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Prognostic Value of Systemic Immune-Inflammation Index in Head and Neck Carcinoma Patients Undergoing Definitive Radio(Chemo)Therapy

Definitif Radyo(kemo)terapi ile Tedavi Edilen Baş Boyun Kanserli Hastalarda Sistemik İmmun-İnflamasyon İndeksinin Prognostik Etkisi

Necla Gurdal[1], Yaren Ceran[1], Ayse Kotek Sedef[2]

[1]Prof. Dr. Cemil Tascioglu City Hospital, Department of Radiation Oncology, Istanbul, Turkey
[2]Dr. Ersin Arslan Research and Training Hospital, Department of Radiation Oncology, Gaziantep, Turkey

Abstract

Aim: The aim of this study is to investigate the prognostic effect of the systemic immune-inflammation index (SII) in non-surgically managed head and neck carcinoma patients who underwent definitive radio(chemo)therapy.

Material and Method: Twenty four patients who were all treated with radio(chemo)therapy with curative intent for head and neck cancer (HNC) were included in the study. All patients were analyzed in terms of age at diagnosis, gender, body mass index, stage, radiotherapy dose/ fraction, chemotherapy (CT), pre-treatment complete blood count parameters, the pre-treatment systemic immune-inflammation index, local relapse, distant failure, overall survival (OS), and disease-free survival (DFS).

Results: SII index was observed to be higher in locally advanced patients than in stage I/II patients (p=0.004). In addition, as a result of the evaluation made with ROC (receiver operating characteristic) analysis, it was observed that the SII index had a diagnostic value in predicting locally advanced disease (AUC: 0.867, 95% CI: 0.721-1.00, p=0.002). DFS and OS rates were 79% and 90% at a median follow-up of 9 months.

Conclusion: The systemic immune-inflammation index predicts more advanced disease in non-surgically managed head and neck cancer patients. It can be considered as a biomarker that can contribute to the management of definitive radio(chemo)therapy.

Keywords: Head and neck carcinoma, radiotherapy, systemic immune-inflammation index

Öz

Amaç: Cerrahi uygulanmayıp definitif radyo(kemo)terapi ile tedavi edilen baş boyun kanserli hastalarda sistemik immun –inflamasyon indeksinin prognostik etkisinin araştırılmasıdır.

Gereç ve Yöntem: Küratif yaklaşımla radyo(kemo)terapi uygulanan baş boyun kanseri tanılı yirmi dört hasta çalışmaya dahil edilmiştir. Hastalar tanı yaşı, cinsiyet, vücut kitle indeksi, evre, radyoterapi doz/ fraksiyon verisi, uygulanan kemoterapiler, tedavi öncesi tam kan sayım parametreleri, tedavi öncesi sistemik immun –inflamasyon indeksi, lokal relaps, uzak hastalık, genel sağkalım (OS), and hastalıksız sağkalım (DFS) açısından retrospektif olarak incelenmiştir.

Bulgular: Sistemik immun –inflamasyon indeksinin lokal ileri evre hastalarda, evre I/II olan hastalara göre daha yüksek olduğu gözlenmiştir (p=0,004). Bununla birlikte yapılan ROC analiz sonucuna göre sistemik immun –inflamasyon indeksinin lokal ileri evre hastalığı öngörmede tanısal değeri olduğu belirlenmiştir (AUC: 0,867, %95 CI: 0,721-1,00, p=0,002). Medyan 9 aylık takip sonunda DFS ve OS oranı sırasıyla %79 ve %90 olarak bulunmuştur.

Sonuç: Sistemik immun –inflamasyon indeksi cerrahi uygulanmadan tedavi edilen baş boyun kanserli hastalarda lokal ileri evre hastalığı öngördürmektedir. Definitif radyo(kemo)terapi yönetimine katkı sağlayabilecek bir biyobelirteç olarak gözönünde bulundurulabilir.

Anahtar Kelimeler: Baş boyun kanseri, radyoterapi, sistemik immun–inflamasyon indeksi

Corresponding *(İletişim)*: Necla Gurdal, Prof. Dr. Cemil Tascioglu City Hospital, Department of Radiation Oncology, Şişli, 34384, Istanbul, Turkey
E-mail *(E-posta)*: gurdalnecla@hotmail.com
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INTRODUCTION

The head and neck region includes the upper aerodigestive tract (oral cavity, paranasal sinuses, pharynx, larynx, cervical esophagus), thyroid, associated lymph nodes, bone and soft tissues.[1] As with other cancers, there is increasing evidence that inflammation is associated with prognosis in head and neck cancers. Tumor cells also secrete various chemotactic substances and invoke macrophages, secrete damage-related molecular structures , activate neutrophils, and acidify the tumor microenvironment and prepare the environment for inflammatory responses.[2]

The cancer-induced inflammatory response leads to changes in peripheral blood neutrophils, lymphocytes, monocytes, and platelets, and this can be used to predict survival rates of patients with cancer. There have been many studies investigating the effects of systemic inflammatory responses such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and monocyte/lymphocyte ratio (MLR) on prognosis.[3] Systemic immune-inflammation index (SII) is an inflammatory response marker calculated based on absolute platelet, neutrophil, and lymphocyte counts. It shows the patient's systemic immune stimulation level and immune response level. SII has been shown to have a prognostic effect in different malignancies.[4,5] It has also been observed to be associated with decreased DFS and OS in different cancer types.[6] In this study, the importance of SII in head and neck cancers (HNC) treated with definitive radio(chemo)therapy was examined.

MATERIAL AND METHOD

Study Population

Between February 2021 and August 2022, twenty four patients who were all treated with radio(chemo)therapy with curative intent for head and neck cancer were included in the study. All patients were analyzed in terms of age at diagnosis, gender, body mass index, stage, radiotherapy (RT) dose/fraction, chemotherapy (CT), pre-treatment complete blood count parameters, the pre-treatment systemic immune-inflammation index, local relapse, distant failure, overall survival, and progression-free survival. The tumors were staged according to the American Joint Committee on Cancer (AJCC, 8th ed.,2017) TNM staging system.[7] The patients were followed up 1-3 times a week during the RT treatment, and enteral and/or parenteral nutrition support was provided if necessary. The systemic immune-inflammation index (SII), was calculated as : platelet count * neutrophil count/lymphocyte count. The study was carried out with the permission of Istanbul Prof. Dr. Cemil Tascioglu City Hospital. Ethics Committee (Date: 2023, Decision No: E-48670771-514.99-210779036).

Statistical Analysis

The descriptive statistics of the numerical variables obtained in the study are given as the median (range) value. The descriptive statistics of the categorical variables are given as numerical values and percentages. Data distribution was assessed by the Kolmogorov–Smirnov test. In consideration of the sample size, the non-normal distribution of variables was assumed, and nonparametric tests were used for between-group comparisons. So the categorical and numerical variables were compared using the chi-square test and Mann–Whitney U-test, respectively. Receiver operating characteristic (ROC) curves were also used to analyze the SII for predicting the advanced stage (T3-T4) disease . Kaplan–Meier curves were generated for overall survival (OS) and disease-free survival (DFS) and significance was assessed using the log-rank test . Statistical analyses were performed using SPSS 25 software (SPSS Inc., Chicago, IL, USA). A probability value of $p<0.05$ was considered significant.

RESULTS

Patient Characteristics

The median age of the patients was 65,5. Median follow-up was 9 (range, 3-22) months. All of the patients had squamous cell carcinoma histology and none of them had undergone surgical treatment. 67% of the patients were node-positive patients, and the incidence of N2-N3 disease was higher in patients aged 65 years and younger than those over 65 years of age (83% vs 25% ,p=0,004). The rate of locally advanced patients was 71% and SII index was observed to be higher in locally advanced patients than in Stage I/II patients (p=0.004). In addition, as a result of the evaluation made with ROC analysis, it was observed that the SII index had a diagnostic value in predicting locally advanced disease (AUC: 0.867, 95% CI: 0.721-1.00, p=0.002) (**Figure 1**). Curative RT was applied to all patients with intensity-modulated radiotherapy (IMRT) and 79% of the patients received concomitant chemotherapy. The baseline characteristics of the patients are presented in **Table 1**.

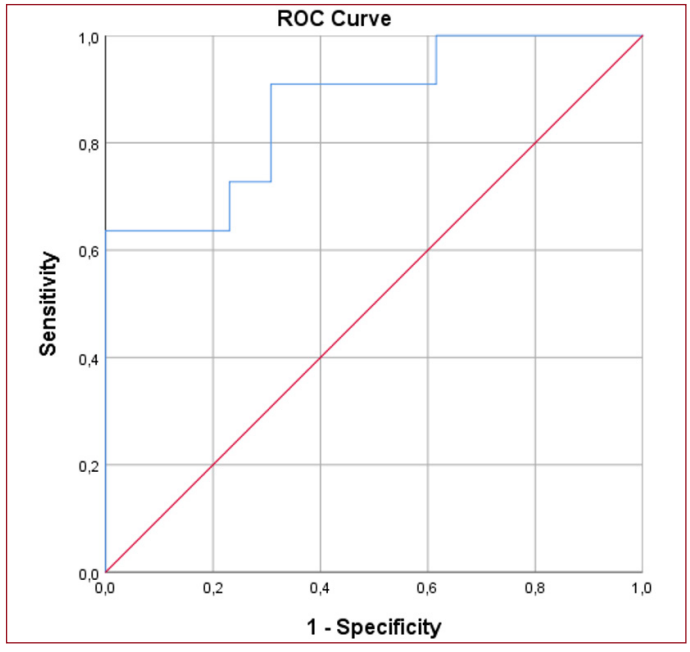

Figure 1. ROC analysis for the SII index predicting locally advanced disease

Table 1: Patient characteristics and basic statistical findings

	Patients (n:24 , %) / median (range)
Age	65.5 (32-82)
Gender	
Female	4 (16.7%)
Male	20 (83.3%)
BMI (kg/m²)	24.2 (18.7-36.1)
Location	2 (8.4%)
Paranasal sinus	8 (33.2%)
Nasopharynx Oropharynx	1 (4.2%)
Oral cavity	1 (4.2%)
Hypopharynx	1 (4.2%)
Larynx	10 (41.6%)
Unknown primary	1 (4.2%)
T stage	
X	1 (4.2%)
I	5 (20.8%)
II	8 (33.3%)
III	6 (25%)
IV	4 (16.7%)
N stage	
0	8 (33.3%)
I	3 (12.5%)
II	7 (29.2%)
III	6 (25%)
Stage	
I	5 (20.8%)
II	2 (8.3%)
III	6 (25%)
IVA	9 (37.5%)
IVB	2 (8.3%)
Radiotherapy (Gy)	70 (63-70)
Chemotherapy	
Yes	19 (79.2%)
No	5 (20.8%)
Lymphocyte ($\times 10^3/\mu L$)	1.62 (0.3-3.9)
Neutrophil ($\times 10^3/\mu L$)	4.6 (1.8-9.1)
Platelet ($10^3/L$)	248 (133-374)

Oncological Results

After a median follow-up of 9 months, local recurrence was observed in 12.5% of patients. Distant metastasis was encountered three of the patients. Two patients died due to disease-related reasons. DFS and OS rates were 79% and 90% at a median follow-up of 9 months (**Figure 2**-**3**).

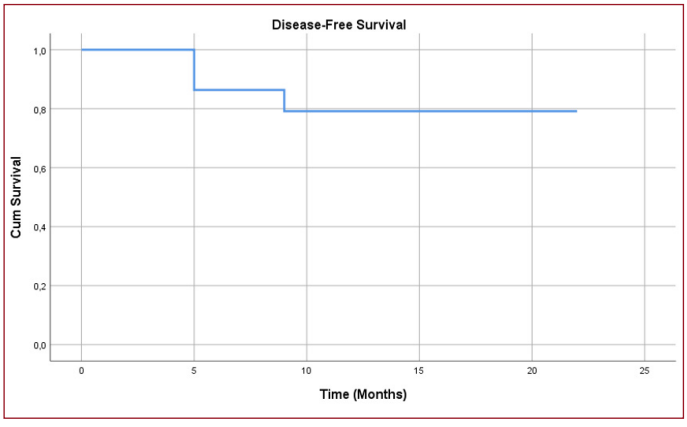

Figure 2. Kaplan-Meier plots of disease free survival.

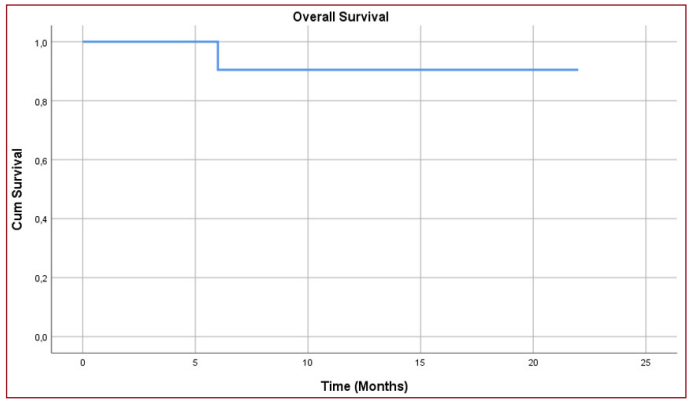

Figure 3. Kaplan-Meier plots of overall survival.

DISCUSSION

In different studies, it has been observed that SII is a better prognostic marker than other inflammation indices in many cancer types.[8-11] Also , most of the studies on head and neck cancers are on patients who underwent surgical treatment.

Zhilin Li et al. retrospectively evaluated 147 patients who underwent surgery for laryngeal cancer. They observed that high SII was associated with advanced T stage ($p<0.005$), locoregional recurrence ($p<0.005$), lower PFS ($p<0.001$) and OS ($p<0.001$).[12]

Kubota et al. retrospectively analyzed 183 patients with oral cavity cancer diagnosis. Most of the patients in the study were surgical patients and were evaluated in terms of SII and inflammation-based prognostic scores. Worse DFS results ($p=0.003$) were observed in patients with higher SII, and higher SII was also found to be an independent predictive factor on OS ($p=0.016$).[13]

Ruiz-Ranz et al. retrospectively analyzed 348 patients who underwent surgical treatment for oral cavity cancer. They reported that patients with high SII had a larger tumor volume ($p<0.001$) and these patients were more advanced stage ($p=0.003$).[14]

Cho et al. analyzed 269 patients who underwent surgical treatment for oral cavity tumor.

74% of these patients underwent surgery for tongue cancer, and 52% of them were stage 3-4. It was observed that patients with high SII had lower disease-specific survival and PFS rates ($p<0.05$).[15]

In a multicenter retrospective analysis covering the years 2004-2018, Rizzo et al. examined 925 patients with a diagnosis of HNC. All of the patients were surgical patients and patients who underwent curative RT were excluded from the study. Besides different systemic inflammatory response parameters, SII was also investigated in the study. Patients were analyzed by dividing them into 3 groups according to SII value, and it was observed that OS and DFS decreased significantly in the group with high SII value ($p=0.013$ and $p=0.003$,respectively).[16]

Lu et al. aimed to develop a nomogram on the prognostic effect of different inflammation indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte- to- monocyte ratio (LMR), and SII in predicting survival. For this purpose, 120 patients who underwent primary surgery for tongue cancer were analyzed. At the end of the study, it was observed that high SII was associated with tumor differentiation (P=0.011), tumor size (P=0.002), tumor invasion depth (P=0.011) and lymph node density (P=0.003). In the multivariate analysis, it was observed that SII had an independent prognostic effect on DFS and OS.[17]

Wang et al. published a meta-analysis of 12 studies involving 4369 patients to investigate the effect of SII on survival outcomes in patients with head and neck cancer treated with different treatment modalities. Worse OS results were observed in patients with high SII ($p<0.001$). In addition, when they looked at nasopharynx, larynx, and oral cavity tumors separately, they again found that SII elevation was significantly associated with poor OS results ($p=0.004$, $p<0.001$,and $p<0.002$, respectively) . It was also observed that high SII was associated with worse DFS and PFS results (both $p<0.001$). In this meta-analysis, no relationship was observed with tumor differentiation or gender, but it was observed that SII elevation was associated with more advanced T stage ($p<0.001$) and lymphatic involvement ($p=0.002$).[18]

All of the patients in our study were patients treated with definitive radio(chemo)therapy . 71% of the patients are stage 3-4 patients and 67% of them have lymph node positivity. Similar to these studies, also, we observed that high SII predicted more advanced stage disease.

Wu-Chia Lo et al. studied 147 patients with oropharyngeal cancer. 87% of this patient group is stage IV and all of them are treated with chemoradiotherapy. It was observed that SII was an independent risk factor for death ($p=0.011$) and patients with high SII had lower OS ($p<0.001$).[19]

Zeng et al. analyzed the data of 2169 patients from 6 studies conducted only on patients with nasopharyngeal carcinoma between 2017-2021. It was observed that patients with higher SII values exhibited worse OS and PFS results (HR=1.69, 95% CI=1.36–2.09, $P<0.001$ and HR=1.60, 95% CI=1.29–1.98, $P<0.001$, respectively).[20]

CONCLUSION

SII is a noninvasive, accessible and prognostically effective marker in patients with head and neck cancer treated with curative radio(chemo)therapy without surgery. A pre-treatment SII elevation indicates more advanced disease and may contribute to treatment management.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul Prof. Dr. Cemil Tascioglu City Hospital. Ethics Committee (Date: 2023, Decision No: E-48670771-514.99-210779036).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Patterson RH, Fischman VG, Wasserman I, et al. Global Burden of Head and Neck Cancer: Economic Consequences, Health, and the Role of Surgery. Otolaryngol Head Neck Surg 2020;162(3):296-303.
2. Zhou Q, Su S, You W, Wang T, Ren T, Zhu L. Systemic Inflammation Response Index as a Prognostic Marker in Cancer Patients: A Systematic Review and Meta-Analysis of 38 Cohorts. Dose Response 2021;19(4):15593258211064744.
3. Li X, Zhang S, Lu J, Li C, Li N. The prognostic value of systemic immune-inflammation index in surgical esophageal cancer patients: An updated meta-analysis. Front Surg 2022;9:922595.
4. Han R, Tian Z, Jiang Y, et al. Prognostic significance of systemic immune-inflammation index and platelet albumin-bilirubin grade in patients with pancreatic cancer undergoing radical surgery. Gland Surg 2022;11:576-87.
5. Xu S, Cao S, Yu Y. High systemic immune-inflammation index is a predictor of poor prognosis in patients with nonsmall cell lung cancer and bone metastasis. J Cancer Res Ther 2021;17:1636-42.
6. Nie D, Gong H, Mao X, et al. Systemic immuneinflammation index predicts prognosis in patients with epithelial ovarian cancer: A retrospective study. Gynecol Oncol 2019;152:259-64.
7. Zanoni DK, Patel SG, Shah JP. Changes in the 8th Edition of the American Joint Committee on Cancer (AJCC) Staging of Head and Neck Cancer:Rationale and Implications. Curr Oncol Rep 2019;21(6):52.
8. Chen JH, Zhai ET, Yuan YJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World J Gastroenterol 2017;23:6261–72.
9. Lolli C, Caffo O, Scarpi E, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with mCRPC treated with abiraterone. Front Pharmacol 2016;7:376.
10. Deng C, Zhang N, Wang Y, et al. High systemic immune-inflammation index predicts poor prognosis in advanced lung adenocarcinoma patients treated with EGFR-TKIs. Medicine 2019;98:e16875.
11. Jomrich G, Gruber ES, Winkler D, et al. Systemic Immune-Inflammation Index (SII) Predicts Poor Survival in Pancreatic Cancer Patients Undergoing Resection. J Gastrointest Surg 2020;24(3):610-8.
12. Li Z, Qu Y, Yang Y, et al. Prognostic value of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and systemic immune-inflammation index in patients with laryngeal squamous cell carcinoma. Clin Otolaryngol 2021;46(2):395-405.
13. Kubota K, Ito R, Narita N, et al. Utility of prognostic nutritional index and systemic immune-inflammation index in oral cancer treatment. BMC Cancer 2022;22(1):368.

14. Ruiz-Ranz M, Lequerica-Fernández P, Rodríguez-Santamarta T, et al. Prognostic implications of preoperative systemic inflammatory markers in oral squamous cell carcinoma, and correlations with the local immune tumor microenvironment. Front Immunol 2022;13:941351.
15. Cho U, Sung YE, Kim MS, Lee YS. Prognostic Role of Systemic Inflammatory Markers in Patients Undergoing Surgical Resection for Oral Squamous Cell Carcinoma. Biomedicines 2022;10(6):1268.
16. Boscolo-Rizzo P, D'Alessandro A, Polesel J, et al. Different inflammatory blood markers correlate with specific outcomes in incident HPV-negative head and neck squamous cell carcinoma:a retrospective cohort study. BMC Cancer 2022;22(1):243.
17. Lu Z, Yan W, Liang J, et al. Nomogram Based on Systemic Immune-Inflammation Index to Predict Survival of Tongue Cancer Patients Who Underwent Cervical Dissection. Front Oncol 2020;10:341.
18. Wang YT, Kuo LT, Weng HH, et al. Systemic Immun e-Inflammation Index as a Predictor for Head and Neck Cancer Prognosis: A Meta-Analysis. Front Oncol 2022;12:899518.
19. Lo WC, Chang CM, Wu CY, et al. A predictive model for advanced oropharyngeal cancer patients treated with chemoradiation. BMC Cancer 2022;22(1):615.
20. Zeng Z, Xu S, Wang D, Qin G. Prognostic significance of systemic immune-inflammation index in patients with nasopharyngeal carcinoma: a meta-analysis. Syst Rev 2022;11(1):247.