

## Research Article

# The Prognostic Value of Pathological Extranodal Extension and Staging Change According to the 8<sup>th</sup> Edition Pathologic Staging Modifications for Head and Neck Cancer

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### Abstract

**Objectives:** We aimed to determine the prognostic value of pathological extranodal extension (pENE) and to evaluate the stage change by restaging according to the 8th edition of the AJCC staging system (AJCC 8) based on the addition of pENE in head and neck cancer (HNC).

**Methods:** This study involved 30 HNC patients with lymph node metastasis who staged according to AJCC 7 underwent surgery and neck dissection.

**Results:** The median age of patients was 57 years, and 86.7% were male patients. Twenty patients (66.7%) were pENE+, 10 patients (33.3%) were pENE-. After re-staging based on the presence of pENE according to the AJCC 8 criteria, the TNM stage of 20 patients were up-staged due to up-staging in pN stage. One patient (3.3%) classified as pN1 according to the AJCC 7 criteria was up-staged to pN1b. Similarly, 1 patient (3.3%) classified as pN1, 1 patient (3.3%) classified as pN1a, 3 patients (10%) classified as pN1b, and 14 patients (46.7%) classified as pN1c by AJCC 7 were upstaged pN1d. Median disease-free survival (DFS) and median overall survival (OS) were 16.6 months and 32.7 months, respectively. The pENE+ patients had shorter median DFS and median OS than those with pENE- (DFS: 9.6 vs. 22.2 months,  $p=0.24$  and OS: 24.1 vs. 32.7 months,  $p=0.95$ , respectively), but not statistically significant.

**Conclusion:** The incorporating of pENE to N classification up-staged the TNM stage. In our study, although pENE could not be shown as a statistically significant prognostic marker, the presence of pENE would contribute to the improvement of survival as it would increase the number of patients requiring adjuvant therapy. Therefore pENE indirectly would be appropriate to consider as a prognostic factor.

**Keywords:** Head and neck cancers, extranodal extension, prognosis

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Head and neck cancers (HNC) originate from the mucosal surfaces of the upper aerodigestive system and more than 90% are squamous cell carcinomas (SCC).<sup>[1]</sup> Head and neck cancers are the 7<sup>th</sup> most common cancer in 2018 data and the rate of all cancers is 4%. With 13740 cases, it causes 2% of all cancer-related deaths.<sup>[2,3]</sup> The most

common associated risk factors include smoking, alcohol consumption, human papilloma virus (HPV) infection, and Epstein-Barr virus (EBV) infection.<sup>[4]</sup> The American Joint Committee on Cancer (AJCC) 7 staging system published in 2010, stage I and II cancers consist of smaller primary tumors and limited disease, stage III and IV tumors are de-

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defined as cancers invading the surrounding structures, causing regional lymph node involvement and/or distant metastasis.<sup>[5]</sup> The 8<sup>th</sup> edition of the AJCC staging system (AJCC 8) was published in 2017 and some revisions have been made. One of these was the addition to the staging system of clinical and pathological extranodal extension (ENE) status in the metastatic lymph nodes. The presence of ENE in the metastatic lymph node has long been known as a poor prognostic factor.<sup>[6]</sup>

The aim of study was to evaluate the prognostic value of pathological extranodal extension (pENE) and to re-stage N classification according to the addition of pENE with the current and previous AJCC N classifications in patients with HNC who had primary operated and lymph node metastasis.

## Methods

### Patients

We retrospectively evaluated patients diagnosed with head and neck SCC (HNSCC) were included, excluding nasopharyngeal cancer, who had undergone primary surgical treatment and neck dissection at our hospital between October 2009 and December 2019. Patients who had no metastasis in lymph node, metastatic disease at the initial diagnosis, and previously treated or recurrent HNSCC were excluded. Also, those with insufficient information from clinical records and pathology reports were excluded. Clinical information obtained from patient records included demographic data, operative reports and pathology reports. The age of patients, gender, primary tumor location, side of neck dissection (bilateral vs. unilateral), adjuvant treatment, recurrence status, past T, N, and overall stage, and pathologic results such as tumor grade, lymphovascular invasion (LVI), perineural invasion (PNI), pENE, the number of metastatic lymph nodes, and the margin status were recorded. Then, every patient were staged according to AJCC 7 and AJCC 8 based on the presence and absence of pENE. Patients were divided into two groups as pENE + and pENE- depending on the presence or absence of pENE. The data of 30 patients who met the inclusion criteria were analyzed.

### Statistical Analysis

All analyses were carried out using the SPSS version 22.0 statistical software package. Descriptive statistics were calculated as proportions and medians. The clinical end points of interest were disease-free survival (DFS) and overall survival (OS). Survival curves were created using the Kaplan-Meier method. Disease-free survival (DFS) was defined as the time from the date of surgery to the date of local regional relapse or distant metastases. Overall survival

(OS) was defined as the time from the date of surgery to the date of death from any cause. The effect of the pENE on the PFS and OS was investigated using a log-rank test. A p value of <0.05 was considered significant.

## Results

### Patient Characteristics

A total of 30 HNSCC patients undergoing primary surgery and lymph node dissection, the median age at diagnosis was 57 years (range, 36-80 years), and median follow-up of 22.7 months, 86.7% were male, 33.3% had grade 1 histology, 40% had LVI, 36.7% had PNI. And, the most common primary tumor locations were supraglottic larynx (36.7%), tongue (26.7), and subglottic larynx (16.7%). Twenty six patients (86.7%) underwent bilateral neck dissection and the other 4 patients (13.3%) underwent unilateral neck dissection. The margin status of 23 (76.7%) was clear. After surgery, 5 patients (16.7%) received adjuvant radiotherapy, 20 patients (66.7%) received adjuvant concurrent chemoradiotherapy. Twenty of 30 patients (66.7%) were pENE+, and 10 of 30 (33.3%) were pENE-. Detailed clinicopathological data are summarized in Table 1.

### Distribution of TNM and pN Stage According to AJCC 7 and AJCC 8

According to AJCC 7, 5 patients (16.7) had stage III disease, 24 patients (80%) had stage IVA disease, and 1 patients (3.3%) had stage IVC disease. There were also 8 (26.7%) pNI, 1 (3.3%) pNIIA, 4 (13.3%) pNIIB, and 17 (56.7%) pNIIC patients.

According to AJCC 8, 4 patients (13.3%) had stage III, 6 patients (20%) had stage IVA, 19 patients (63.3%) had stage IVB, and 1 patient (3.3%) had stage IVC disease. Six (20%) patients were pNI, 1 (3.3%) patient was pNIIB, 4 (13.3%) patients were pNIIC, and 19 (63.3%) patients were pNIIB.

Distributions of TNM and pN stage according to AJCC 7 and AJCC 8 are presented in Table 2 and 3.

### Up-Staging of TNM and pN Stage Following Application of AJCC 8 Criteria

After re-staging based on the presence of pENE according to the AJCC 8 criteria, the TNM stage of 20 patients were up-staged due to up-staging in pN stage. From patients classified as pNI according to the AJCC 7 criteria, 1 patient (3.3%) was up-staged to pNIIB and 1 patient (3.3%) was up-staged to NIIB. Similarly, 1 patient (3.3%) classified as pNIIA, 3 patients (10%) classified as pNIIB, and 14 patients (46.7%) classified as pNIIC by AJCC 7 were upstaged pNIIB. Since the pN stage of 10 patients (33.3%) did not change, the TNM stage remained unchanged (Table 4).

**Table 1.** Clinicopathological characteristics of patients

	n	%
Characteristics		
Median age, years (range)	57 (36-80)	
Gender		
Male	26	86.7
Female	4	13.3
Grade		
I	10	33.3
II	5	16.7
III	5	16.7
Subsite		
Supraglottic larynx	11	36.7
Glottic larynx	1	3.3
Subglottic larynx	5	16.7
Tonsil	1	3.3
Oral cavite	1	3.3
Lip	1	3.3
Tongue	8	26.7
Paranasal sinus	2	6.6
Neck dissection		
Bilateral	26	86.7
Right	1	3.3
Left	3	10
LVI		
Present	12	40
Absent	18	60
PNI		
Present	11	36.7
Absent	19	63.3
ENE		
Yes	20	66.7
No	10	33.3
Margin status		
Clear	23	76.7
Involved	7	23.3
Treatment		
Surgery alone	5	16.7
Surgery + radiotherapy	5	16.7
Surgery + chemoradiotherapy	20	66.7

LVI: Lymphovascular invasion; PNI: Perineural invasion; ENE: Extranodal extension.

## Outcomes

During follow-up, 7 patients (23.3%) had developed locoregional recurrence, 13 patients (43.3%) had developed distant metastasis, and 19 patients (63.3%) died. Median DFS and median OS were 16.6 months and 32.7 months, respectively (Fig. 1). The median DFS and median OS were compared according to pENE. The pENE+ patients had shorter median DFS and median OS than those with pENE- (me-

**Table 2.** Distribution of pN stage according to AJCC 7 and AJCC 8

	AJCC 7 n (%)	AJCC8 n (%)
pN category		
NI	8 (26.7)	6 (20)
NIIA	1 (3.3)	-
NIIB	4 (13.3)	1 (3.3)
NIIC	17 (56.7)	4 (13.3)
NIIIA	-	-
NIIBB	-	19 (63.3)

**Table 3.** Distribution of TNM stage according to AJCC 7 and AJCC 8

	AJCC 7 n (%)	AJCC8 n (%)
TNM stage		
III	5 (16.7)	4 (13.3)
IVA	24 (80)	6 (20)
IVB	-	19 (63.3)
IVC	1 (3.3)	1 (3.3)

**Table 4.** pN stage change from AJCC 7 to AJCC 8

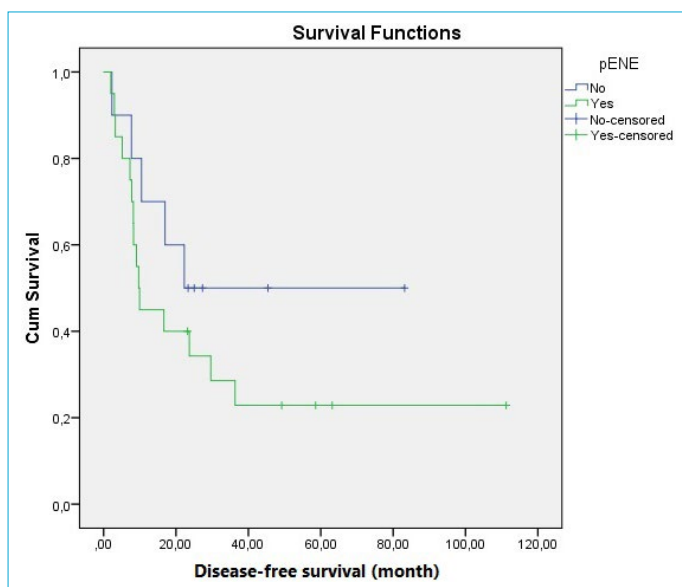
pN stage, AJCC 7, n (%)	pN stage, AJCC 8, n (%)				
	NI	NIIA	NIIB	NIIC	NIIBB
NI	6 (20)	0	0	1 (3.3)	1 (3.3)
NIIA	0	0	0	0	1 (3.3)
NIIB	0	0	1 (3.3)	0	3 (10)
NIIC	0	0	0	3 (10)	14 (46.7)

dian DFS: 9.6 vs. 22.2 months,  $p=0.24$  and median OS: 24.1 vs. 32.7 months,  $p=0.95$ , respectively), but not statistically significant (Fig. 2).

## Discussion

This study is a study evaluating whether pENE has the prognostic utility of for the AJCC 8 nodal staging system for HNSCC. According to our results, the incorporation of pENE to the AJCC 8 criteria up-staged the stage 66.7% of patients, and the survival of pENE+ patients was shorter than pENE- patients, it was not statistically significant. Addition, the presence of pENE (66.7%) was similar reported in previous studies (59.2%, 67% and 76%, respectively).<sup>[7-9]</sup>

Extranodal extension has emerged as an important prognostic factor in HNSCC4-6 and it was added to AJCC 8 TNM staging in 2017, except for p16+ oropharyngeal cancer. In a study of 298 HNSCC patients who underwent surgical resection and neck dissection, the presence of pENE was poor prognostic factor for DFS. Moreover, the clinical



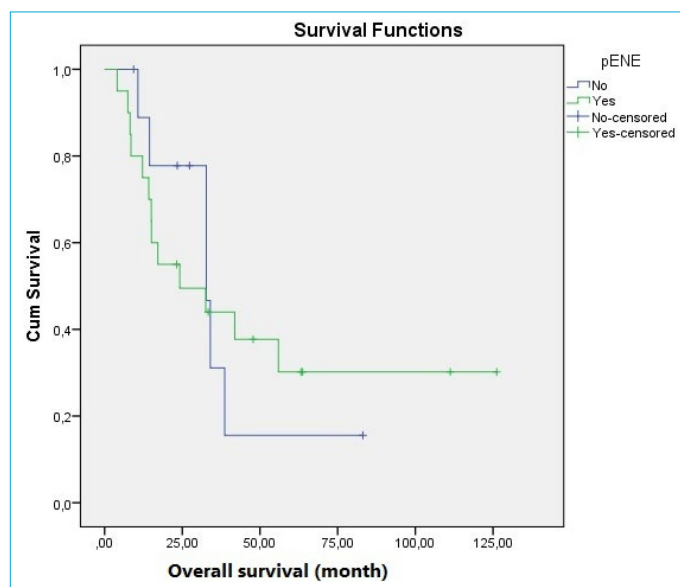
**Figure 1.** Kaplan–Meier curve of disease-free survival (DFS) based on extranodal extension (ENE).

significance of pENE was much greater for patients with laryngeal and hypopharyngeal cancer than oral cancer.<sup>[10]</sup> In a study performed by Ho et al in 8351 patients with hypopharyngeal and laryngeal SCC undergoing surgery and neck dissection, there were 4710 patients with metastatic lymph nodes and 3641 patients with no metastatic lymph nodes, and they found that ENE was associated with increased mortality.<sup>[11]</sup> Similarly, in cases of salivary gland cancer, ENE has been identified as an independent indicators of recurrence and was associated with poor DFS and OS outcomes.<sup>[12, 13]</sup>

In the study evaluating staging change by using tumor invasion depth (DOI) and pENE according to AJCC 8 in patients with OCSCC undergoing definitive surgery, up-staging was seen in 12.4% of patients for the pT classification, in 13.3% for the pN classification, and in 24.8% for the overall stage. Also, up-staging led to similar 5-year OS for every AJCC 8 pT/N classification except pStage IVB.<sup>[14]</sup> We did not DOI because tumor sites of our patient group were heterogeneous. That's why we only used pENE for pN classification, 66.7% of our patients were up-staging in the pN classification. We could not analyze survival change based on stage due to the small number of patients and heterogeneity of tumor site. In addition, pENE in our study did not provide useful prognostic information for patients with lymph nodal metastases as per the AJCC 8 staging system.

## Conclusion

In conclusion, these data show that pENE positivity is not an uniformly poor prognostic indicator, and nodal staging can be further improved in future editions.



**Figure 2.** Kaplan–Meier curve of overall survival (OS) based on extranodal extension (ENE).

The major 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.

## Disclosures

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**Ethics Committee Approval:** The study was performed according to the Declaration of Helsinki and approved by the Local Ethics Committee (Ethics Committee approval number: 2020/2750).

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