# Systemic Inflammation Score for Predicting Radiation-Induced Trismus and Osteoradionecrosis of the Jaw Rates in Locally Advanced Nasopharyngeal Carcinoma Patients

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**ABSTRACT**

We sought to determine the predictive value of the systemic inflammation score (SIS) for radiation-induced trismus (RIT) and osteoradionecrosis of the jaw (ORNJ) in locally advanced nasopharyngeal carcinoma (LA-NPC) patients treated with concurrent chemoradiotherapy (C-CRT). LA-NPC patients (n= 188) who underwent C-CRT and pre- and post-C-CRT oral examinations from August 2010 to January 2022 were included. The three-tiered SIS groups were created using the serum albumin and lymphocyte-to-monocyte ratio (LMR) measures obtained on the first day of C-CRT: SIS-0: Albumin ≥ 40 g/dL and LMR ≥ 4.44); SIS-1: Albumin < 40 g/dL and LMR < 4.44 or albumin ≥ 0 g/dL and LMR ≥ 4.44; and SIS-2: Albumin < 40 g/dL and LMR <4.44. The primary objective was to ascertain whether there were irrefutable associations between pretreatment SIS groups and the respective post-C-CRT RIT and ORNJ rates. RIT and ORNJ were diagnosed in 33 (17.6%) and 21 (11.1%) patients, respectively. There were 12 (32.4%), 13 (12.7%), and 18 (45.0%) cases diagnosed with RIT in the respective SIS-0, SIS-1, and SIS-2 groups (p< 0.001). Similarly, there were 1 (2.7%), 11 (9.9%), and 9 (22.5%) cases with ORNJ diagnoses in the corresponding SIS groups (p< 0.001). The multivariate analysis's findings revealed that the SIS grouping was an independent predictor of RIT (p< 0.001) and ORNJ incidence rates (p< 0.001). Our study's findings indicate that the novel pretreatment SIS grouping is a dependable biomarker-based system, which can accurately predict the rates of RIT and ORNJ in LA-NPC patients who receive definitive C-CRT.

**Keywords:** Nasopharyngeal carcinoma, Systemic inflammation score, Radiation-induced trismus, Osteoradionecrosis, Biomarker

## INTRODUCTION

Despite significant advances in diagnostic imaging and screening approaches, most cases of nasopharyngeal carcinoma (NPC) are diagnosed at the locally advanced NPC (LA-NPC) stage, likely due to the disease's particular location and latent nature.[1,2] In the treatment of LA-NPC, concurrent chemoradiotherapy (C-CRT) replaces radiation alone or sequential chemoradiotherapy regimens.[3,4] Unfortunately, in addition to the advantages of C-CRT, a significant percentage of patients experience serious late complications, including radiation-induced trismus (RIT) and osteoradionecrosis of the jaw (ORNJ).

RIT and ORNJ rates have shown a downward trend despite innovations and developments in RT applications, but could not be completely prevented, so they should be considered as medical difficulties that need to be protected and treated as their negative effects on the quality of life (QoL) of patients continue to be seen.[5,6]

A wide variation in the prevalence of RIT (ranging from 5% to 65%) and trismus-related factors was found due to the limited inclusion criteria, single tumor localization, treatment modality, small sample sizes, and different cut-off points for trismus.[7-9] Similarly, in various head and neck tumors treated with RT or C-CRT, including LA-NPC[10,11], a large number of conventional disease, patient, and dosimetry-related factors were associated with increased ORNJ rates and approximately tumor, it has been reported to occur in 4-20% depending on the localization of the tumor, the extension of the tumor to the chewing apparatus or the jaw, treatment-related variables, and the definitions used.[12,13] Although patient, disease, and treatment-related risk factors are frequently blamed for both RIT and ORNJ[14,15], the patient's biological status and accompanying biomarkers are generally rarely addressed. However, Yilmaz et al. recently reported that pre-C-CRT low hemoglobin (Hb) and low hemoglobin-to-platelet ratio (HPR) values were associated with increased ORNJ rates after C-CRT (32.5% and 30%, respectively) in LA-NPC patients.[14,15] Moreover, Somay et al. recently declared that high neutrophil-to-lymphocyte value in parotid gland cancer, low HPR, and low Hb in LA-NPC were significant predictors of RIT after C-CRT and RT (35.2%, 34.1%, and 41.9%, respectively).[16-21] Findings of all these recent studies raise the possibility of using biomarkers reflecting a patient's overall immunological and inflammatory status as reliable indicators of treatment efficacy and late toxicity rates.

Another recently described biomarker is systemic inflammation score (SIS), derived from a combination of serum albumin and lymphocyte-to-monocyte ratio (LMR) scores, which has been proposed as a marker of inflammation and a predictor of the prognosis in several malignancies including oral, gastric, pancreatic and hepatic cancer.[22-25] Previously, Chang et al.[26] created SIS as a prognostic prediction score, a predictor of postoperative prognosis for patients with clear-cell renal cell carcinoma. Later, Li et al.[27] showed that in nasopharyngeal carcinoma and renal cell cancer, higher SIS was associated with worse outcomes in terms of overall survival. While further research has confirmed these findings in various cancer types[22-25],

it is regrettable that only the survival results of patients with NPC were analyzed, with no focus on the potential benefit of SIS in predicting treatment-associated side effects like RIT and ORNJ.

Chronic systemic inflammation[28], the seventh hallmark of cancer, has been shown to increase monocyte counts while decreasing lymphocyte levels.[29] Also, hypoalbuminemia can indicate malnutrition and is considered a significant and effective part of the systemic inflammatory response in cancer patients.[30,31] Additionally, the negative prognostic impact of low Hb, which is a possible indicator of tissue hypoxia has led to some unexpected toxicities in cancer patients.[32] Since previous studies have mentioned that the key determinants in the pathogenesis of RIT and ORNJ are inflammation and inflammation-induced tissue hypoxia, vascular occlusion, and fibrotic tissue repair[33,34], we hypothesized in this study that SIS could reliably predict the risk of severe late toxicity in LA-NPC patients. Thus, we aimed to evaluate the SIS, the combination of serum albumin and LMR, and their impact on RIT and ORNJ rates in LA-NPC patients after definitive C-CRT in this study.

## PATIENTS AND METHODS

### Study Population

This retrospective study was planned and conducted with the participation of Baskent University Faculty of Medicine, Department of Radiation Oncology and Dentistry. All data were collected through a retrospective review of the medical records of LA-NPC patients who underwent radical C-CRT and pre- and post-CRT radiological and oral examinations at our facility between August 2010 and January 2022.

Patients were considered eligible if they were between the ages of 18 and 80, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, had histopathologic evidence of squamous cell NPC, had evidence of locally advanced disease per the American Joint Cancer Committee (AJCC) 8th edition (T1-2N1-3M0 or T3-4aN0-3M0), had no prior cancer history, had not received systemic chemotherapy or RT to the head and neck, had received definitive C-CRT with at least one course of concurrent chemotherapy, and had available electronic records of RT dosimetry, an oral

and radiological examination, and complete blood counts before the starting of C-CRT. All patients with LA-NPC who did not have a diagnosis of temporomandibular disorder (TMD) before CCRT were included in the study cohort based on the current diagnostic criteria for TMD (DC/TMD).[35]

The inclusion criteria are as follows; (1) no history and proof of trismus or osteoradionecrosis at baseline oral examinations; (2) no evidence of head and neck or trauma; (3) no evidence of masticatory apparatus disorders including the temporomandibular joint; (4) no history of immunosuppressive or fibrotic disorders; (5) no history of immunosuppressive drug usage at past 30 days before the onset of C-CRT; (6) no history of blood transfusion at past 90 days and no evidence of dehydration; (7) no evidence of acute and chronic infectious disease. Also, individuals presenting with missing maxillary and/or mandibular central incisors, prior TMJ surgery, TMJ ankylosis, head and neck trauma, muscle-related pain or myofascial pain syndrome, or primary tumor or lymph node invasion of the masticatory muscles were also excluded from this study.

### Treatment Protocol

The simultaneous integrated boost intensity-modulated RT (SIB-IMRT) is the standard of care for treating LA-NPC at our institution. All RT target volumes were defined using pretreatment co-registered computed tomography (CT), 18-fluorodeoxy-glucose-positron emission tomography (PET)-CT, and/or magnetic resonance imaging (MRI) scans of the affected primary site and the entire neck.[36] Target volumes and their respective RT doses were defined in accordance with previous literature.[36] To give an overview, the doses to the planning target volumes (PTVs) were 70.0 Gy for high-risk PTVs, 59.5 Gy for intermediate-risk PTVs, and 54.0 Gy for low-risk PTVs, all delivered using single daily fractions over the course of 33 days.[36] Depending on patient tolerance, one to three cycles of chemotherapy with cisplatin were administered concurrently with RT (every 21 days). Adjuvant treatment, which consisted of two cycles of cisplatin and 5-fluorouracil chemotherapy regimen (every 21 days), was also recommended for all patients.

### Baseline and follow-up oral evaluation and the determination of RIT and ORNJ

RIT was defined as having a maximum mouth opening (MMO) ≤ 35 mm, in accordance with the standards previously established by Dijkstra et al.[37] We used Therabite® (Atos Medical AB, Hörby, Sweden) to measure MMOs due to its proven measurement accuracy and ease of application.[38] During the MMO measurement, the patient was instructed to position his/her head parallel to the Frankfurt horizontal plane and face forward. Patients were also instructed to open their mouths as wide as they could while wearing the Therabite® motion scale to measure the distance between the lower edge of one of the upper central incisors and the upper edge of one of the corresponding mandibular central incisors. The mean MMO was calculated as the arithmetic mean of three consecutive measurements per session. MMO measurements after C-CRT were collected for each patient at 1, 3, 6, 9, and 12 months using the same protocol to assess RIT status. These measurements were then taken as needed or at each regular appointment thereafter.

Regardless of the presence of symptoms, each patient underwent a detailed oral examination prior to C-CRT, as recommended routinely by the American Dental Association and the U.S. Food and Drug Administration.[39] An experienced oral and maxillofacial surgeon (ES) performed a comprehensive clinical and radiological evaluation of the oral cavity and associated structures in all cases. Also, panoramic radiographs were used in radiographic oral and dental examinations in all patients in accordance with our institutional norms. The same Veraviewepocs 2D X-ray machine (J Morita, Kyoto, Japan) was used for all digital panoramic radiographs and patients were positioned following the manufacturer's instructions. Exposure times were 70 kV, 10 mA, and 9 seconds.

In this study, when determining ORNJ status, radiological evidence of ORNJ with intact mucosa and clinical and radiological ORNJ diagnostic criteria were followed.[40] Based on these criteria, ORNJ was defined clinically as irradiated necrotic bone tissue that did not heal over a 3-month period without any sign of tumor progression or metastasis (40). In addition, Notani's classification was ap-

plied for ORNJ staging, which takes into account both radiological and clinical minor bone changes and the anatomical boundaries of lesions.[41]

**Calculating Baseline Systemic inflammation score (SIS), serum albumin, and lymphocyte-to-monocyte ratio (LMR) scores**

The SIS, serum albumin levels, and LMR were computed using the complete blood count and biochemistry test results obtained before the initiation of C-CRT. The LMR was calculated and the SIS was defined according to the methods of a previous report[26], using the combination of the LMR and the serum albumin concentrations. As a result, the SIS groups were created according to the original report[26]: SIS-0: Albumin ≥ 40 g/dL and LMR ≥ 4.44); SIS-1: Albumin < 40 g/dL and LMR < 4.44 or albumin ≥ 0 g/dL and LMR ≥ 4.44; and SIS-2: Albumin < 40 g/dL and LMR < 4.44.

*Ethics approval*: This retrospective study protocol adhered to the official rules of the Declaration of Helsinki and its amendments and was approved by the institutional Baskent University Medical Faculty Ethics and Science Committee (DKA:19/39–20.09.2019) before collecting patient data.

**Statistical Analysis**

The main objective of this retrospective study was to investigate any potential link between pre-CCRT SIS groups and post-CCRT RIT and ORNJ rates. In order to achieve this objective, we utilized the initial SIS groups that were previously established by Chang et al.[26] Categorical variables were expressed as percent frequency distributions, while continuous variables were expressed as medians and intervals. Chi-square test, Student's t-test, Pearson's exact test, ANOVA, or Spearman's correlation estimates were used as indicated to compare the frequency distributions of the desired factor according to different clinical variables, such as SIS groups. Only factors that were significant in univariate analysis were included in multivariate analysis. Each P value was bilateral and a value of < 0.05 was considered significant. Bonferroni corrections were applied to the P-values to reduce the possibility of false positive outcomes between the comparisons of three or more groups. The resultant P-values were subsequently employed to ascertain the degree of statistical significance.

**RESULTS**

The present investigation included 188 patients with LA-NPC who underwent C-CRT and met the specified inclusion criteria. Table 1 presents the patient and disease characteristics of the entire study cohort. The median age of the entire group was 55 years (range: 18–53 years). Males made up the majority (65.3%) of the study participants, and most had T3-4 tumor (75.5%) and N2-3 nodal (73.4%) stages. Smoking histories were present.in 68.6% of patients. All patients had dental extractions; the time between extractions and C-CRT ranged from 10 to 24 days, with a median of 16 days. Table 2 reveals that 138 (73.4%) patients received 1-2 cycles of adjuvant chemotherapy, while 149 (79.3%) received 2-3 cycles of concurrent chemotherapy. At a median follow-up of 37.8 months (range: 6–151.2 months) after C-CRT, all patients had additional teeth extracted, possibly as a result of poor oral hygiene. The mean masticatory apparatus dose (MAD) (consisted of TMJ, masseter, temporalis, lateral, medial pterygoids and related raphes) mean mandibular dose (MMD), and mean maximum mandibular point dose (MMPD) were 37.4 Gy (20.7-76.1), 34.3 Gy (10.2-52.4), and 52.7 Gy (30.6-77.2), respectively, for the entire study population (Table 2).

After the C-CRT, there was a 7.5% decline in MMO, which decreased from the baseline value of 41.3 mm (37.8-46.8) to 38.2 mm (25.9-41.0 mm). The median C-CRT-to-RIT interval was 10 months (range: 6–18 months), and RIT was diagnosed in 33 (17.6%) patients. 21 (11.1%) patients were diagnosed with ORNJ. The median interval between C-CRT and ORNJ diagnosis was 19 months (range: 15–32 months). Notani's ORNJ staging classified ORNJs into stages I and II in 14 (7.4%) and 7 (3.8%) patients, respectively (41). Simultaneous diagnosis of RIT and ORNJ was not observed in any of the cases.

We utilized ROC curve analysis to identify relevant cutoff points for continuous variables such as age, pre-C-CRT MMO, mean MAD, mean MMPD, MMD, and SIS, which may interact with

**Table 1.** Pretreatment patient and disease characteristics

| Characteristic | All patients (n= 188) | SIS-0 (n= 37) | SIS-1 (n= 111) | SIS-2 (n= 40) | P-value |
|---|---|---|---|---|---|
| Median age, years (range) | 55 (18-53) | 56 (37-75) | 56 (17-78) | 53.5 (18-77) | 0.071 |
| Age group, n (%) | | | | | |
| ≤ 55 years | 95 (50.5) | 18 (0.49) | 55 (49.5) | 23 (57.5) | 0.65 |
| > 55 years | 93 (49.5) | 19 (0.51) | 56 (50.5) | 17 (42.5) | |
| Gender, n (%) | | | | | |
| Female | 65 (34.6) | 13 (35.1) | 33 (29.7) | 19 (47.5) | 0.13 |
| Male | 125 (65.4) | 24 (64.9) | 78 (70.3) | 21(52.5) | |
| Body mass index; kg/m² (range) | 22.3 (18.9-30.2) | 21.7 (19.2-28.1) | 22.8 (19.4-26.8) | 21.3(18.9-30.2) | 0.52 |
| Smoking status, n (%) | | | | | |
| No | 59 (31.4) | 9 (24.3) | 35 (31.5) | 15 (37.5) | 0.46 |
| Yes | 129 (68.6) | 28 (75.7) | 76 (68.5) | 25 (62.5) | |
| Alcohol consumption, n (%) | | | | | |
| No | 80 (42,6) | 18 (0.49) | 79 (71.2) | 21 (52.5) | 0.78 |
| Yes | 108 (57.4) | 19 (0.51) | 42 (28.8) | 19 (47.5) | |
| Interval from dental extraction to C-CRT, days (range) | 16 (10-24) | 16(13-24) | 15 (13-21) | 15.5 (11-22) | 0.45 |
| Median pre-C-CRT MMO, mm (range) | 41.3 (37.8-46.8) | 41.6 (38-44) | 41.2 (33-44) | 40.6 (38-44) | 0.16 |
| Pre-C-CRT MMO group, n (%) | | | | | |
| ≤ 41.3 mm | 93 (49.5) | 16 (43.2) | 56 (50.5) | 23 (57.5) | 0.45 |
| > 41.3 mm | 95 (50.5) | 21(56.8) | 55 (49.5) | 17 (42.5) | |
| T-stage group, n (%) | | | | | |
| 1-2 | 46 (24.5) | 9 (24.3) | 24 (21.6) | 13 (32.5) | 0.29 |
| 3-4 | 142 (75.5) | 28 (75.7) | 87 (78.4) | 27 (67.5) | |
| N-stage, n (%) | | | | | |
| 0-1 | 50 (26.6) | 8 (21.6) | 27 (24.3) | 15 (37.5) | 0.37 |
| 2-3 | 138 (73.4) | 29 (78.4) | 84 (75.7) | 25 (62.5) | |

*Abbreviations*: SIS= systemic inflammation score, C-CRT= concurrent chemoradiotherapy, MMO= maximum mouth opening

clinical outcomes of RIT and ORNJ (Tables 1 and 2). We found that the pre-C-CRT MMO and the mean MAD dose had critical cutoffs of 41.3 mm and 37.4 Gy, respectively, that dichotomized patients based on RIT incidence rates. The MMD and mandibular V55.1 Gy had cutoffs of 34.3 Gy and 34%, respectively, which divided the study cohort into two groups with distinctive ORNJ rates.

Based on the previously established three-tiered SIS classification system, the distribution of patients across the SIS-0, SIS-1, and SIS-2 groups was as follows: 34, 111, and 40 patients, respectively. The prevalence of RIT in groups SIS-0, SIS-1, and SIS-2 were 2 (5.4%), 13 (12.7%), and 18 (45.0%) cases (p< 0.001 for each comparison), respectively. Similarly, 1 (2.7%), 11 (9.9%), and

9 (22.5%) cases of ORNJ were diagnosed in the respective SIS groups (p< 0.001 for each comparison). As illustrated in Table 2, the difference between SIS groups was also retained across the ORNJ stages according to Notani's staging scale (P < 0.05 for each comparison).

As shown in Table 3, univariate analyses revealed that the N2-3 nodal stage (p= 0.003), a pre-C-CRT MMO of 41.3 mm (p= 0.006), a mean MAD of 37.4 Gy (p< 0.001), and SIS-1 and SIS-2 groups (P < 0.001) were associated with increased rates of RIT (Figure 1). In the multivariate analysis (Table 4), all factors maintained their significance on higher RIT rates (p< 0.05). Similarly, the presence of smoking history (p= 0.02), N 2-3 nodal stages (p= 0.004), an MMD 34.3 Gy (p< 0.001), a mandibular

**Table 2.** Treatment characteristics and outcomes

| Characteristic | All patients (n= 188) | SIS-0 (n= 37) | SIS-1 (n= 111) | SIS-2 (n= 40) | p |
|---|---|---|---|---|---|
| Concurrent chemotherapy cycles, n (%) | | | | | |
| 1 | 39 (20.7) | 9 (24.3) | 21(18.9) | 9 (22.5) | 0.44 |
| 2-3 | 149 (79.3) | 28 (75.7) | 90 (81.1) | 31 (77.5) | |
| Adjuvant chemotherapy cycles, n (%) | | | | | |
| 0 | 50 (26.6) | 9 (24.3) | 30 (27.0) | 11 (27.5) | 0.80 |
| 1-2 | 138 (73.4) | 28(75.7) | 81 (73.0) | 29 (72.5) | |
| Median C-CRT to dental extraction internal, mo (range) | 8 (2-19) | 8(6-18) | 8 (5-18) | 8 (2-19) | 0.63 |
| Median post-C-CRT MMO, mm (range) | 38.2 (25.9-41) | 39 (28.3-40.3) | 37.5 (34-40) | 36.4 (27.4-41) | 0.001 |
| Mean MAD, Gy (range) | 37.4 (20.7-76.1) | 37.1 (20.9-75.3) | 37.8 (21.2-76.1) | 36.6 (20.7-75.9) | 0.74 |
| Mean MAD dose, n (%) | | | | | |
| < 37.4 Gy | 98 (52.1) | 20 (54.1) | 58 (52.3) | 20 (50.0) | 0.61 |
| ≥ 37.4 Gy | 90 (47.9) | 17 (45.9) | 53 (47.7) | 20 (50.0) | |
| Median MMPD; Gy (range) | 52.7 (30.6-77.2) | 53.1 (31.4-76.6) | 52.8 (30.6-76.8) | 52.2 (32.1-77.2) | 0.79 |
| MMD, Gy (range) | 34.3 (10.2-52.4) | 35.1 (10.7-50.9) | 33.6 (11.4-51.6) | 34.9 (10.2-52.4) | 0.55 |
| MMD group, n (%) | | | | | |
| < 34.3 Gy | 101(53.7) | 20 (54.1) | 60 (54.1) | 21 (52.5) | 0.48 |
| > 34.3 Gy | 87 (46.3) | 17 (45.9) | 51 (45.9) | 19 (47.5) | |
| Mandibular V55.1 Gy group, n (%) | | | | | |
| < 34% | 124 (65.9) | 24 (64.9) | 74 (66.7) | 26 (65) | 0.39 |
| ≥ 34% | 64 (34.1) | 13 (65.1) | 37 (33.3) | 16 (35) | |
| Median C-CRT to RIT interval, mo. (range) | 10 (6-18) | 9 (7-11) | 8 (6-14) | 10 (7-18) | 0.98 |
| RIT, n (%) | | | | | |
| Absent | 155 (82.4) | 25(67.6) | 98 (88.3) | 22 (55.0) | <0.001 |
| Present | 33 (17.6) | 12 (32.4) | 13 (12.7) | 18 (45.0) | |
| Median C-CRT to ORNJ interval, mo. (range) | 19 (15-32) | 32 (32-32) | 18 (17-24) | 19 (15-24) | 0.75 |
| ORNJ, n (%) | | | | | |
| Absent | 167 (88.9) | 36 (97.3) | 100 (90.1) | 31 (77.5) | 0.02 |
| Present | 21 (11.1) | 1 (2.7) | 11 (9.9) | 9 (22.5) | |
| Notani's ORNJ stage | | | | | |
| 0 | 167 (88.8) | 36 (97.3) | 100 (90.1) | 31 (77.5) | 0.05 |
| 1 | 14 (7.4) | 1 (2.7) | 8 (7.2) | 5 (12.5) | |
| 2 | 7 (3.8) | 0 (0) | 3 (2.7) | 4 (10.0) | |

*Abbreviations: SIS= systemic inflammation score, C-CRT= concurrent chemoradiotherapy, MMO= maximum mouth opening,  MAD= maximum apparatus dose, MMPD= mean maximum mandibular point dose, MMD; mean mandibular dose, V= volume, RIT= radiation-induced trismus, ORNJ= osteoradionecrosis of jaw*

V55.1 Gy 34% (p< 0.001), and SIS Groups 2 and 3 (p< 0.001) appeared to be significant associates of increased ORNJ rates (Figure 2) in univariate analysis, all of which maintained their independent significance in multivariate analysis (p< 0.05 for each) (Table 3 and Table 4).

## DISCUSSION

The objective of the present study was to investigate the potential usefulness of SIS grouping as a predictor of RIT and ORNJ incidence rates in patients with LA-NPC who underwent definitive C-CRT. This study represents the first attempt to explore this relationship in this patient population.

**Table 3.** Results of univariate analyse

| Characteristic | All Patients (n= 188) | RIT (%) | p | ORNJ (%) | p |
|---|---|---|---|---|---|
| **Age group** | | | | | |
| ≤ 55 years | 95 | 13(13.4) | 0.12 | 12(6.3) | 0.65 |
| > 55 years | 93 | 20 (21.1) | | 9 (9.7) | |
| **Gender** | | | | | |
| Male | 123 | 20 (16.3) | 0.55 | 13(10.6) | 0.81 |
| Female | 65 | 13 (20.0) | | 8(12.3) | |
| **Smoking status** | | | | | |
| No | 59 | 8 (13.6) | 0.41 | 2 (3.4) | 0.02 |
| Yes | 129 | 25 (19.4) | | 19 (14.7) | |
| **Alcohol consumption** | | | | | |
| No | 108 | 13(12.0) | 0.017 | 12 (11.3) | 1.0 |
| Yes | 80 | 20(25.0) | | 9 (11.3) | |
| **T-stage group** | | | | | |
| 1-2 | 46 | 7 (15.2) | 0.47 | 4 (8.7) | 0.23 |
| 3-4 | 142 | 26 (18.3) | | 17 (12.0) | |
| **N-stage group** | | | | | |
| 0-1 | 50 | 4 (8.0) | 0.003 | 3 (6.0) | 0.004 |
| 2-3 | 138 | 29 (21.0) | | 18 (13.0) | |
| **Pre-C-CRT MMO group** | | | | | |
| ≤ 41.3 mm | 93 | 22(23.7) | 0.006 | – | – |
| > 41.3 mm | 95 | 11(11.6) | | | |
| **Concurrent chemotherapy cycles** | | | | | |
| 1 | 51 | 9 (17.6) | 0.97 | 5 (9.8) | 0.33 |
| 2-3 | 137 | 24 (17.5) | | 16 (11.7) | |
| **Adjuvant chemotherapy cycles** | | | | | |
| 0 | 50 | 8 (16.0) | 0.66 | 5 (10.0) | 0.84 |
| 1-2 | 138 | 25 (18.1) | | 16 (11.6) | |
| **Mean MAD dose** | | | | | |
| < 37.4 Gy | 98 | 6 (6.1) | < 0.001 | – | – |
| ≥ 37.4 Gy | 90 | 27 (30.0) | | | |
| **MMD group** | | | | | |
| < 34.3Gy | 101 | – | – | 5 (5.0) | < 0.001 |
| ≥ 34.3Gy | 87 | | | 16 (18.4) | |
| **Mandibular V55.1 Gy group, n (%)** | | | | | |
| < 34% | 124 | – | – | 6 (4.8) | < 0.001 |
| ≥ 34% | 64 | | | 15 (23.4) | |
| **SIS group** | | | | | |
| SIS-0 | 37 | 2 (5.4) | <0.001 | 1(2.7) | <0.001 |
| SIS-1 | 111 | 13 (11.7) | | 11(9.9) | |
| SIS-2 | 40 | 18 (45.0) | | 9 (22.5) | |

*Abbreviations: RIT= radiation-induced trismus, ORNJ= osteoradionecrosis of jaw, C-CRT= concurrent chemoradiotherapy, MMO= maximum mouth opening, MAD= maximum apparatus dose, MMD= mean mandibular dose, V= volume, SIS= systemic inflammation scor*

The findings of our study indicate that the pretreatment SIS grouping was efficient for categorizing LA-NPC patients into three distinct risk groups concerning their likelihood of experiencing RIT and ORNJ following C-CRT (p< 0.001).

Several factors have been identified as risk factors for the development of RIT, including gender, age, primary tumor location and stage, total radiation dose, MAD, fractionation scheme, per fraction and total RT doses, the presence of previous surgery,
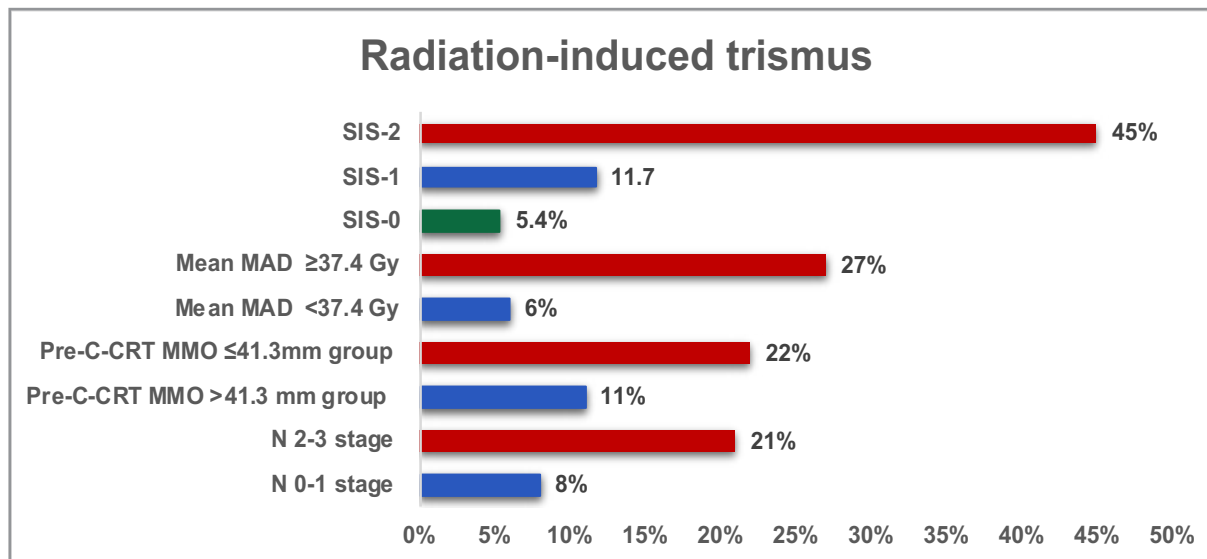
**Figure 1.** The bar chart depicting the rates of radiation-induced trismus according to the factors that showed independent significance in multivariate analyses

and the use of concurrent chemotherapy (8, 9). Previous studies have investigated RIT rates based on risk factors following C-CRT in patients with LA-NPC.[18-21] Somay et al. conducted two studies on LA-NPC patients and established the critical doses for RIT as mean MAD >57.2 Gy and mas-

**Table 4.** Results of multivariate analysis

| Characteristic | RIT | | ORNJ | |
|---|---|---|---|---|
| | p | HR (95% CI) | p | HR (95% CI) |
| Smoking status | | | | |
|   No | – | – | 0.04 | 3.14 (2.07-4.12) |
|   Yes | | | | |
| N-stage group | | | | |
|   0-1 | 0.006 | 2.73 (1.82-4.28) | 0.008 | 2.14 (1.52-3.38) |
|   2-3 | | | | |
| Pre-C-CRT MMO group | | | | |
|   ≤ 41.3 mm | 0.007 | 2.03 (1.62-2.80) | – | – |
|   > 41.3 mm | | | | |
| Mean MAD dose | | | | |
|   < 37.4 Gy | < 0.001 | 4.88 (2.91-7.14) | – | – |
|   ≥ 37.4 Gy | | | | |
| MMD group | | | | |
|   < 34.3 Gy | – | – | 0.001 | 3.72 (2.22-5.97) |
|   ≥ 34.3 Gy | | | | |
| Mandibular V55.1 Gy group, n (%) | | | | |
|   < 34% | – | – | < 0.001 | 3.98 (1.76-6.71) |
|   ≥ 34% | | | | |
| SIS group | | | | |
|   SIS-0 | < 0.001 | 6.46 (1.85-10.72) | < 0.001 | 6.84 (3.67-10.87) |
|   SIS-1 | | | | |
|   SIS-2 | | | | |

*Abbreviations: N= node, C-CRT= concurrent chemoradiotherapy, MMO= maximum mouth opening, MAD= maximum apparatus dose, MMD= mean mandibular dose, V= volume, SIS= systemic inflammation score, RIT= radiation-induced trismus, ORNJ= osteoradionecrosis of jaw*

## Osteoradionecrosis
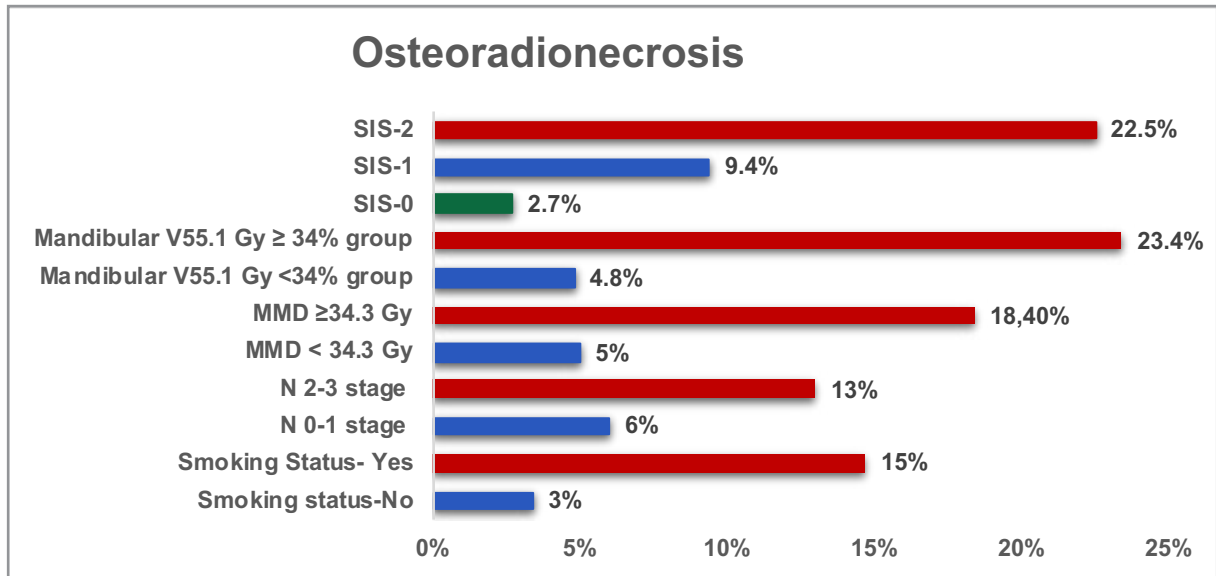


**Figure 2.** The bar chart depicting the rates of osteoradionecrosis of the jaw per factor demonstrated independent significance in multivariate analyses

ticatory apparatus V58 Gy ≥ 32%, respectively.[19,21] These studies also reported that the critical pre-C-CRT MMO cutoff values for higher RIT risk were ≤ 40.7 mm (p= 0.017) and ≤ 41.4 mm (p< 0.001). Our present study has found that a MAD dose of ≥ 37.4 Gy increases the risk of RIT. The rate of RIT is statistically higher in this group compared to those with a MAD dose of < 37.4 Gy (30.0% vs. 6.1%; p< 0.001). This finding is consistent with previous research.[19,21] Although Kraaijenga et al. suggested that a pre-C-CRT MMO of ≤ 46 mm could predict higher RIT incidence rates[42], Owosho et al. established a cutoff of 40 mm[43], which is comparable to our current 41.3 mm.

Patients presenting with N2-3 disease stage had a significantly higher RIT rate compared to those with N0-1 disease stage (21% vs. 8% for N0-1; p= 0.003) in our study. Advanced N-stage is often considered a significant risk factor for increased incidence rates of RIT.[44,45] This is likely due to the higher radiation doses received by the masticatory apparatus in patients with advanced N-stage, leading to activation or exacerbation of fibrotic tissue changes in the components of the masticatory apparatus, especially in those with affected level 1 and 2 lymph nodes.[46,47]

The results of our analyses indicate that smoking history (p= 0.02), N2–3 stage (p= 0.03), MMD ≥

34.3 Gy (p< 0.001), and mandibular V55.1 Gy ≥ 34% (p< 0.001) were the factors that had a statistically significant correlation with higher ORNJ rates. In a previous study, Zevallos et al.[46] conducted a retrospective evaluation of the data from 86 patients who underwent RT and reported a 32% increase in the incidence of ORNJ in patients who smoked during RT. The present study has determined that advanced N-stage (N2-3) poses a significant risk for ORNJ comparable to RIT, potentially attributable to the unavoidable delivery of elevated RT doses to the mandible.[48] Previously, Moon et al. reported that MMD ≥ 49 Gy and V70 Gy ≥ 17% were significant risk factors for the higher occurrence of ORNJ in patients with oral cavity or oropharyngeal cancers.[49] Similarly, in a recent study, Yilmaz et al. reported that the high-risk dosimetric factors for ORNJ were MMD ≥ 50.6 Gy (p= 0.012) and mandibular V 64 Gy ≥ 27% (p= 0.005), respectively[17], which are in good accordance with our current MMD ≥ 34.3 Gy, and mandibular V55.1 Gy ≥ 34%.

Our study's most notable finding was that SIS groups, created by utilizing pre-C-CRT serum albumin and LMR measures, were highly predictive of RIT and ORNJ outcomes in LA-NPC patients who received definitive C-CRT. As far as we know, while SIS has previously been established as a

prognostic factor in HNC patients[22-25], this discovery is the first of its kind in LA-NPC patients for RIT and ORNJ research. In our study, the incidence rates of RIT (p< 0.001) and ORNJ (p< 0.001) tended to increase substantially from SIS-0 to SIS-2, with SIS-2 group exhibiting the highest rates. We recognize that it is challenging to construct plausible hypotheses regarding these relationships due to the lack of similar research. Regarding the potential contributions of the SIS components, namely albumin, and LMR, to the pathogenesis of RIT and ORNJ, we can still infer some rational causal relationships. According to Soeters et al.[50], reduced serum albumin levels, the first component of SIS, are strongly correlated with exacerbated systemic inflammation induced by any cause. In this context, it is well established that radiation-induced inflammation and the secretion of numerous pro-inflammatory chemokines exert crucial functions in the initiation and progression of fibrotic repair processes in various tissues, including the RIT and ORNJ. Consequently, hypoalbuminemia indicates an aggravated inflammatory status, which is a potent precipitant of RIT and ORNJ. Furthermore, hypoalbuminemia is a hallmark of compromised nutritional status and an inappropriate immune response condition[50], Both of which can potentially exacerbate the existing hyperinflammation during the progression toward RIT and ORNJ. The second component of the SIS, LMR, is a reliable biomarker for assessing inflammatory status and immunity. A low LMR value implies impairment of inappropriate inflammatory and immune responses, which typically manifests as a state of hyperinflammation and suppressed immunity. Therefore, hypoalbuminemia indicates an aggravated inflammatory Considering these facts, the SIS-2 group represents the worst inflammatory and immune state among all three SIS groups, with albumin < 40 g/dL and LMR <4.44 measures. Although the exact mechanisms are probably more complex, such evidence cumulatively suggests that the simultaneous presence of hypoalbuminemia and a high LMR (SIS-2) offer the best physiological conditions for the development of RIT and ORNJ.

Several factors contributed to the strength of the current study. First, the SIS constitutes a two-factor formula, which theoretically provides more reliable results than single-factor indices, as they are more prone to physiological changes and external factors. And second, SIS serves as an easily measurable, reproducible, and cost-effective biomarker. Nevertheless, there are also certain limitations associated with this study. First, this study is a retrospective and single-center investigation, which may be susceptible to unpredictable biases typical of such studies. Second, we did not perform periodic SIS measurements during and after C-CRT, although the SIS components are dynamic biological markers. Therefore, the SIS cutoff utilized in this study and its impact on RIT and ORNJ rates represent only a single time point estimate, rather than the fittest one. And third, it is possible that we missed the opportunity to clarify the potential mechanistic links between a higher SIS group and levels of cytokines/chemokines, nutritional status, and immune-inflammatory factors. Therefore, the findings presented in this study should be considered hypothetical and not definitive recommendations until well-designed research results support them.

## Conclusion

The results of the current study showed that the novel pretreatment SIS grouping is a robust biomarker-based system that can reliably predict the rates of RIT and ORNJ in LA-NPC patients treated with conclusive C-CRT. If these findings are validated by additional research, they may aid in the risk stratification of these patients and the creation of more stringent follow-up algorithms for high-risk groups.

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