Relationship between local and systemic inflammatory response and prognosis in laryngeal squamous cell carcinoma

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ABSTRACT

OBJECTIVE: Laryngeal squamous cell carcinoma (LSCC) is the most frequently seen head and neck malignancy. Despite improvements in the treatment modalities within the last 20 years, the desired improvement in survival outcomes has not been achieved yet which led researchers to investigate factors that might affect prognosis in LSCCs.

METHODS: A total of 116 previously operated patients were included in the study. To assess systemic inflammation neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated. The cut–off values for NLR, and PLR were accepted as 2.79 and 112, respectively. To evaluate intratumoral inflammation, hematoxylin-eosin stained tumor sections were evaluated. Tumor-infiltrating lymphocyte (TIL) densities in the tumor area were scored as 1+, 2+ and 3+.

RESULTS: The mean overall survival was 29.5±17.7 months. In univariate analysis, a statistically significant correlation was seen between age group of 60 years, tumor stage, site and OS (p=0.025, p=0.026, p=0.029). There was no statistically significant relationship between PLR, NLR and TIL density and OS. In the multivariate analysis, 60-year-old group and tumour stage were still significantly associated with the OS (p=0.033, p=0.046).

CONCLUSION: Age and tumor stage were significantly associated with survival in our study, but contrary to the literature, no correlation was found between local and systemic inflammatory response.

Keywords: Inflammation; laryngeal carcinoma; prognosis.

Larynx is the most common site of head and neck cancers and laryngeal squamous cell carcinoma (LSCC) is the most frequently seen head and neck malignancy [1, 2]. Treatment modalities are surgery, radiotherapy, chemotherapy, or combination of them [2]. Within the last 20 years, improvement in LSCC survival outcomes is minimal despite improvements in treatment modalities [3], which has led researchers to investigate factors that may affect prognosis in LSCCs. There are studies in the literature reporting that neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), which reflect systemic inflammation, are effective predictors associated with decreased survival rates in various types of cancer [4].

However, some studies have indicated that the increased density of tumor-infiltrating lymphocytes (TILs), which demonstrates intratumoral inflammation, is a good prognostic factor [4]. Herein the relationship...
between systemic and local inflammatory response and total survival was investigated in cases with LSCC.

**MATERIALS AND METHODS**

Local ethics committee approval was obtained for the study. A total of 116 patients who were operated in our hospital with the diagnosis of LSCC, whose clinical follow-up records, and archival data were available were included in the study. Patients’ age, sex, tumor location and tumor size were learnt from pathology reports, while survival data and tumor stages from the otorhinolaryngology clinic. To assess systemic inflammation, whole blood results were routinely obtained from all patients within the preoperative 1 week, and NLR and PLR were calculated by recording blood neutrophil, lymphocyte and platelet ratios.

The cut-off values for NLR, and PLR were accepted as 2.79 and 112, respectively [4].

To evaluate intratumoral inflammation, hematoxylin-eosin stained tumor sections of the cases in our archive were re-evaluated by two pathologists (Olympus BX51, Japan). Tumor sections with the highest TIL densities were identified. TIL densities in the tumor area were scored as 1+ (<30%), 2+ (30–60%) and 3+ (60%) scans [5] under 100x, and 400x magnification.

**Statistical Analyses**

Statistical analyses was performed using Statistical Package of Social Sciences version 24 (IBM Corp: Armonk, NY, USA). OS rates were estimated using the Kaplan-Meier method. The log-rank test was used to evaluate survival rates in univariate analyzes. The possible factors identified with the univariate analyzes were further entered into the Cox regression analyzes, with backward selection, to determine independent predictors of OS. Only those with clinical significance were included. A p value <0.05 was considered to indicate statistical significance.

**RESULTS**

The mean age of the study population (n=116) which consisted of 5 (4.3%) female, and 111 (95.7%) male patients was 61±9.50 (min: 34, max: 82) years. The patients were either ≤60 (n=59: 50.9%) or >60 (n=57; 49.1%) years of age. Eighty six (74.1%) patients alived, and 30 (25.9%) patients died. The median OS was 26.5±17.7 months (min: 2 months, max: 81 months).

Twenty (17.2%) supraglottic, 83 (71.6%) glottic and 13 (11.2%) subglottic. 43 (37.1%) tumors with stages I, 10 (8.6%) stage II, 22 (19%) stage III and 41 (35.3%) were detected. Blood NLR was either <2.79 in 47 (40.5 %) or ≥ 2.79 in 69 (59.5%) and TLR was <112 in 20 (17.2%), and ≥112 in 96 (82.8%) cases.

In the hematoxylin-eosin stained sections, 32 mild (27.6%), 43 moderate (37.1%) and 41 severe (35.3%) TIL densities were detected when the patients with moderate and severe inflammation were accepted as severe, the density of TIL was mild in 32 (27.6%) and severe in 84 (72.4%) patients. Clinicopathological characteristics are summarized in Table 1.

**Table 1. Clinicopathologic features of the cases NLR, PLR, TIL**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values n (%)</th>
</tr>
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<tbody>
<tr>
<td>Age (years), mean±SD (range)</td>
<td>61±9.50 (34-82)</td>
</tr>
<tr>
<td>60 year old group</td>
<td>(≤60/&gt;60)59 (50.9%)/57 (49.1%)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>111 (95.7%)/5 (4.3%)</td>
</tr>
<tr>
<td>Survey (alive/died)</td>
<td>86 (74.1%)/30 (25.9%)</td>
</tr>
<tr>
<td>Overall survival (month), median±SD (range)</td>
<td>26.5±17.7 (2-81)</td>
</tr>
<tr>
<td>Tumor subsite (supraglottic/glottic/subglottic)</td>
<td>20 (17.2%)/83 (71.6%)/13 (11.2%)</td>
</tr>
<tr>
<td>Tumor stages (I/II/III/IV)</td>
<td>43 (37.1%)/10 (8.6%)/22 (19%)/41 (35.3%)</td>
</tr>
<tr>
<td>NLR (&lt;2.79/≥2.79)</td>
<td>47 (40.5%)/69 (59.5%)</td>
</tr>
<tr>
<td>TLR (&lt;112/≥112)</td>
<td>20 (17.2%)/96 (82.8%)</td>
</tr>
<tr>
<td>TIL (mild/moderate/severe)</td>
<td>32 (27.6%)/43 (37.1%)/41 (35.3%)</td>
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</table>

NLR: Neutrophil to lymphocyte ratio; PLR: Platelet/to lymphocyte ratio; TIL: Tumor infiltrating lymphocyte; SD: Standard deviation.
The relationship between data, and OS was evaluated individually. Accordingly statistically significant relationship was detected between age groups (<60, ≥60), tumor stages (stages 1, 2, 3, 4), location and OS in univariate analysis (p=0.025, p=0.026, p=0.029) (Fig. 1). There was no statistically significant correlation between PLR, NLR and TIL density and OS (p=0.745, p=0.987, p=0.107).

When data about 60 year-old group, tumor stage, and location which were statistically significant correlated with OS in univariate analysis were evaluated using multivariate analysis, 60-year-old group and tumor stage were still significantly associated with the OS (p=0.033, p=0.046) (Table 2).

### DISCUSSION

LSCC is the most frequent malignancy of the head and neck region and is the major cause of morbidity and
mortality [2]. American Cancer Society reported that, despite improvements in the treatment modalities, patients with laryngeal cancer had a tendency to decline at 5-year survival rates [6]. This has prompted researchers to search for effective biomarkers that can aid in predicting high-risk patients with poor prognosis or early recurrence. Recent findings as a result of researches suggest that the interaction between tumor cells and tumor microenvironment may play effective roles in tumor aggressiveness and treatment resistance [7].

Recently, it has been suggested that inflammation and immune status associated with the tumor are likely to be involved in the development of cancer and in the progression of the disease. This can be explained by the change in the distribution of circulating blood cells (such as relative neutrophilia, thrombocytosis and relative lymphopenia) in the cancer-related systemic inflammatory response [4, 8]. Cytokines and chemokines produced by the increased number of neutrophils are thought to be effective in the growth and progression of the tumor. Growth factors secreted by platelets are thought to exert important effects on tumor growth and dissemination due to their roles in increased stimulation of angiogenesis and microvessel permeability [4]. Lymphocytes are known to play an important role in the cancer-related host immune response by suppressing proliferation and metastasis of tumor cells, and this role may be thought to be depressed because of the presence of relative lymphopenia [4].

Recent studies have reported that NLR and PLR are effective markers of systemic host immunity, and associated with advanced stage and poor prognosis in various types of solid tumors, in addition to their being predictive factors for decreased survival [2, 4].

Ping Tu et al. reported that high NLR in 141 LSCC series was associated with short disease-free survival (DFS) and short-term OS in univariate and multivariate analysis [2]. They also reported that in univariate analysis OS correlated statistically significantly with stage, location, histologic grade of the tumor, and NLR, however in multivariate analysis significant correlations among T classification, lymph node metastasis and NLR were maintained.

Fu et al. indicated that in univariate analysis age group (60 years) alcohol consumption, location, stage, histology grade of the tumor and NLR were significantly associated with cancer-specific survival in a series of 420 cases with LSCC, however in multivariate analysis, correlations among age, alcohol consumption, lymph node metastasis and NLR were still maintained [9]. Similar findings have been reported in the same study for OS [9].

In univariate analysis, Wang et al. reported that the preoperatively higher PLR and NLR were associated with decreased OS and DFS in their series of 120 cases, but in the multivariate analysis only higher PLR retained its correlation [4]. In the same study, it was also found that there was no statistically significant relationship between tumor location and tumor stage with OS and RFS.

In our series, univariate analysis showed a statistically significant relationship between age (60 age group), tumor stage and location of the tumor and OS. However, a statistically significant relationship was not observed between NLR, PLR and OS in our series, unlike the literature findings. In our study, in the multivariate analysis 60-year-old group, and tumour stage continued to have significant association with the OS (p=0.033, p=0.046). Unlike studies reporting that the increased intensity of systemic inflammatory response is associated with poor prognosis, some studies have indicated that intratumoral inflammatory response, which responds to local inflammatory response, is a good prognostic marker [4]. Chronic inflammatory cells infiltrating the tumor consist of lymphocytes, plasma cells, and macrophages [10]. In particular, TIL is thought to reflect host immune responses to the tumor [4]. In studies of head and neck region SCCs, it has been reported that increased TIL density is associated with prolonged survival [4, 5, 11]. In a series of 120 LSCC cases by Wang et al. TIL density of tumors was morphologically evaluated, and 2 groups as low TIL and high TIL were determined [4]. In their studies they detected higher recurrence rates in the low TIL group when compared with the high TIL group and they reported that low TIL density could be used as a marker for early recurrence [4]. In our study, there was no statistically significant relationship between TIL density and OS, unlike the literature data.

However in studies that determined TIL subtypes, it has been reported that lymphocytes characterized as CD8-positive T-cytotoxic/suppressor cells were correlated with prognosis, whereas FoxP3 cells, a subset of CD4-positive T helper lymphocytes, did not exert negative effect on survival [11]. The differences in TIL assessment methods in studies suggest that the lack of a generally accepted standardized cut-off value may explain our outcome different from that of the literature.
Conclusion

In recent studies, the relationship of host immunity status to tumor recurrence, response to treatment and survival has begun to be better understood and its prognostic significance has been reported in a wide variety of tumors including head and neck region SCCs. However, in our study of LSCC cases, a significant correlation was observed between especially age and tumor stage with survival contrary to the literature data, a significant correlation between local and systemic inflammatory response and survival was not detected which suggested lack of a standardized method of assessing the local inflammatory response and heterogeneity in the treatment modalities.

Ethics Committee Approval: Local ethics committee approval was obtained for the study.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors have declared that they didn’t receive any financial support of this study.

Authorship Contributions: Concept – AEK, OB; Design – AEK, OB; Supervision – AEK, OB; Data collection and/or processing – AEK, OB, MMB; Analysis and/or interpretation – AEK, OB, MMB; Literature review – AEK, OB, MMB; Writing – AEK, OB, MMB; Critical review – AEK, OB, MMB.

REFERENCES


