Introduction

Head and neck cancers are the 6th most common cancers worldwide. They constitute 6% of all cancers and 1-2% of cancer-related deaths.[1] According to the cancer statistics data of ASCO (American Society of Clinical Oncology) in 2019, the number of newly diagnosed patients with oral cavity cancer (OCC) has been reported to be approximately 35,000.[2] According to the cancer statistics data of the Ministry of Health-Turkey, between 2011-2015 13,778 cases with newly diagnosed head and neck cancers were recorded, and 25% of them were OCC.

Genetic susceptibility, viruses, autoimmunity, inflammatory mechanisms, hormonal and metabolic factors have been blamed for the pathogenesis of OCCs. Some proinflammatory cytokines have been measured to investigate the inflammatory mechanism of the oral cavity. The relationship between cancer and chronic inflammation first began with Rudolf Virchow's definition of leukocytes in tumor tissue.[3,4] In studies on chronic inflammation having an effect on tumor development, metastasis, prognosis and treatment response, the relationship between systemic inflammation degree and cancer has been demonstrated using systemic inflammation markers including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic immune inflammation index (SII).[5-11] In some studies, the increase in NLR has been associated with a negative prognosis in cancer patients.[5-11] It has also been suggested that the survival of tumor cells and the development of metastasis are affected by the number of platelets.[12-14] A prognostic indicator based on neutrophil, lymphocyte and platelet counts is expected to be more robust than an indicator based on only one factor. Therefore, in 2014, Hu et al [15] developed an indication that they named the SII to predict the prognosis of patients after curative resection for hepatocellular carcinoma. According to the SII equation, preoperative peripheral blood platelets (P), and neutrophil (N) and lymphocyte (L) counts per liter were calculated. The researchers thus tested the hypothesis that a high SII score (SII>330×109 cells/L) negatively affected the differentiation and prognosis in these patients. However, some studies have investigated whether this SII threshold is appropriate for predicting prognosis in all cancer patients. Studies suggest that SII is a useful and accurate independent prognostic indicator for all types of tumor patients.[16-19] Also, unlike many inflammatory cytokines, measurement of PLR, NLR and SII is thought to be a very practical and easily accessible method to detect inflammation without extra cost, as it can be easily calculated from a simple whole blood cell count (CBC).

In this study, we aimed to evaluate the relationship between NLR, PLR and SII values at the beginning of treatment and overall survival (OS) and disease-free survival (DFS) in patients undergoing radiotherapy with a diagnosis of OCC.

Materials and Methods

The study protocol was approved by the institutional review board (2020-03/10). Fifty-eight patients who were admitted to Cumhuriyet University Medical Faculty Radiation Oncology Clinic between January 2009 and December 2018 were treated with a diagnosis of OCC. Patient files were evaluated in terms of age, gender, method of treatment, perineural invasion, lymphovascular invasion, pathological grade, extracapsular invasion, smoking habit, tumor stage, comorbidity, recurrence and metastasis NLR, PLR and SII (Platelet x Neutrophil/Lymphocyte) values were calculated from the hemogram examination at the beginning of treatment.

All patients had a squamous cell carcinoma (SCC) of the oral cavity. Surgery was performed on 35 patients (60%). Radiotherapy was applied to all patients after surgery. Also, 28 (48%) of the patients were added simultaneously to chemotherapy, in addition to RT. RT conventional fraction (60-70 Gy, from 1.8-2 Gy daily) was applied to 44 (76%) patients, whereas simultaneous integrated boost (54 Gy from 1.8 Gy longitudinal, 66-70 Gy from 2.33 Gy) was performed to 14 (24%) patients. All patients receiving concurrent chemoradiotherapy were given weekly cisplatin (35 mg/m2) simultaneously.

SPSS Version 23 was used for statistics. Descriptive tests (median, mean, standard deviation, etc.) for demographic data of the patients, Chi-square test to identify characteristics of the groups and Kaplan-Meier analysis to determine OS and DFS were used. Multivariate Cox regression analysis was also performed to detect independent prognostic factors. ROC analysis was performed to determine NLR, PLR and SII cut-off values. In ROC analysis, cut-off values were as follows; 954 [Area=0.665 (0.511-0.800), p=0.045] for SII, 174 [Area=0.659 (0.608-0.795), p<.001] for PLR and 3.2 [Area=0.699 (0.556-0.841), p=0.016] for NLR.

Results

Fifty patients had tongue SCC, whereas a buccal SCC was presented in 8 patients. Median age of the patients was

67 (range, 23-90), 69% were male and 31% were female. According to their stages, 7 (12%) patients were in Stage I, 16 (28%) patients were in Stage II, 11 (19%) patients were in Stage III, 24 (41%) patients were in Stage IV and distant metastasis was absent in all patients. The patients' data regarding the pathological grades were present in 47 patients composed of 21 patients with grade 1, 17 patients with grade 2 and 9 patients with grade 3. Perineural invasion was present in 20 patients, whereas it was absent in 11 patients. Twenty-seven patients had no records regarding perineural invasion. Extracapsular invasion was detected in 11 patients, but absent in 24 patients. The data of extracapcular invasion could not be obtained in 23 patients. Lymphovascular invasion was found in 9 patients.

Prognostic factors affecting OS were SII, PLR, NLR and age (<65 vs. ≥65 years). In multivariate analysis, high SII was found to be associated with increased extracapsular invasion and older age. The results of the analysis of prognostic factors affecting OS are detailed in Table 1. SII, NLR, PLR and grade were statistically significant prognostic factors for DFS, however, SII has been identified as an independent prognostic factor. Analysis results affecting DFS are shown in Table 2.

There was no relationship between SII and PLR and perineural invasion, lymphovascular invasion, grade, extracapsular invasion, smoking, age, stage, comorbidity, recurrence or metastasis (p>0.05). For NLR, a statistically significant difference was detected for disease stage (p=0.046). The disease stage of patients with NLR<3.2 was deter-

Table 1. Prognostic factors affecting overall survival.

Univariate analysis	5-year OS %	Median OS (month)	p value
SII			
<954	47	59	<0.001
≥954	8	17	
PLR			
<174	54	54	0.019
≥174	17	17	
NLR			
<3.2	48	59	0.001
≥3.2	11	18	
Age			
<65 years	48	42	0.039
≥65 years	14	23	
ECE			
No	40	54	0.104
Yes	22	18	
Stage			
Stage I	42	54	0.211
Stage II	31	26	
Stage III	37	20	
Stage IV*	19	13	
Multivariate analysis	**HR**	**95% CI**	**p value**
SII			
<954	1	2.14-15.47	0.001
≥954	5.76		
Age			
<65 years	1	1.32-10.04	0.012
≥65 years	3.64		
ECE			
No	1	1.14-7.58	0.025
Yes	2.95		

HR: hazard ratio, OS: overall survival
* Stage IV disease without distant metastasis

Table 2. Prognostic factors affecting disease-free survival.

Univariate analysis	5-year DFS %	Median DFS (month)	p value
SII			
<954	35	53	<0.001
≥954	4	10	
PLR			
<174	29	25	0.008
≥174	13	11	
NLR			
<3.2	35	32	<0.001
≥3.2	9	17	
Grade			
Grade 1	11	13	0.036
Grade 2	40	53	
Grade 3	-	13	
Stage			
Stage I	29	32	0.201
Stage II	25	19	
Stage III	21	20	
Stage IV*	20	10	
Multivariate analysis	**HR**	**95% CI**	**p value**
SII			
<954	1	1.27-16.56	0.019
≥954	4.60		

CI: Confidence Interval, DFS: disease-free survival, HR: hazard ratio

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