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Anatomic extent of lymph node metastases as an independent prognosticator in node-positive major salivary gland carcinoma: A study of the US SEER database and a Chinese multicenter cohort

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ABSTRACT

Background: We aimed to explore whether the anatomic extent of lymph node metastases (AE-LNM) could independently predict prognosis of node-positive major salivary gland carcinoma (MaSGC).
Methods: A total of 376 pathologically node-positive MaSGC patients were identified from the Surveillance, Epidemiology and End Results database and constituted the training cohort. Using the X-Tile program, these patients were divided into three groups based on AE-LNM degrees. Discrimination of overall survival (OS) and disease-specific survival (DSS) was evaluated and compared with the 8th American Joint Committee on Cancer (AJCC) pN classification. The results were externally validated by 220 patients in a Chinese multicenter cohort (Validation cohort).
Results: Using the training cohort, AE-LNM was divided into Extent 1 (spread to parotid LNs or level I), Extent 2 (spread to level II-IV) and Extent 3 (spread to level V or bilateral LNs or rare LNs). Regarding both OS and DSS, the AE-LNM model revealed clear separation of survival curves, while the pN classification failed to discriminate the prognosis of pN1 and pN2 patients. When we incorporated both the AE-LNM model and AJCC pN classification into the same multivariate Cox analyses, AE-LNM was still an independent prognostic factor, while the AJCC pN classification lost its significance. These results were externally validated by the validation cohort.

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Conclusion: AE-LNM is an independent nodal prognosticator for node-positive MaSGC and may have improved discriminative ability over the current AJCC pN classification. Integration of anatomic extent of LNM into the current AJCC N classification could be considered.

Introduction

Major salivary gland carcinoma (MaSGC) is composed of a relatively rare group of neoplasms accounting for fewer than 5% of head and neck malignancies [1]. Unlike the majority of head and neck cancers that are predominated by squamous cell carcinoma (HNSCC), MaSGCs are highly heterogeneous with over 20 histologic types [2]. Although different histotypes demonstrate different clinicopathological features, complete surgical resection with/without adjuvant radiotherapy is the mainstay of management for locoregionally confined MaSGC patients [3], for whom a pathologic staging system is important for predicting prognosis. The American Joint Committee on Cancer (AJCC) TNM classification is the most widely employed staging system. For MaSGCs, the eighth edition of AJCC staging system has undergone modification regarding the inclusion of extranodal extension (ENE) into pN definition [4]. However, there is a lack of validation of the updated staging system.

Previous studies have reported different patterns of lymph node metastases (LNM) among subsites of head and neck cancers [5–7]. On the basis of these studies, Xing et al. proposed site-specific models for oral, hypopharyngeal and laryngeal carcinoma based on the anatomic extent of LNM (AE-LNM), showing better clinical relevance than the 7th AJCC pN classification [8]. On the other hand, MaSGC generally follows a sequential pattern of nodal dissemination [4], indicating that AE-LNM of MaSGCs progresses in a sequential manner. Inspired by the relevant researches, in this study, we aimed to investigate whether AE-LNM could be an independent nodal prognosticator for node-positive MaSGC. In addition, we compared the prognostic discrimination of the AJCC pN classification with that of a classification based on AE-LNM.

Patients and methods

Study population

US SEER database: The SEER database, which covers approximately 26% of US population, was used to identify eligible patients diagnosed from 2004 to 2012. The inclusion criteria were as follows: **(1)** Primary MaSGCs were identified by International Classification of Diseases for Oncology-3rd edition (ICD-O-3) Topography Codes C07.9 to C08.9 and Histology Codes 8000-8576, 8940-8950 and 8980-8981 according to the AJCC staging manual [4]. **(3)** pathologically node-positive (pN+); **(4)** absence of distant metastases at diagnosis; **(5)** with definite pathologic T classification; **(6)** treated by curative-intent primary surgery; **(7)** with complete information (size, number, laterality and ENE) to restage per the 8th AJCC N classification; **(8)** with definite information on the anatomic location of LNM; **(9)** LNM confirmed by pathology. The exclusion criteria were as follows: **(1)** LNM was confirmed by biopsy/aspiration rather than neck dissection; **(2)** treated with unknown method of radiation (radiation-not otherwise specific [NOS]), as whether beam radiotherapy was administered was unknown; **(3)** underwent beam radiation prior to surgery; **(4)** Primary squamous cell carcinoma (SCC) represents fewer than 1% of salivary gland tumors [2]. However, it is the second most common histology (over 25%) in the SEER database; in reality, most of them are metastases from a cutaneous primary tumor [9,10]. Consequently, patients with SCC were excluded, just as a previous study [10]. The selection process of SEER data is presented as a flowchart (Supplementary Fig. S1).

Chinese multicenter cohort: Postoperative pN + MaSGC patients were consecutively identified from six Chinese collaborative centers with the same in- and exclusion criteria as used for the SEER database: Fudan University Shanghai Cancer Center ($N = 83$, from 1998 to 2015), Sun Yat-sen University Cancer Center ($N = 60$, from 2005 to 2015), Chinese Academy of Medical Sciences National Cancer Center ($N = 40$, from 2005 to 2015), Zhejiang Cancer Hospital ($N = 16$, from 2010 to 2015), Nanjing Stomatological Hospital ($N = 11$, from 2012 to 2015) and Gansu Province Cancer Hospital ($N = 10$, from 2012 to 2015). In each institution, Patients' deidentified clinicopathologic and follow-up information was recorded and cross-checked for inconsistencies by providers blinded to the purpose of this study. The cutoff follow-up date of the multicenter cohort was March 1, 2018.

Demographics (age at diagnosis, and sex), tumor characteristics (primary site, histotype, tumor grade, laterality, T stage, nodal status, ENE and extent of LNM), treatment (status of surgery and radiation) and follow-up data were retrieved. Since MaSGCs were composed of overcomplicated histotypes, including some exceedingly rare types, we used an updated histologic risk stratification rather than specific histotypes to facilitate multivariate analysis [11]. Specifically, the high-risk pathologies included intermediate-/high-grade (G2/3) cystadenocarcinoma/adenocarcinoma-NOS; G2/3 mucoepidermoid carcinoma/carcinoma ex pleomorphic adenoma; sebaceous carcinoma/lymphadenocarcinoma; adenoid cystic carcinoma; salivary duct carcinoma; mucinous adenocarcinoma; small-cell/large-cell/lymphoepithelial carcinoma; metastasizing pleomorphic adenoma and carcinosarcoma; other histotypes in the WHO classification belonged to low-risk pathologies [11]. In addition, cases unable to be classified based on the updated histologic stratification (e.g., 8000/3 [malignant tumor-unspecified], or mucoepidermoid carcinoma without definite tumor grade) were assigned to the "Unspecified" group.

The Institutional Review Boards of all participating hospitals approved this study.

Statistical analysis

The endpoints of this study were overall survival (OS) and disease-specific survival (DSS). Duration of OS was calculated as the interval from initial pathological diagnosis to the date of death from any cause or the last contact, whichever occurred first; while the duration of DSS was calculated as the interval from initial pathological diagnosis to the date of death from MaSGC or the last contact, whichever occurred first.

The Kaplan-Meier method and log-rank tests were used to generate and compare survival curves. Among the various histologies, adenoid cystic carcinoma (AdCC) is a very special one because its most common way of tumor spread is perineural invasion, not LNM. In addition, AdCC is generally more sensitive to radiotherapy. Therefore, we also performed subgroup Kaplan-Meier survival analyses to evaluate the prognostic value of AE-LNM and AJCC pN classification in AdCC. Multivariate Cox

proportional hazards regression models were performed to evaluate the hazard ratio (HR) and 95% confidence interval (CI), bootstrapping method with 1000 replications was used to avoid the overfitting problem. The discriminatory powers were evaluated by the bootstrap-corrected Harrell's concordance index (C-index) with 1000 replications.

X-Tile software version 3.6.1 (Yale University, New Haven, CT) was used for cut-point optimization. The X-Tile program can help divide patients into subgroups (e.g., tertiles, quartiles) by determining the optimal cutoff points of a continuous variable or ordinal categorical variable based on the maximum $\chi 2$ statistic value in the log-rank test [12–14]. Log-rank tests were conducted by SPSS 24.0 (SPSS, Chicago, IL). Kaplan-Meier survival curves were drawn with GraphPad Prism 7.0 (GraphPad Software, San Diego, CA). The multivariate Cox analyses and the C-indexes were evaluated by the "*rms*" package in R program version 3.4.3 (Bell Laboratories, Murray Hill, NJ). A two-sided $P < 0.05$ was regarded as statistically significant.

Results

Patient characteristics

A total of 376 patients were selected from the SEER database for the training cohort. Baseline characteristics are listed in Table 1. For the training cohort,. according to the 8th AJCC pN classification, pN1, pN2 and pN3 disease accounted for 35.4%, 39.4% and 25.3%, respectively. The median follow-up time was 53 months.

In total, 220 patients in the six Chinese collaborative centers met the in-and exclusion criteria and were included in the validation cohort. Baseline characteristics are also listed in Table 1. For the validation cohort, according to the 8th AJCC pN classification, 20.5%,

Table 1
Baseline characteristics for patients in the training cohort and validation cohort.

Characteristics	Training Cohort ($N = 376$)		Validation cohort ($N = 220$)	
	No. of patients	%[a]	No. of patients	%[a]
Age, years, median (Mean±SD)	61 (60.2 ± 16.5)		56 (53.0 ± 15.2)	
Age group, years				
<60	167	44.4	137	62.3
≥60	209	55.6	83	37.7
Sex				
Female	133	35.4	65	29.5
Male	243	64.6	155	70.5
Race[b]				
White	304	80.9	0	0.0
Black	35	9.3	0	0.0
Other	37	9.8	220	100.0
Site				
Parotid	329	87.5	176	80.0
Non-parotid	47	12.5	44	20.0
Laterality				
Left	176	46.8	110	50.0
Right	194	51.6	108	49.1
Bilateral/NOS	6	1.6	2	0.9
Histotype (Specific)				
Mucoepidermoid carcinoma	94	25.0	41	18.6
Adenocarcinoma-NOS	73	19.4	33	15.0
Salivary duct carcinoma	29	7.7	59	26.8
Adenoid cystic carcinoma	25	6.6	18	8.2
Acinic cell carcinoma	23	6.1	8	3.6
Carcinoma in pleomorphic adenoma	14	3.7	4	1.8
Malignant Tumor-Unspecified	32	8.5	10	4.5
Others	86	22.9	47	21.4
Histotype (Risk stratification)				
Low-risk pathology	93	24.7	26	11.8
High-risk pathology	233	62.0	177	80.5
Unspecified	50	13.3	17	7.7
Radiation				
No evidence	72	19.1	60	27.3
Received	304	80.9	160	72.7
AJCC pT classification				
pT1	50	13.3	27	12.3
pT2	93	24.7	61	27.7
pT3	112	29.8	68	30.9
pT4a	94	25.0	57	25.9
pT4b	27	7.2	7	3.2
AJCC pN classification				
pN1	133	35.4	45	20.5
pN2	148	39.4	120	54.5
pN3	95	25.3	55	25.0
AE-LNM				
Extent 1	154	41.0	58	26.4
Extent 2	136	36.2	114	51.8
Extent 3	86	22.9	48	21.8

Abbreviation: SD, Standard Deviation; NOS, Not Otherwise Specified; AJCC, American Joint Committee on Cancer.
[a] Percentages are column percentages and may not add up to 100 because of rounding.
[b] The "Other" race category includes Asian, Pacific Islander and Alaska Natives.

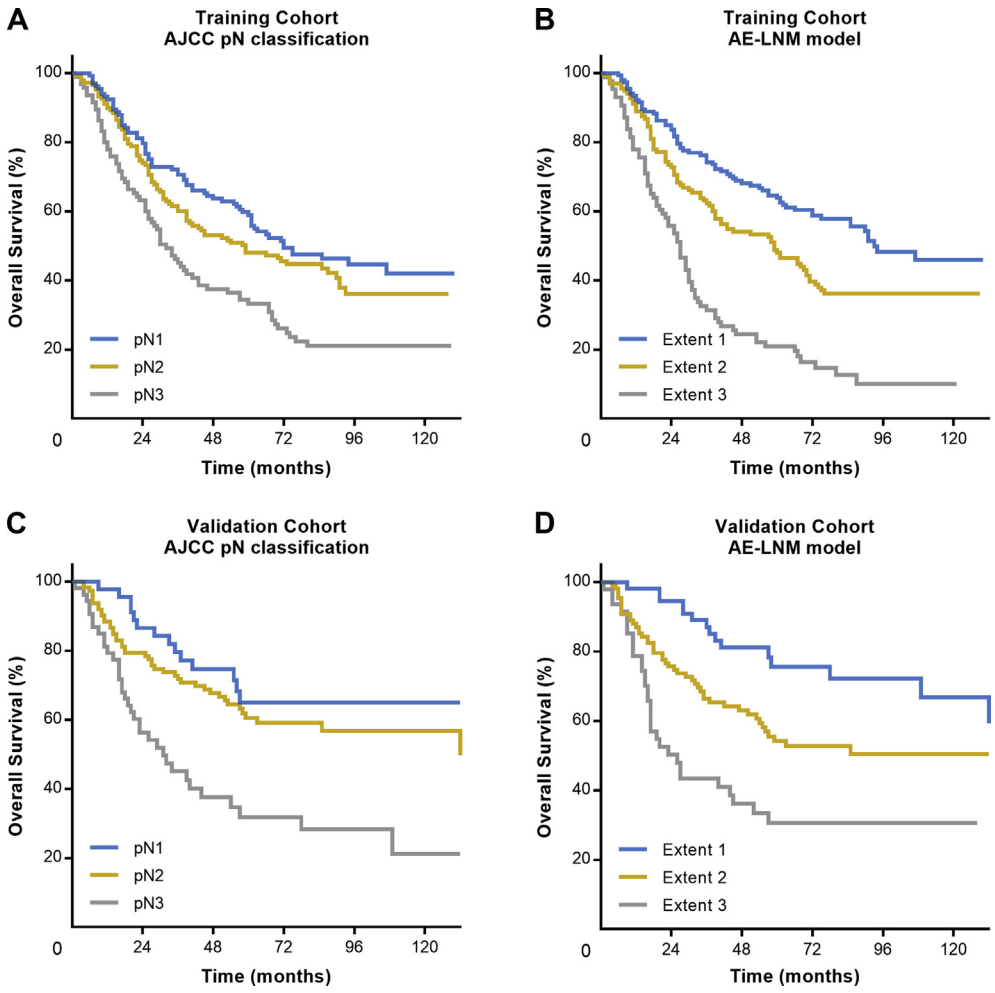

Fig. 1. Kaplan-Meier survival plots for OS according to the 8th AJCC pN classification and the AE-LNM model for the training cohort **(A and B)** and the validation cohort **(C and D)**.

54.5%, and 25.0% of the patients had pN1, pN2 and pN3 lesions, respectively. The median follow-up time was 45 months.

Development of the three-tiered AE-LNM model

MaSGC generally follows a sequential pattern of nodal spread, from intra-/periglandular nodes to level II-IV lymphatic chain, and subsequently to level V, while other LNs or bilateral metastases are rare [4]. For parotid cancers, the intra-/periglandular LNs are parotid LNs, level I metastases are also common and generally occur before level II involvement (explained in Discussion section). For submandibular/sublingual cancers, there is almost no parotid LN involvement, the intra-/periglandular LNs are level I nodes. Therefore, AE-LNM can be divided into six degrees progressing in a sequential manner: Spread to **(1)** parotid LNs or level I; **(2)** level II; **(3)** level III; **(4)** level IV; **(5)** level V; **(6)** bilateral LNs or rare LNs.

Using the training cohort, the X-Tile program was used to determine the optimal cutpoints to divide the abovementioned six AE-LNM degrees into tertiles. For both endpoints, the optimal cutpoints were the same. The three-tiered AE-LNM model was defined as the Extent 1 (spread to parotid LNs or level I), Extent 2 (to level II-IV) and Extent 3 (to level V or bilateral LNs or rare LNs) (Supplementary Figs. S2 and S3). Patient distribution of the AE-LNM categories is also presented in Table 1. Patient reclassification by the AE-LNM model is shown in Supplementary Table S1.

OS of the AJCC pN classification and AE-LNM model

For the training cohort, the 5-year OS of the pN1, pN2 and pN3 classifications based on the AJCC staging system were 54.1%, 48.0% and 33.2%, respectively. No significant differences were observed between the pN1 and pN2 classifications ($P = 0.221$) (Fig. 1A). By contrast, the 5-year OS of the Extent 1, Extent 2 and Extent 3 categories based on the X-Tile-based classification of AE-LNM were 61.5%, 46.4% and 20.9%, respectively, and the survival curves were clearly separated (Extent 2 *vs* Extent 1, $P = 0.005$; Extent 3 *vs* Extent 1, $P < 0.001$; Extent 3 *vs* Extent 2, $P < 0.001$) (Fig. 1B). The C-indexes of the AE-LNM model and AJCC pN classification were 0.626 (95%CI 0.591–0.661) and 0.576 (95%CI 0.539–0.612), respectively.

For the validation cohort, similar results were obtained. The 5-year OS of the AJCC pN1, pN2 and pN3 categories were 64.8%, 60.3% and 31.8%, respectively. No significant differences were observed between the pN1 and pN2 classifications ($P = 0.261$) (Fig. 1C). By contrast, the 5-year OS of the Extent 1, Extent 2 and Extent 3 categories based on the AE-LNM classification were 75.5%, 54.0% and 30.5%, respectively, and the survival curves of AE-LNM categories were also well separated (Extent 2 *vs* Extent 1, $P = 0.013$; Extent 3 *vs* Extent 1, $P < 0.001$; Extent 3 *vs* Extent 2, $P = 0.003$) (Fig. 1D). The C-indexes of the AE-LNM model and AJCC pN classification were 0.634 (95%CI 0.594–0.674) and 0.587 (95%CI 0.547–0.627), respectively.

To better evaluate the prognostic relevance of the AE-LNM model, in terms of OS, two types of multivariate analyses (MVA)

Table 2
Multivariate Cox proportional hazards regression models separately including AJCC pN classification or AE-LNM to identify prognostic predictors for OS.

Characteristics	Training Cohort				Validation Cohort			
	Including AJCC pN classification		Including AE-LNM		Including AJCC pN classification		Including AE-LNM	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Age, years								
<60	1		1		1		1	
≥60	1.471 (1.099-1.968)	0.009	1.470 (1.099-1.966)	0.009	1.135 (0.718-1.794)	0.589	1.199 (0.751-1.916)	0.446
Sex								
Female	1		1		1		1	
Male	1.249 (0.937-1.665)	0.130	1.291 (0.968-1.722)	0.082	1.195 (0.724-1.973)	0.486	1.132 (0.680-1.884)	0.633
Race[a]								
White	1		1		Not Included		Not Included	
Black	0.998 (0.614-1.623)	0.995	0.985 (0.607-1.598)	0.950				
Other	0.589 (0.349-0.993)	0.047	0.634 (0.378-1.062)	0.083				
Site								
Parotid	1		1		1		1	
Non-parotid	0.884 (0.587-1.332)	0.557	0.953 (0.628-1.445)	0.824	1.109 (0.640-1.920)	0.713	1.199 (0.699-2.058)	0.510
Laterality								
Left	1		1		1		1	
Right	1.114 (0.849-1.460)	0.434	1.138 (0.869-1.489)	0.346	0.748 (0.487-1.149)	0.185	0.749 (0.487-1.152)	0.188
Bilateral/NOS	2.714 (1.062-6.931)	0.037	2.138 (0.825-5.546)	0.118	1.016 (0.222-4.649)	0.984	2.426 (0.541-10.873)	0.247
Histotype (Risk stratification)								
Low-risk pathology	1		1		1		1	
High-risk pathology	1.686 (1.169-2.433)	0.005	1.587 (1.098-2.293)	0.014	1.184 (0.549-2.551)	0.668	1.098 (0.520-2.319)	0.806
Unspecified	1.509 (0.931-2.448)	0.095	1.280 (0.777-2.108)	0.332	0.949 (0.339-2.658)	0.921	1.229 (0.443-3.404)	0.692
Radiation								
No evidence	1		1		1		1	
Received	0.837 (0.598-1.170)	0.298	0.838 (0.596-1.179)	0.311	0.952 (0.589-1.535)	0.839	0.902 (0.563-1.446)	0.669
AJCC pT classification								
pT1	1		1		1		1	
pT2	1.693 (0.975-2.939)	0.061	1.473 (0.848-2.559)	0.169	1.504 (0.638-3.547)	0.351	1.889 (0.793-4.506)	0.151
pT3	1.783 (1.054-3.016)	0.031	1.646 (0.969-2.795)	0.065	2.199 (0.949-5.096)	0.066	2.645 (1.144-6.118)	0.023
pT4a	2.945 (1.747-4.965)	<0.001	2.515 (1.479-4.273)	0.001	2.608 (1.102-6.169)	0.029	3.005 (1.278-7.065)	0.012
pT4b	3.266 (1.673-6.375)	0.001	2.521 (1.268-5.013)	0.008	1.496 (0.178-12.594)	0.711	1.191 (0.140-10.167)	0.873
AJCC pN classification								
pN1	1				1			
pN2	1.094 (0.793-1.509)	0.588			1.372 (0.744-2.533)	0.311		
pN3	1.677 (1.181-2.380)	0.004			2.789 (1.462-5.323)	0.002		
AE-LNM								
Extent 1			1				1	
Extent 2			1.515 (1.092-2.103)	0.013			1.965 (1.076-3.587)	0.028
Extent 3			2.603 (1.829-3.702)	<0.001			4.124 (2.142-7.941)	<0.001

Abbreviation: HR, Hazard Ratio; CI, Confidence Interval; AJCC, American Joint Committee on Cancer.
[a] For the multicenter validation cohort, the variable "Race" was not included because all the patients in this cohort were Chinese.

were performed. The first type of MVA separately incorporated the pN classification or AE-LNM model into two Cox regression models, while the second type incorporated both parameters in a same Cox regression model.

The first type of MVA showed the prognosis of pN2 classification was comparable to that of pN1 classification for both cohorts (Training cohort: $P = 0.588$; Validation cohort: $P = 0.311$). Nevertheless, AE-LNM proved to be an independent prognostic factor (Training cohort: Extent 2 *vs* Extent 1: $P = 0.013$; Extent 3 *vs* Extent 1: $P < 0.001$) (Validation cohort: Extent 2 *vs* Extent 1: $P = 0.028$; Extent 3 *vs* Extent 1: $P < 0.001$) (Table 2).

The second type of MVA showed that AE-LNM was still an independent prognosticator for OS (Training cohort: Extent 2 *vs* Extent 1: $P = 0.029$; Extent 3 *vs* Extent 1: $P < 0.001$) (Validation cohort: Extent 2 *vs* Extent 1: $P = 0.043$; Extent 3 *vs* Extent 1: $P < 0.001$). Interestingly, the AJCC pN classification completely lost its significance (Training cohort: pN2 *vs* pN1: $P = 0.430$; pN3 *vs* pN1: $P = 0.631$) (Validation cohort: pN2 *vs* pN1: $P = 0.877$; pN3 *vs* pN1: $P = 0.093$) (Supplementary Table S2).

DSS of the AJCC pN classification and AE-LNM model

For both the training and validation cohort, log-rank tests showed there was no significant difference in DSS between the pN1 and pN2 classifications (Training cohort: $P = 0.077$; Validation cohort: $P = 0.246$) (Fig. 2A and C). By contrast, the survival curves were clearly separated by the AE-LNM categories (Training cohort: Extent 2 *vs* Extent 1, $P = 0.001$; Extent 3 *vs* Extent 1, $P < 0.001$; Extent 3 *vs* Extent 2, $P < 0.001$) (Validation cohort: Extent 2 *vs* Extent 1, $P = 0.008$; Extent 3 *vs* Extent 1, $P < 0.001$; Extent 3 *vs* Extent 2, $P < 0.001$) (Fig. 2B and D). For patients in the SEER training cohort, the C-indexes of the AE-LNM model and AJCC pN classification were 0.648 (95%CI 0.599–0.697) and 0.614 (95%CI 0.563–0.665), respectively. For patients in the multicenter validation cohort, the C-indexes of the AE-LNM model and AJCC pN classification were 0.678 (95%CI 0.623–0.733) and 0.612 (95%CI 0.555–0.669), respectively.

In terms of DSS, similarly, two types of MVA were performed. The first type of MVA showed the prognosis of pN2 classification was comparable to that of pN1 classification for both cohorts (Training cohort: $P = 0.259$; Validation cohort: $P = 0.282$), while AE-LNM was an independent prognostic factor (Training cohort: Extent 2 *vs* Extent 1: $P = 0.005$; Extent 3 *vs* Extent 1: $P < 0.001$) (Validation cohort: Extent 2 *vs* Extent 1: $P = 0.027$; Extent 3 *vs* Extent 1: $P < 0.001$) (Table 3).

The second type of MVA revealed that AE-LNM was still an independent prognosticator for DSS (Training cohort: Extent 2 *vs* Extent 1: $P = 0.020$; Extent 3 *vs* Extent 1: $P < 0.001$) (Validation

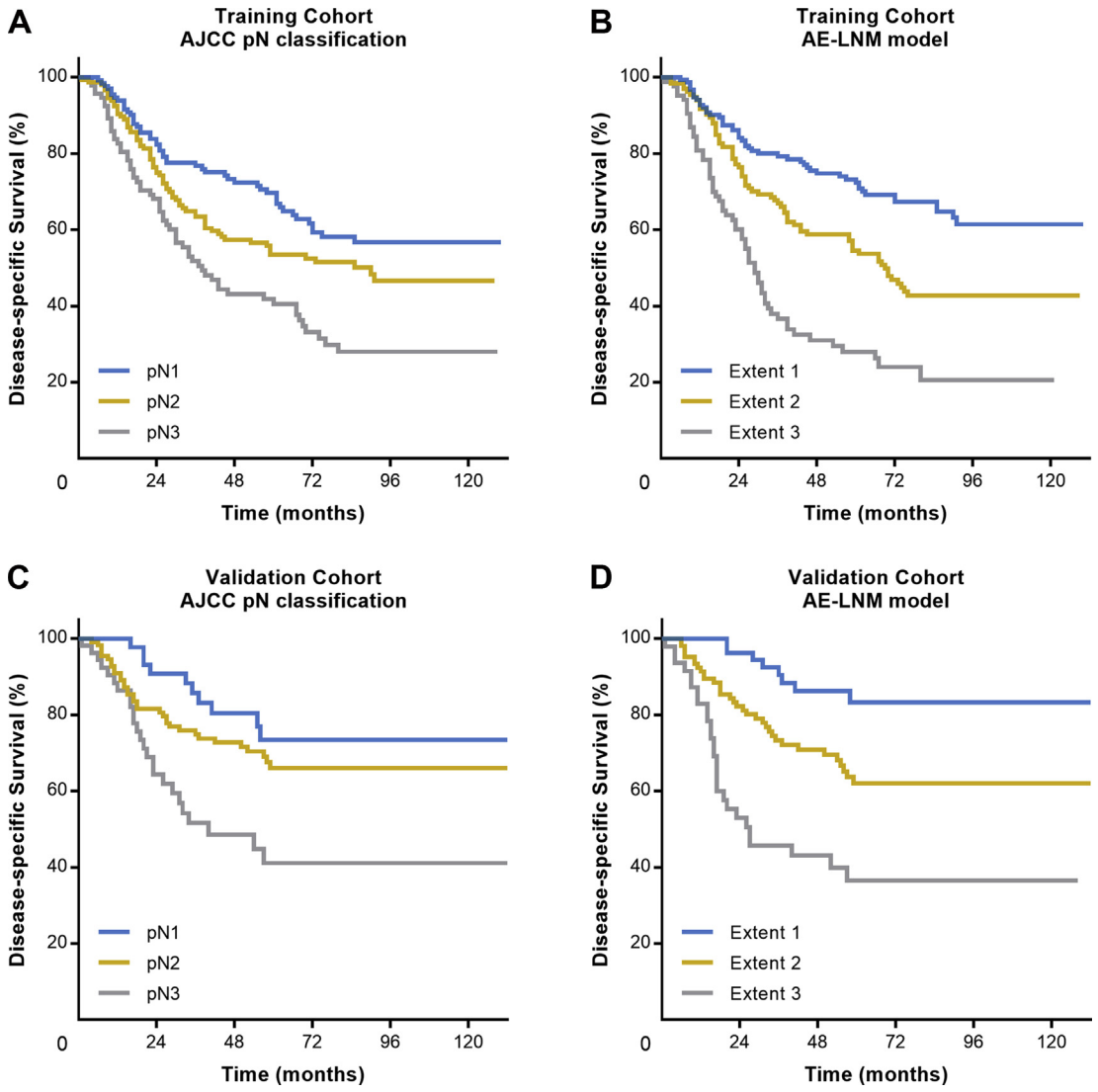

Fig. 2. Kaplan-Meier survival plots for DSS according to the 8th AJCC pN classification and the AE-LNM model for the training cohort **(A and B)** and the validation cohort **(C and D)**.

cohort: Extent 2 *vs* Extent 1: $P = 0.040$; Extent 3 *vs* Extent 1: $P < 0.001$). However, the AJCC pN classification completely lost its significance (Training cohort: pN2 *vs* pN1: $P = 0.863$; pN3 *vs* pN1: $P = 0.422$) (Validation cohort: pN2 *vs* pN1: $P = 0.756$; pN3 *vs* pN1: $P = 0.283$) (Supplementary Table S3).

AE-LNM model and AJCC pN classification for adenoid cystic carcinoma

We separately evaluated the prognostic value of AE-LNM and AJCC pN classification in AdCC. For 25 AdCC patients in the SEER training cohort, 13 have died in the study period, of whom 12 were due to AdCC. For 18 cases in the Chinese validation cohort, one patient died of non-tumor cause, among seven patients who developed distant recurrence during postoperative follow-up (lung only: n = 5; liver only: n = 1; lung + bone + liver: n = 1), six have died of AdCC.

For both cohorts, in terms of both OS (Supplementary Fig. S4) and DSS (Supplementary Fig. S5), the AE-LNM model appeared to clearly separate the survival curves without overlaps, while overlapping curves were observed using the AJCC pN classification. Regarding OS, the C-indexes of the AE-LNM model and AJCC pN classification were respectively 0.638 and 0.603 for the training cohort, and were respectively 0.625 and 0.574 for the validation cohort. Regarding DSS, the C-indexes of the AE-LNM model and AJCC pN classification were respectively 0.659 and 0.593 for the training cohort, and were respectively 0.678 and 0.576 for the validation cohort. Log-rank tests and multivariate Cox analyses were not conducted due to the very small number of AdCC patients in the two cohorts.

Discussion

Staging is a crucial component for cancer management. One of the most important functions of a staging system is to accurately predict outcomes, improvement of prognostic evaluation is a prerequisite for staging modification. Adding ENE to size, number and laterality of metastatic LNs is regarded as one of the most critical modifications of the 8th AJCC N classification [4]. However, regarding prognostic discrimination of either OS or DSS, the survival differences between the AJCC pN1 and pN2 classifications failed to reach the 95% significance level in both cohorts, suggesting that appropriate modifications should be carried out.

On the other hand, the proposed AE-LNM model could better stratify both OS and DSS of node-positive MaSGC patients in the two independent cohorts. We observed good separation of the

Table 3
Multivariate Cox proportional hazards regression models separately including AJCC pN classification or AE-LNM to identify prognostic predictors for DSS.

Characteristic	Training Cohort				Validation Cohort			
	Including AJCC pN classification		Including AE-LNM		Including AJCC pN classification		Including AE-LNM	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Age, years								
<60	1		1		1		1	
≥60	1.276 (0.925-1.759)	0.137	1.298 (0.941-1.790)	0.112	0.987 (0.578-1.686)	0.962	1.098 (0.636-1.896)	0.737
Sex								
Female	1		1		1		1	
Male	1.033 (0.754-1.415)	0.839	1.062 (0.776-1.455)	0.705	1.760 (0.934-3.314)	0.080	1.626 (0.851-3.107)	0.141
Race*								
White	1		1		Not Included		Not Included	
Black	1.042 (0.621-1.749)	0.876	0.994 (0.594-1.663)	0.983				
Other	0.419 (0.215-0.817)	0.011	0.436 (0.224-0.849)	0.015				
Site								
Parotid	1		1		1		1	
Non-parotid	1.116 (0.724-1.720)	0.619	1.247 (0.806-1.928)	0.321	1.165 (0.617-2.199)	0.638	1.236 (0.662-2.309)	0.505
Laterality								
Left	1		1		1		1	
Right	1.036 (0.764-1.404)	0.821	1.065 (0.787-1.441)	0.685	0.669 (0.405-1.104)	0.115	0.624 (0.375-1.040)	0.070
Bilateral/NOS	1.302 (0.372-4.551)	0.680	0.909 (0.256-3.233)	0.883	0.759 (0.093-6.196)	0.797	2.123 (0.265-17.016)	0.478
Histotype (Risk stratification)								
Low-risk pathology	1		1		1		1	
High-risk pathology	1.601 (1.064-2.407)	0.024	1.065 (0.787-1.441)	0.685	1.639 (0.747-3.597)	0.218	1.321 (0.615-2.833)	0.475
Unspecified	1.409 (0.811-2.450)	0.224	0.909 (0.256-3.233)	0.883	0.564 (0.174-1.833)	0.341	0.722 (0.227-2.301)	0.582
Radiation								
No evidence	1		1		1		1	
Received	0.841 (0.573-1.234)	0.375	0.821 (0.555-1.213)	0.322	0.889 (0.501-1.575)	0.686	0.914 (0.516-1.621)	0.759
AJCC pT classification								
pT1	1		1		1		1	
pT2	1.907 (1.008-3.607)	0.047	1.689 (0.891-3.201)	0.108	3.009 (0.880-10.280)	0.079	4.113 (1.179-14.354)	0.027
pT3	1.732 (0.931-3.222)	0.083	1.614 (0.864-3.012)	0.133	4.362 (1.291-14.740)	0.018	5.534 (1.623-18.865)	0.006
pT4a	3.285 (1.789-6.032)	<0.001	2.815 (1.521-5.210)	0.001	4.835 (1.402-16.678)	0.013	5.388 (1.563-18.575)	0.008
pT4b	4.336 (2.092-8.988)	<0.001	3.502 (1.663-7.376)	0.001	1.895 (0.189-19.029)	0.587	4.007 (0.386-41.628)	0.245
AJCC pN classification								
pN1	1				1			
pN2	1.238 (0.855-1.792)	0.259			1.482 (0.724-3.034)	0.282		
pN3	1.886 (1.263-2.817)	0.002			2.808 (1.311-6.015)	0.008		
AE-LNM								
Extent 1			1				1	
Extent 2			1.708 (1.175-2.485)	0.005			2.450 (1.108-5.416)	0.027
Extent 3			2.790 (1.862-4.183)	<0.001			6.518 (2.836-14.979)	<0.001

survival curves in Kaplan-Meier survival plots and improved prognostic stratification in MVA. More importantly, the AE-LNM model maintained its independent prognostic discriminative ability even when AJCC pN classification was simultaneously incorporated as a confounding factor in the second type of MVA. These results suggested that the anatomic extent of LNM was an independent and strong prognostic factor for patients with pN + MaSGCs.

For parotid cancers, it is also reasonable to classify level I spread into the Extent 1 category together with parotid LNs spread. Previous studies have reported a relatively common level I metastases in pN + parotid cancers, especially for tumors located at the anterior part of parotid gland that tend to metastasize to level Ib LNs [15–19]. In a review, Lombardi et al. indicates that in parotid cancers, the metastatic level Ib LNs are most likely to be LNs located posteriorly to the submandibular gland, involvement of these nodes generally occurs before metastasis to their closest level II area [20], which is categorized as Extent 2 in the AE-LNM model.

It is worth mentioning that the AE-LNM model is approached more as a prediction model in this research, our purpose is not to replace the AJCC pN classification using this single nodal factor. The present study aims to investigate the prognostic relevance of a nodal characteristic that has not been well studied before, in order to provide an optional variable to combine with other nodal features with prognostic value in future modification of N staging. However, direct integration of AE-LNM with all other existing AJCC N factors (size, number, laterality and ENE) should be avoided. Aro et al. reported that three (size, laterality and ENE) of the four AJCC N factors had no significant impact on survival [10]. Similarly, Cheraghlou et al. and Hsieh et al. also reported the negative prognostic value of ENE [21,22]. Therefore, prognostic relevance of these factors is uncertain and must be re-analyzed before the modification.

Some limitations should be acknowledged. **First**, the conclusions are limited by the retrospective nature of our study. **Second**, level I, level II and level V are not divided into sublevels for many cases in the two cohorts, therefore these sublevels cannot be distinguished in the AE-LNM model. **Third**, some factors such as surgical margins and perineural/vascular invasion are not recorded in the SEER database. **Fourth**, there were only 376 and 220 eligible patients in the nationwide SEER database and Chinese multicenter cohort, respectively. However, as another large-scale dataset National Cancer Database (NCDB) is not available to non-US clinicians, of our knowledge, they are already the two largest cohorts for pN + MaSGCs that we can obtain. **Sixth,** the two cohorts had different distributions regarding some baseline aspects, including race, histology and radiotherapy administration.

In summary, using two independent cohorts, we demonstrated and validated that AE-LNM is an independent nodal prognosticator for patients with pN + MaSGCs, while the unsatisfactory prognostic discrimination of the AJCC pN classification suggests the necessity

of modification. In the future, AE-LNM may be integrated into the novel version of AJCC N classification.

Conflict of interest

The authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.06.029.

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