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Perineural invasion is a better prognostic factor than extranodal extension in head and neck cancer

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Abstract

Background: The prognostic value of perineural invasion (PNI) in head and neck squamous cell carcinoma (HNSCC) remains controversial. This study investigated the impact of PNI on prognosis in HNSCC. A total of 49 patients with HNSCC who underwent primary surgical treatment were selected for the study. Univariate analysis of the survival curve was performed using the Kaplan-Meier method. Multivariate analysis was carried out by Cox regression.

Results: PNI was present in 17 of 49 (34.7%) patients. The median follow-up was 18.7 months. The median DFS and OS were 16.6 months and 41.9 months, respectively. Univariate analyses showed that PNI was associated with OS (p : 0.02), but not with DFS (p : 0.50). ENE was associated only with DFS in univariate analysis (p : 0.04), but not OS (yes vs. no; 24.1 vs. 44.6 months, p : 0.21), and in multivariate analysis, ENE lost its significance for DFS (p : 0.12). Also, PNI was the only significant independent adverse prognostic factor for OS in multivariate analysis (p : 0.02). The median OS for patients with and without PNI was 17.1 months and 92.1 months, respectively.

Conclusion: PNI was an independent factor for poor prognosis in patients with HNSCC. The presence of PNI compared to ENE was associated with a greater risk of death in HNSCC. Therefore, it would be appropriate to consider adjuvant therapy in the presence of PNI alone without other adverse risk features.

Keywords: Head and neck cancer, Perineural invasion, Extranodal extension, Prognosis

Background

Head and neck cancers (HNC) can occur in the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands and include various histopathological tumors. However, squamous cell carcinoma (SCC) is the most common histological type in these tumors. The stage at the time of diagnosis predicts survival rates and guides management in HNC patients. The 2017 version of the tumor, node, metastases (TNM) staging system of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is used to stage HNC [1]. More advanced stages of TNM are associated with

worse survival. Close or positive surgical margins and other adverse prognostic risk features such as perineural invasion (PNI), lymphovascular invasion (LVI), and extranodal extension (ENE) increase the risk of local recurrence [2, 3]. Therefore, postoperative adjuvant therapy is recommended for patients with positive surgical margins, lymph node metastases (N2-3), or ENE to improve survival and loco-regional tumor control for HNC [4–6].

The prognostic significance of PNI seems to vary depending on different subtypes of HNSCC and tumor stages, so we aimed to evaluate the prognostic impact of PNI in patients with HNC.

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Methods

We retrospectively reviewed the medical records of HNC patients. Patients diagnosed with head and neck squamous cell carcinoma (HNSCC) who underwent surgical resection of the primary tumor with appropriate neck dissection at our hospital between January 1, 2009, and December 31, 2019, were included. This study was performed according to the Declaration of Helsinki and was approved by the Local Ethics Committee of Meram Faculty of Medicine, Necmettin Erbakan University, Turkey (Ethics Committee approval number: 2020/2750). Patients with nasopharyngeal cancer were not included. Also, HNSCC patients with metastatic disease at initial diagnosis, previously treated, and with recurrent disease were excluded from the study. In addition, patients who had inadequate information about PNI and ENE in their pathological reports, who did not continue their oncological follow-up, and whose records in their electronic or manual medical files could not be accessed were not included in the study. As a result, the data of 49 patients who met the inclusion criteria were analyzed.

The detailed clinicopathological data such as age, gender, adjuvant treatment methods, recurrence status at follow-up, tumor location, tumor diameter, tumor invasion depth, tumor cell differentiation, lymph node status, pathological ENE, borderline status, LVI, and PNI were recorded. The pathological T and N staging of the patients, which were previously performed according to the 7th edition of the AJCC staging system, was restaged according to the 8th edition of the AJCC staging system. The patients were divided into two groups as PNI+ and PNI- according to the presence or absence of PNI.

The patient's demographic and clinical features were compared according to PNI status using chi-square tests or Fisher's exact test for categorical variables and independent *t*-tests for continuous variables. Continuous variables were expressed as medians (ranges), and categorical variables were expressed as numbers and percentages. Survival rate estimates between PNI+ and PNI- groups were calculated by the Kaplan-Meier method and compared via a stratified log-rank test. Disease-free survival (DFS) was defined as the time from the surgery to the date of development of locoregional recurrence or distant metastasis. And, overall survival (OS) was defined as the time from the surgery to the date of death from any cause. Multiple logistic regression analyses were performed to determine the predictors on DFS and OS. The factors that revealed a statistical significance in univariate analyses were controlled in multivariate analysis. Multivariate

analyses were performed using the Cox proportional hazards regression model. A *p*-value of <0.05 was considered significant. We also calculated the 95% CI for the median time to event.

Results

The study included 49 patients, 39 men (79.6%) and 10 women (20.4%), with a median age of 57 years (range 36–82 years), and a median follow-up of 18.7 months. Tumors were most commonly found in supraglottic larynx (*n*=11, 22.4%), followed by the tongue (*n*=11, 22.4%), and subglottic larynx (*n*=8, 16.3%). The common tumor grade was grade 1 (49%). PNI, LVI, and ENE were present in 17 (34.7%), 16 (32.7%), and 20 (40.8%) patients, respectively. Positive resection margins were observed in 10 patients (20.4%). Bilateral neck dissection was performed in 37 patients (75.5%). Adjuvant RT was given to 39 (79.5%) patients, with 33 of these also receiving concurrent chemotherapy. A summary of relevant demographic and clinicopathologic features is provided in Table 1.

Perineural invasion was significantly associated with LVI (*p*=0.02), but not lymph node metastasis (*p*=0.72). Apart from that, there was no difference between PNI- and PNI+ groups regarding median age, gender, T stage, ENE, grade, surgery margin, adjuvant treatment, and recurrence (Table 2).

At the last follow-up, 13 patients (26.5%) were alive without disease, and 11 patients (22.4%) were living with the disease (particularly with distant metastasis). During follow-up, recurrence at any site was found in 31 patients (63.3%): local recurrence in 8 patients (16.3%), regional in 7 (14.3%), and distant in 16 (32.7%). Also, 25 patients (51%) had died. The median DFS and OS were 16.6 months and 41.9 months, respectively (Figs. 1 and 2).

Univariate analyses of other clinicopathological factors and the presence of PNI were performed to explore the factors affecting the prognosis. Among the factors analyzed, pathological N stage (N0-1 vs. N2-3; 69.5 vs. 9 months; *p*: 0.001), ENE (yes vs. no; 9.6 vs. 22.2 months, *p*: 0.04), and adjuvant treatment (yes vs. no; 22.2 vs. 8.2 months, *p*: 0.003) were significant prognostic factors for DFS. The significant factors affecting OS were pathological N stage (N0-1 vs. N2-3; 92.1 vs. 32.5 months, *p*: 0.04) and PNI (yes vs. no; 17.1 vs. 92.1 months, *p*: 0.02, Fig. 3). PNI (yes vs. no; 10.4 vs. 16.9 months, *p*: 0.50) was not a significant prognostic factor for DFS. Similarly, ENE (yes vs. no; 24.1 vs. 44.6 months, *p*: 0.21) was not a significant prognostic factor for OS. Other factors such as age, sex, pathological T stage, and LVI did not significantly affect DFS and OS (Table 3).

Table 1 Clinicopathological characteristics of all patients

Variable	n (%)
Median age, years (range)	57 (36–82)
Sex	
Men	39 (79.6)
Women	10 (20.4%)
Grade	
Well differentiated	24 (49)
Moderately differentiated	13 (26.5)
Poorly differentiated	12 (24.5)
Site of tumor	
Supraglottic larynx	11 (22.4)
Glottic larynx	5 (10.2)
Subglottic larynx	8 (16.3)
Tonsil	2 (4.1)
Oral cavity	2 (4.1)
Lip	4 (8.2)
Tongue	11 (22.4)
Paranasal sinus	2 (4.1)
Salivary gland	3 (6.1)
Hypopharynx	1 (2)
LVI	
Yes	16 (32.7)
No	33 (67.3)
PNI	
Yes	17 (34.7)
No	32 (65.3)
ENE	
Yes	20 (40.8)
No	19 (59.2)
Margin status	
Clear	39 (79.6)
Involved by tumor	10 (20.4)
Pathological T classification	
T1	2 (4.1)
T2	17 (34.7)
T3	17 (34.7)
T4a	13 (26.5)
Pathological N classification	
N0	16 (32.7)
N1	6 (12.2)
N2b, N2c	3 (6.1), 5 (10.2)
N3b	19 (38.8)
Treatment	
Surgery	10 (20.4)
Surgery + radiotherapy	6 (12.2)
Surgery + chemoradiotherapy	33 (67.3)

LVI lymphovascular invasion, PNI perineural invasion, ENE extranodal extension

Table 2 Demographic and disease characteristics of patients according to PNI status

	PNI- (n: 32,%)	PNI+ (n: 17,%)	p value
Characteristics			
Median age, years			
< 57	16 (50)	7 (41.2)	0.55
≥ 57	16 (50)	10 (58.8)	
Gender			
Male	26 (81.3)	13 (76.5)	0.69
Female	6 (18.8)	4 (23.5)	
T stage			
T1-2	15 (46.9)	4 (23.5)	0.11
T3-4	17 (53.1)	13 (76.5)	
Lymph node metastasis			
Yes	21 (65.6)	12 (70.6)	0.72
No	11 (34.4)	5 (29.4)	
ENE			
Yes	10 (31.2)	10 (58.8)	0.06
No	22 (68.8)	7 (41.2)	
Grade			
I	14 (43.8)	10 (58.8)	0.52
II	10 (31.3)	3 (17.6)	
III	8 (25)	4 (23.5)	
LVI			
Yes	7 (21.9)	9 (52.9)	0.02
No	25 (78.1)	8 (47.1)	
Surgery margin			
Clear	25 (78.1)	14 (82.4)	0.72
Positive	7 (21.9)	3 (17.6)	
Adjuvant treatment			
Radiotherapy	3 (9.4)	3 (17.6)	0.44
Chemoradiotherapy	21 (65.6)	12 (70.6)	
No	8 (25)	2 (11.8)	
Recurrence			
Yes	22 (68.8)	9 (52.9)	0.27
No	10 (31.2)	8 (47.1)	

LVI lymphovascular invasion, PNI perineural invasion, ENE extranodal extension

In multivariate analysis, the only significant independent adverse prognostic factor for OS was the presence of PNI (p : 0.02). In addition, adjuvant treatment (p : 0.001) and low pathological N stage (p : <0.001) were significant independent favorable prognostic factors for DFS (Table 4).

Discussion

Our results showed that PNI was an independent prognostic indicator in surgically resected HNSCC. Also, in our study, survival was worse in patients with PNI than

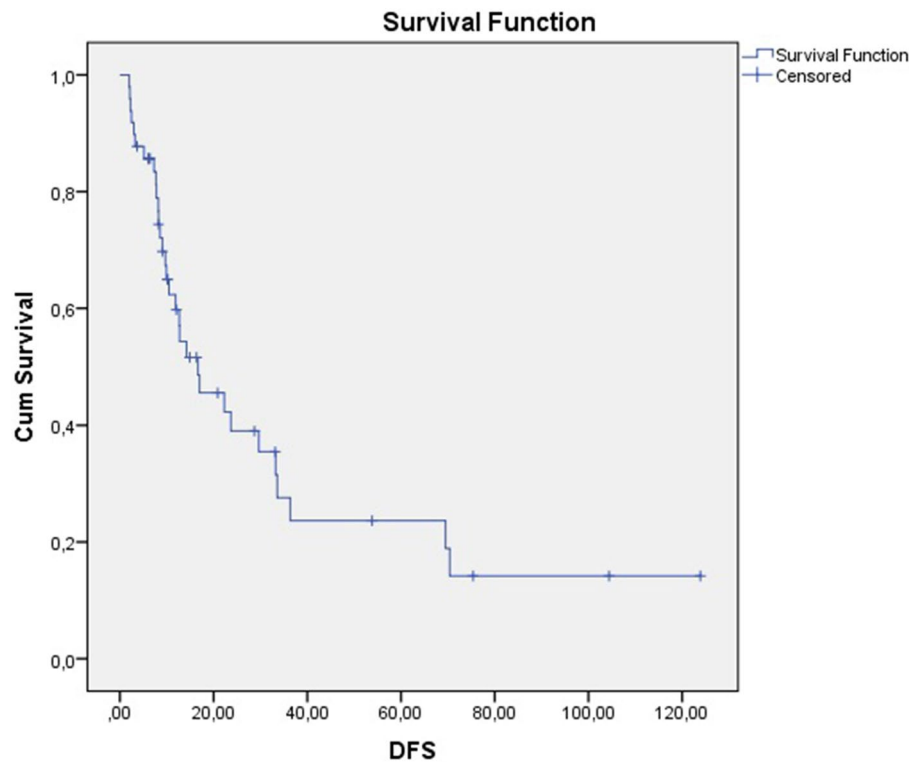


Fig. 1 Kaplan–Meier curve of DFS for all patients

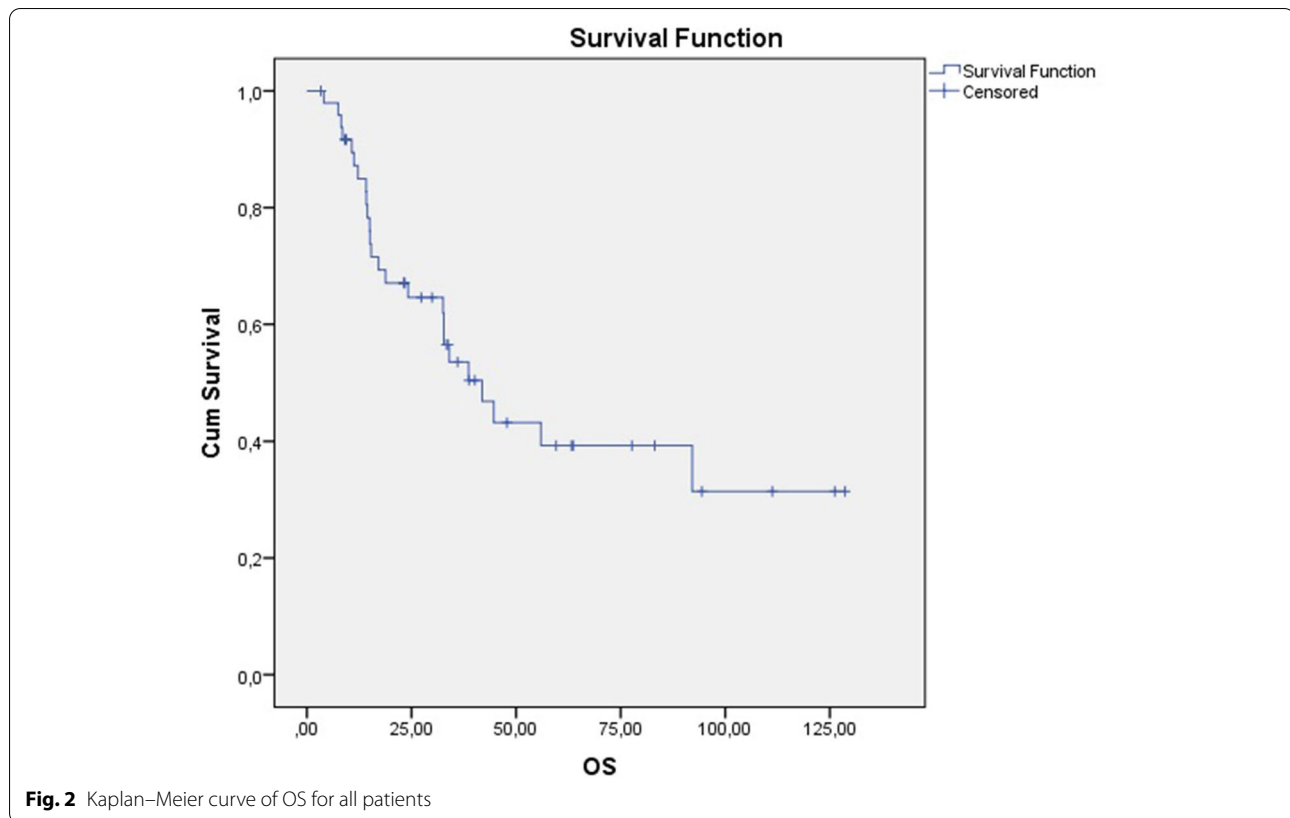
in ENE positive patients, and the presence of ENE did not significantly affect DFS and OS.

PNI is defined as the ability of cancer cells to invade in, around, and through nerves and was first described by Batsakis [7]. Currently, the definition proposed by Liebig is the most widely used and referenced. According to this definition, PNI is considered positive if the presence of tumor cells is detected in any of the three layers of the nerve sheath or if the tumor is close to the nerve and surrounds at least 33% of the nerve [8]. The incidence of PNI in HNSCC is approximately 40% [9]. And, PNI was diagnosed in 34.7% of tumors in our study.

PNI is considered as an adverse feature used in patient selection for postoperative adjuvant therapy in HNC. In a review evaluating whether adjuvant radiotherapy improves locoregional control and survival in HNSCC patients with PNI, in the absence of other indications for adjuvant therapy, 13 relevant retrospective studies were found and analyzed. Among these studies, three studies recommended adjuvant RT, and five studies showed that adjuvant RT was not beneficial [10]. Therefore, there is insufficient evidence to support current guidelines recommending adjuvant RT for all patients

with early-stage HNSCC with PNI in the absence of other indications. However, the presence of PNI is one of the predictive indicators of cervical lymph node metastasis in HNC [11–15]. Also, a significant relationship between preoperative otalgia and PNI has been demonstrated in patients with tongue SCC and oral cancer [16, 17].

The prognostic importance of PNI is controversial. Although some reports have shown a relationship between PNI and prognosis in HNSCC patients, this is not a general conclusion. However, the prognostic significance of PNI appears to vary depending on the different subtypes and tumor stages of HNSCC. In a retrospective analysis of 194 patients with primary HNC managed surgically with planned adjuvant therapy, PNI was associated with poor OS [18]. PNI was associated with decreased survival in tongue SCC in young adults (< 40 years) and buccal cancers, as well as shortening of DFS in cancers of major salivary glands [19–21]. In a study performed in patients with laryngeal SCC treated surgically, the presence of PNI was associated with a significant increased local recurrence rate and shortened DFS, but not regional recurrence and distant metastasis rate [22]. In contrast, in



oral and oropharyngeal carcinoma, it was significantly associated with regional recurrence and distant metastasis but not with local recurrence [23]. In the study conducted by Fagan JJ et al. in patients who had a primary surgical resection for the oral cavity, oropharynx, hypopharynx, and laryngeal SCC, it has been found that PNI was significantly associated with local recurrence and disease-specific mortality. Also, PNI was associated with an increased risk of local recurrence and cervical metastasis in the only oral cavity and oropharyngeal carcinoma [24]. In a study aimed to determine the risk factors for treatment failure in high-risk head and neck cutaneous squamous cell carcinoma (HNcSCC) patients treated with surgery, the presence of PNI was significantly associated with worsening DFS than patients without PNI (2-year estimated DFS was 54% vs. 78%) [25]. A meta-analysis of 43 studies of 21,530 patients with HNcSCC demonstrated that poor differentiation, PNI, and Breslow thickness greater than 2 mm significantly increased the risk of recurrence, metastasis, and disease-specific death [26]. Unlike those presented above, Tourneau C et al. showed in a study in HNC patients treated with surgery and postoperative RT that PNI was not associated

with survival [27]. But, in a meta-analysis involving 18 studies and 3894 patients with HNcSCC located in different subsites, it has been shown that PNI was statistically associated with poor OS, DFS, and disease-specific survival (DSS). Additionally, when studies were stratified by tumor location, it has been found that PNI was associated with poor OS in the oral cavity, larynx, and hypopharynx cancers [28]. Besides, Ebrahimi A et al. found a wide variation depending on immunosuppression, the number and size of nodal metastases, and PNI in DSS. This heterogeneity is thought to be the reason for the AJCC staging system's inability to predict prognosis. It has been reported that more accurate prognosis estimates can be made by integrating these poor prognostic factors into the staging system [29].

Conclusions

The findings of our study showed an independent association between PNI and poor prognosis in patients with HNcSCC. Additionally, in terms of adverse disease course, the presence of PNI poses a significantly higher threat than ENE added to the 8th edition of the AJCC in 2017.

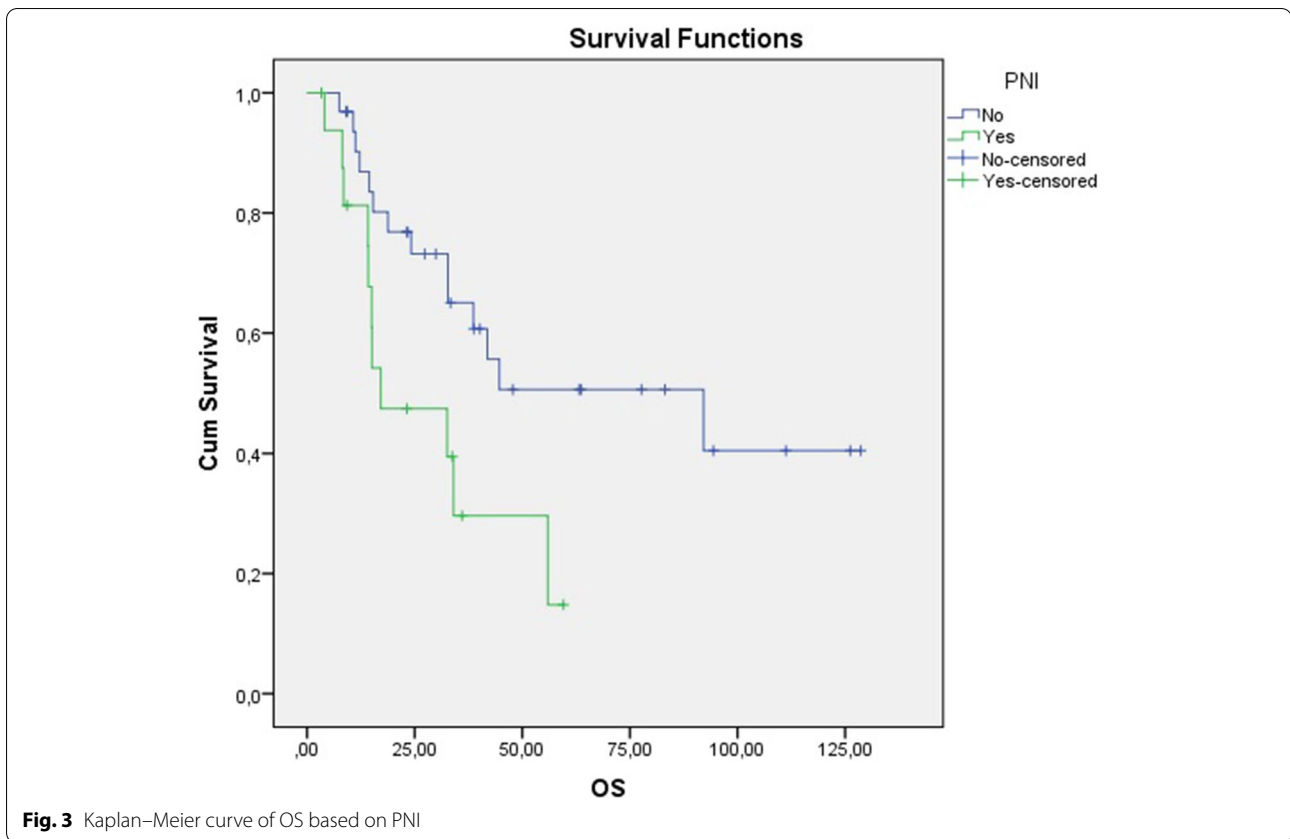


Table 3 Univariate analysis of different variables affecting DFS and OS

Variables	DFS p value	HR (%95 CI)	OS p value	HR (%95 CI)
Age (years)	0.82	1.00 (0.97–1.03)	0.21	1.02 (0.98–1.05)
Sex (men vs. women)	0.36	1.62 (0.56–4.66)	0.71	0.83 (0.31–2.32)
T stage (T1-2 vs. T3-4)	0.50	1.27 (0.62–2.59)	0.82	0.91 (0.40–2.04)
N stage (N0-1 vs. N2-3)	0.001	0.25 (0.11–0.57)	0.04	0.42 (0.18–0.97)
LVI (yes vs. no)	0.17	0.59 (0.28–1.25)	0.34	0.67 (0.29–1.52)
PNI (yes vs. no)	0.50	0.76 (0.34–1.69)	0.02	0.39 (0.17–0.88)
ENE (yes vs. no)	0.04	0.47 (0.23–0.97)	0.21	0.60 (0.27–1.32)
Adjuvant treatment (yes vs. no)	0.03	2.30 (1.04–5.04)	0.83	1.11 (0.41–2.96)

LVI lymphovascular invasion, PNI perineural invasion, ENE extranodal extension, DFS disease-free survival, OS overall survival

Table 4 Multivariate analysis of different variables affecting DFS and OS

Variables	DFS		OS	
	p value	HR (%95 CI)	p value	HR (%95 CI)
N stage (N0-1 vs. N2-3)	<0.001	0.09 (0.02–0.30)	0.05	0.42 (0.18–0.99)
PNI (yes vs. no)	–	–	0.02	0.39 (0.17–0.90)
ENE (yes vs. no)	0.12	2.10 (0.81–5.41)	–	–
Adjuvant treatment (yes vs. no)	0.001	4.74 (1.92–11.69)	–	–

PNI perineural invasion, ENE extranodal extension, DFS disease-free survival, OS overall survival

Therefore, even in the presence of PNI alone without other adverse risk features, adjuvant therapy should be administered.

The main limitations of our study were the retrospective design and the small sample size. Another limitation was that subgroup analysis by tumor location cannot be performed due to the small number of patients.

Abbreviations

AJCC: American Joint Committee on Cancer; DFS: Disease-free survival; DSS: Disease-specific survival; ENE: Extranodal extension; HNC: Head and neck cancers; HNCSCC: Head and neck cutaneous squamous cell carcinoma; HNSCC: Head and neck squamous cell carcinoma; LVI: Lymphovascular invasion; OS: Overall survival; PNI: Perineural invasion; TNM: Tumor, node, metastases; SCC: Squamous cell carcinoma; UICC: Union for International Cancer Control.

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Authors' contributions

MKE: written, literature review, controller, and design. MK: written, literature review, and data collecting. MKa: data collecting and English editing. MA: data controller. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethics Committee of Meram Faculty of Medicine, Necmettin Erbakan University, Turkey (Ethics Committee approval number: 2020/2750). The consent to participate is not applicable since it is a retrospective study.

Consent for publication

Not applicable

Competing interests

The authors have no conflicts of interest to declare.

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