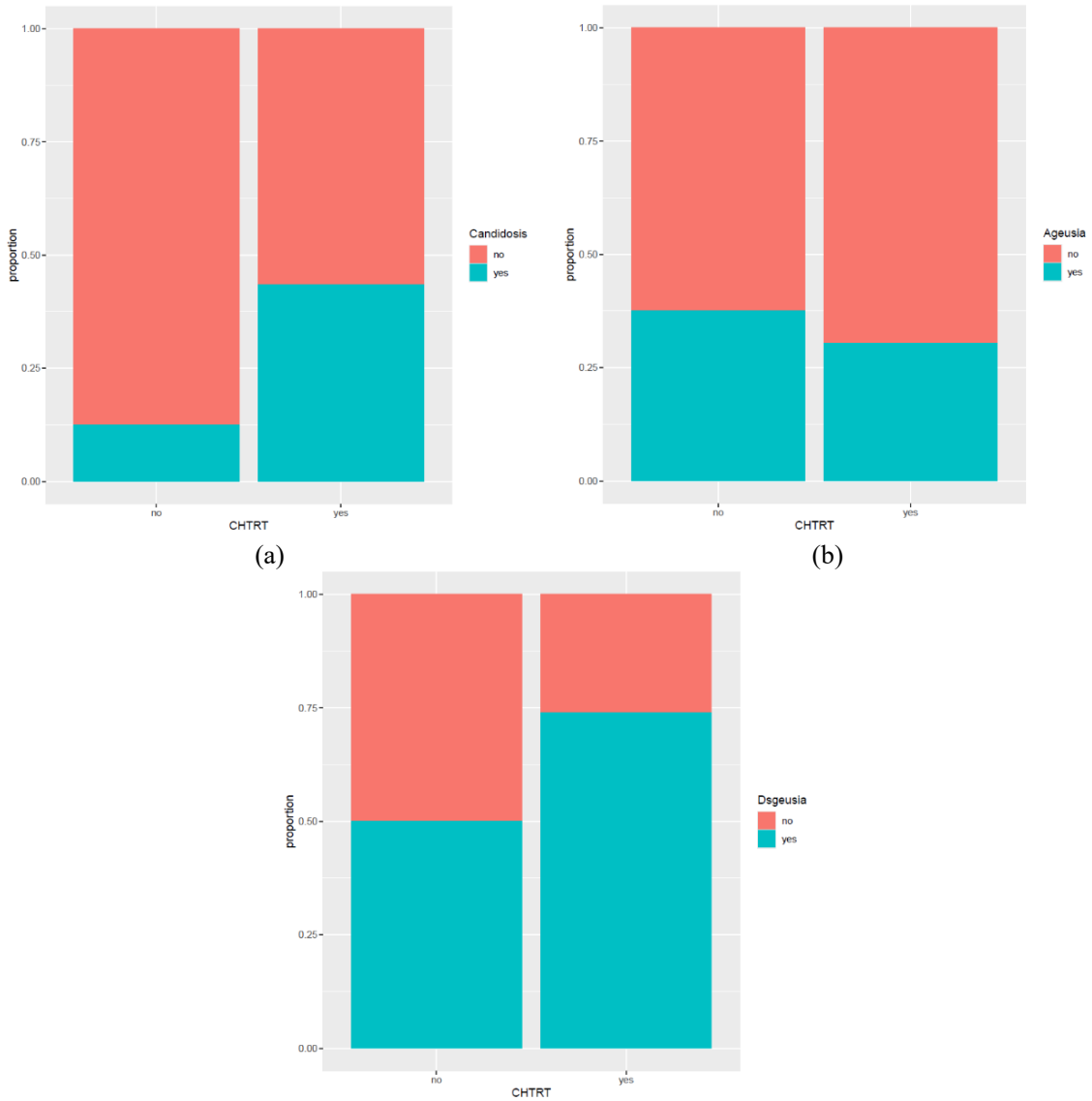


Figure 12.

Association between concomitant administration of radiosensitising chemotherapy and the occurrence of oral candidiasis (a), ageusia (b) and dysgeusia (c) in patients with HNCs undergoing radiotherapy

As the final NRS score increased, the frequency of oral symptoms tended to increase across certain nutritional risk categories. However, the distributions did not follow a linear pattern. Dysgeusia is present in more than half of patients in all categories and tends to increase towards higher NRS scores. These trends could illustrate a gradual worsening of oral symptoms as nutritional risk increases, but we did not identify any statistically significant differences (Figure 13).

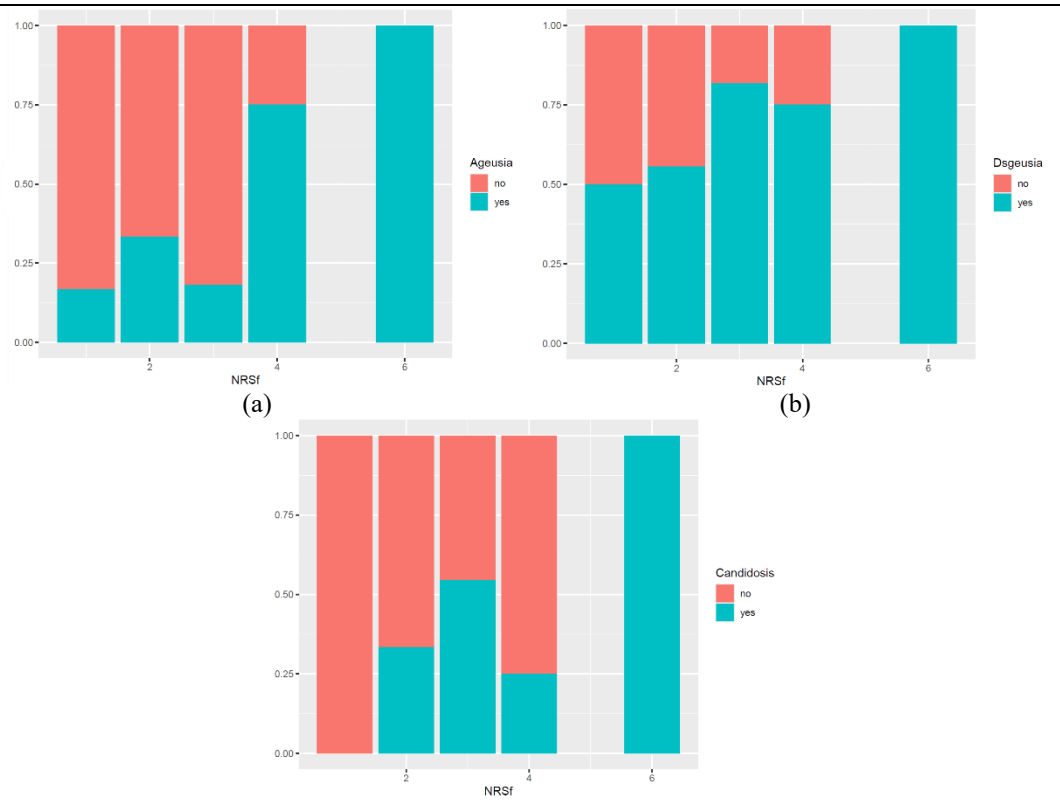


Figure 13.
Association between final NRS score and the presence of taste disorders or oral candidiasis in patients with HNCs: (a) final NRS and ageusia, (b) final NRS and dysgeusia, (c) final NRS and candidiasis

Furthermore, in patients without ageusia, dysgeusia is present in approximately half of cases, whereas all patients who developed ageusia also presented with dysgeusia (Figure 14).

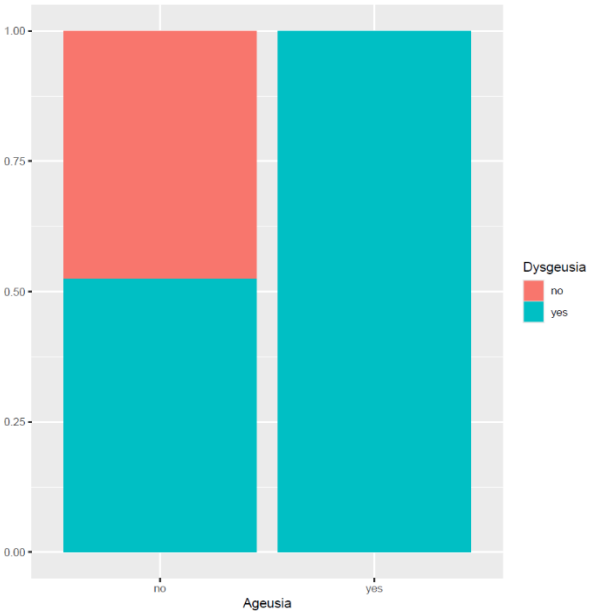


Figure 14.
Association between the presence of ageusia and dysgeusia in HNC patients with HNCs treated with radiotherapy or concomitant chemoradiotherapy

Thus, this observation suggests that HNC patients undergoing radiotherapy may experience worsening of taste disorders, ranging from altered taste perception to complete taste loss.

Our observations are consistent with a recent meta-analysis by Deshpande *et al*. It was determined that the majority of patients (70-100%) had partial or complete taste loss throughout radiotherapy. All five senses were found to be impaired. In contrast to the RT to the tip of the tongue, the bitter and salty flavours were found to be most severely affected, while the sweet taste was least affected. The 4th to 5th week following the commencement of RT saw a decline across all tastes, followed by an improvement in the 11th week. Patients experienced the most severe impairment during the fourth to sixth week [44].

Thus, dysgeusia could represent an intermediate phase, with a risk of progression to complete loss under certain conditions [25]. In HNC patients, taste dysfunction results from cytotoxic injury from chemotherapy, tumour-related inflammation, and radiation-associated epithelial and neural damage. Gustatory function is frequently adversely affected by the synergistic negative impacts of chemotherapy and radiotherapy [23].

Salivary biomarkers in HNC

Interleukin-1β is a proinflammatory cytokine initially synthesised in an inactive form (pro-IL-1β) in immune

cells, particularly macrophages and monocytes. A two-step mechanism regulates its production [45]. On the one hand, the first stage, called the "priming signal," is triggered by the activation of Toll-like receptors TLR2 and TLR4 by microbial ligands or by endogenous danger signals (DAMPs) released during cellular stress, ischaemia, or tissue necrosis. Activation of these receptors leads to signal transduction *via* the MyD88-IRAK-TRAF6 pathway, which activates the NF-κB transcription complex. This induces the expression of the *IL1B* gene and other proinflammatory cytokines, resulting in intracellular accumulation of pro-IL-1β [46]. On the other hand, the second stage, the "activation signal," involves the formation of the NLRP3 inflammasome complex, which is activated by a variety of stimuli, including oxidative stress, mitochondrial damage, changes in intracellular K^+ concentration, uric acid crystallisation, and ionising radiation. Activation of the NLRP3 inflammasome recruits the apoptosis-associated speck-like protein adaptor and caspase-1, which cleaves the pro-IL-1β precursor into its mature, biologically active form, which is then released extracellularly [47]. IL-1β then binds to the specific IL-1R1 receptor and reactivates the MyD88-IRAK-TRAF6 pathway, leading to the phosphorylation of IKK kinases and the transcriptional activation of NF-κB and AP-1. These complexes control the expression of genes involved in acute inflammation, such as IL6, TNFA, COX-2, and ICAM-1, thereby amplifying the local and systemic inflammatory response [48]. Activation of the IL-1β/IL-1R1 axis results in neutrophil recruitment, increased vascular permeability, fever induction, and stimulation of secondary production of other proinflammatory cytokines, reinforcing a self-stimulating cycle of inflammation [49]. In neoplastic pathologies, these mechanisms contribute to the remodelling of the tumour microenvironment, the accentuation of oxidative stress and the perpetuation of chronic inflammation.

In our study, Figure 15 illustrates a progressive increase in median IL-1β values from the control group to the post-radiotherapy time point (IL-1f), with the highest values and greater data dispersion compared to the other two groups. Statistical analysis was performed using the Kruskal-Wallis test, as the data distribution did not meet the normality condition (Shapiro-Wilk test, $p < 0.05$ for all three groups) and statistically significant differences were observed between the medians of the three groups ($p = 0.0159$). Post-hoc analysis showed an important difference between the control group and the IL-1f group ($p = 0.0153$), as well as between the IL-1i and IL-1f groups ($p = 0.0156$). No significant differences were observed between the control and IL-1i groups ($p = 0.459$).

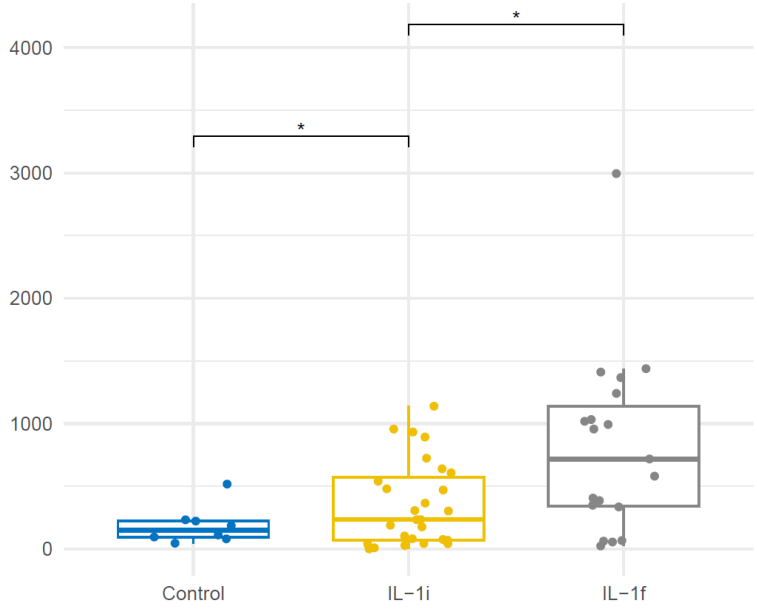


Figure 15.
Distribution of salivary IL-1β values in the control group at the start (IL-1i) and end (IL-1f) of radiotherapy

The increased IL-1β values observed at the end of radiotherapy, compared with baseline and the control group, could suggest an intense activation of the local inflammatory response induced by irradiation in the oropharyngeal mucosa. Thus, the significant increase in IL-1β after radiotherapy might be an indicator of acute inflammation of the irradiated mucosa, frequently correlated with clinical toxicities such as mucositis, xerostomia or dysphagia. The greater variability of post-radiotherapy values can be explained by individual differences in radiation sensitivity, nutritional status and oxidative stress

levels, factors that influence the intensity of inflammasome activation.

IL-6 is a proinflammatory cytokine involved in the regulation of the immune response and tissue regeneration processes, produced by macrophages, epithelial cells, and fibroblasts in response to various infectious or inflammatory stimuli [50]. IL-6 synthesis is predominantly controlled by the NF-κB and AP-1 signalling pathways, which are activated upon interaction of TLR4 receptors with bacterial lipopolysaccharides or endogenous molecules released during oxidative stress and tissue damage. Signal transduction through the MyD88-IRAK-TRAF6 complex leads to the activation of IKK and MAPK kinases, which promote the nuclear translocation of NF-κB and AP-1 factors and induce *IL6* gene expression [51]. After secretion, IL-6 acts by binding to its specific receptor IL-6Rα and the co-receptor gp130, activating the intracellular JAK/STAT3 and MAPK/ERK pathways. The phosphorylation and dimerisation of STAT3 cause its translocation into the nucleus, where it modulates the expression of genes involved in inflammation, cell survival, and angiogenesis [52]. In parallel, activation of the MAPK/ERK pathway contributes to the regulation of genes associated with tissue proliferation and regeneration [53]. The final effect of these processes is the amplification of the inflammatory response and the initiation of the acute phase, through the stimulation of hepatic protein synthesis, such as CRP and fibrinogen, and the recruitment of inflammatory cells locally.

Figure 16 illustrates a marked increase in median IL-6 levels from the control group to the IL-6i group and, subsequently, to the IL-6f group, with greater variability during the post-radiotherapy period. Analysis of the distribution of values showed that none of the three samples (control, IL-6i, IL-6f) met the normality assumption (Shapiro-Wilk test, $p < 0.05$). Consequently, the comparison between groups was performed using the Kruskal-Wallis test, which revealed statistically significant differences between the medians of the three groups ($p = 0.000911$). Post-hoc analysis (Dunn's test with Bonferroni correction) showed significant differences between the control group and the IL-6i group ($p = 0.0142$) and between the control group and the IL-6f group ($p = 0.00055$). No significant differences were found between the values recorded before and after radiotherapy ($p = 0.0997$).

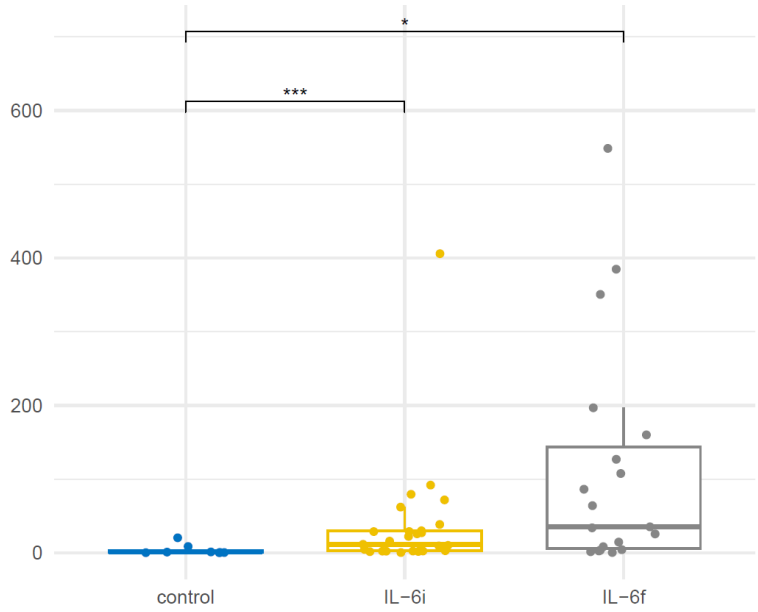


Figure 16.
Salivary IL-6 levels in the control group before (IL-6i) and after (IL-6f) radical radiotherapy

In our study, salivary IL-6 concentrations were significantly higher in HNC patients than in healthy subjects, both at baseline and at the end of radiotherapy. However, no significant post-therapy increase from pre-therapy values was observed.

First, a baseline, tumour-induced increase seems to dominate the IL-6 profile prior to treatment initiation. Malignant and stromal cells, together with tumour microenvironment-associated immune infiltrates, constitutively secrete IL-6, maintaining a chronically activated inflammatory state [54]. In this context, the additional stimulus represented by radiation-induced tissue injury might only result in a ceiling effect, limiting further increases in systemic or salivary IL-6 levels within the analysed detection range.

Second, a possible dissociation between local and systemic compartments may blur apparent changes in saliva. Radiotherapy affects the oral epithelium and salivary glands, reducing flow and secretory capacity [55]. Therefore, even if local inflammation

is amplified, the measurable salivary IL-6 level may not increase proportionally, potentially being diminished by hyposalivation or loss of epithelial integrity.

Additionally, IL-6 kinetics favour early, transient increases, often within days of an inflammatory stimulus [56]. Because samples were collected only at initiation and completion of treatment, it is possible that an intermediate peak of IL-6, coincident with the phase of mucositis intensification [57], may have been missed. By the end of radiotherapy, counter-regulatory mechanisms could have partially returned IL-6 levels to basal levels, despite the persistence of symptoms.

Accordingly, our data support the hypothesis that IL-6 levels are chronically maintained at elevated values in HNC due to persistent tumour inflammation, and that radiotherapy, in the context of the sampling scheme used and therapeutic co-interventions, did not induce a detectable additional amplification.

Conclusions

This study aimed to characterise the profile of patients with HNCs undergoing radiotherapy. An increase in salivary levels of IL-1β and IL-6 was observed at the end of treatment, along with an increase in the nutritional risk score and a decrease in body mass index, suggesting a worsening of inflammatory and nutritional status. The integration of nutritional assessment into the management of cancer patients is necessary to prevent deterioration in metabolic status, improve treatment tolerance, and reduce adverse reactions. In the future, further studies are needed to explore the role of inflammatory biomarkers and potential strategies to control inflammation, to optimise the prognosis and quality of life of these patients.

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Conflict of interest

Arsene AL is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process or any influence in terms of adjudicating on the final decision for this article. The other authors declare that they have no competing interests.

Velescu BȘ is a Managing Editor of the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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