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The impact of nodal status in major salivary gland carcinoma: A multicenter experience and proposal of a novel N-classification

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ABSTRACT

Objectives: Despite differences in oncological behavior, the 8th edition of AJCC TNM staging currently proposes the same N-classification for major salivary glands (MSG) carcinoma and squamous cell carcinoma of the upper aerodigestive tract. The present study aims to investigate a more reliable definition of N-categories for MSG carcinoma.

Materials and methods: A retrospective multicenter study was performed, including 307 patients treated for primary MSG carcinoma from 1995 to 2019. Outcome measures included overall survival (OS), disease specific survival, and local, regional, and distant recurrence. Survival analysis was performed using log-rank test and Cox proportional-hazards model. Overall number (ON) and largest diameter (LD) of nodal metastases, including intra-parotid metastases, were considered to develop three novel proposals of N-classification; their performance were compared with the current TNM staging using Akaike information criterion (AIC), Bayesian information criterion (BIC), and Nagelkerke pseudo-R^2.

Results: Intra-parotid nodes, ON and LD of nodal metastases emerged as major prognosticators for OS, while extra-nodal extension did not impact on any survival. The current N-classification did not show a satisfactory OS stratification. Three novel N-classifications were developed according to number of metastatic nodes (0 vs 1–3 vs $\geq$ 4) and/or their maximum diameter ($<$20 mm vs $\geq$ 20 mm). They all showed better accuracy in OS stratification, and achieved better AIC, BIC and Nagelkerke pseudo-R^2 indices when compared to current N-classification.

Conclusion: All the proposed N-classifications improved OS stratification and could help in defining a specific N-classification for MSG carcinoma. Their validation and assessment in an external cohort is needed.

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Introduction

Malignant major salivary gland (MSG) tumors are extremely rare, only accounting for a small percentage of all head and neck cancers. Nodal involvement is considered as one of the most important factors affecting survival in MSG carcinoma [1–7].

The current AJCC 8th TNM staging system proposes the same N-categories be used for both MSG and upper aerodigestive tract squamous cell carcinoma (SCC) [8]. This is despite significant differences in biological behavior, treatment modalities and outcomes between the two entities. Consequently, there are several limitations to the MSG N-classification. Firstly, the TNM classification does not consider the involvement of parotid lymph-nodes, despite them being the only involved station in a non-negligible proportion of patients [1,9–11]. In addition, parotid nodal metastasis *per se* may increase the risk of recurrence [9,10]. Secondly, contralateral nodal metastasis in MSG carcinoma is considered so rare as to be anecdotal [2,12]. This supports the argument that only the ipsilateral neck should be treated [2,13,14].

Finally, the prognostic relevance of nodal dimensions and extra-nodal extension (ENE) are probably the most important nodal predictors in upper aerodigestive tract SCC, yet their significance in MSG carcinoma is less clear [9,15–18]. In MSG carcinoma, the nodal disease burden, defined by nodal ratio (NR) and/or number of lymph-nodes involved, may have a more significant prognostic relevance [14–18].

The aim of this study is to present a multicenter experience in the treatment of primary MSG carcinoma, with a specific focus on the prognostic significance of different nodal factors. A novel N-classification specific for primary MSG carcinoma will also be proposed.

Materials and methods

A multicenter retrospective analysis of patients affected by carcinoma of the MSG was conducted at the Departments of Otolaryngology-Head and Neck Surgery of the University of Brescia, Brescia, Italy; Queen Elizabeth Hospital, Birmingham, England; University Vita-Salute San Raffaele, Milan, Italy; and University of Genova, Genoa, Italy. Patients affected by MSG primary epithelial malignant tumor receiving surgery with a curative intent as upfront treatment from January 1995 to September 2019 were considered eligible. Exclusion criteria were previous treatment and metastatic tumor to the MSG. Data concerning survival and recurrence outcomes were retrieved from mortality registries, outpatient visits, and radiological follow-up. Data management and study accomplishment are in accordance with principles stated in the Declaration of Helsinki; the study was approved by the local ethics committee (NP-2066, WV-H&N Cancer).

Demographics, clinical and pathological data

Data concerning demographics (gender, age), clinical presentation (facial palsy, skin ulceration, pain), imaging, surgical treatment, pathology, and adjuvant therapy were systematically collected. Histopathological features retrieved included histologic type and grading, margin status, local extension, perineural (PNI) and lympho-vascular invasion (LVI), and characteristics of intraparotid and cervical metastatic nodes (largest diameter, number, ENE). Grading of Muco-Epidermoid Carcinoma (MEC) and Adenoid-Cystic Carcinoma (AdCC) was assessed according to the Brandwein and Perzin-Szanto classification, respectively [20–23]. Patients with pre-operative evidence of cervical nodal metastasis received a comprehensive (radical or modified radical) neck dissection (ND). Conversely, patients without pre-operative evidence of cervical metastasis were treated with a selective or super-selective ND or were observed according to the specific risk profile for occult nodal involvement [24]. Lymph-nodes within the parotid gland were considered part of the cervical lymphatic system and classified as a specific nodal level; the overall count of Nodal Metastases (NM) included both intraparotid and cervical nodes. Tumor staging of all patients was re-evaluated according to the 8th edition of the TNM Classification of Malignant Tumors [8].

Statistical analysis

Characteristics of patients were expressed in terms of mean, standard deviation, median, range of values and percentages. Time to death, first recurrence (any site) and the latest available clinical or radiological evaluation (censored observations) were considered as outcomes. Overall (OS), Disease-Specific (DSS), Recurrence-Free (RFS), Local Recurrence-Free (LRFS), Regional Recurrence-Free (RRFS), and Distant Recurrence-Free (DRFS) Survivals were evaluated using Kaplan-Meier survival curves. Relation between characteristics of intraparotid and cervical NM, and with ENE, was established using logistic regression. Furthermore, the role of demographic, clinical, and pathologic characteristics on survival was evaluated using the Log-rank test (univariate analysis).

The continuous variables "overall number" (ON) and "largest diameter" (LD) of NM were categorized applying cutoff values determined using the X-tile software (3.6.1 - Yale University, New Haven, CT, USA), according to the minimum p-value and the maximum χ^2 [25]. Univariate and multivariable Cox proportional hazard model was performed to analyze the prognostic role of ON and LD on OS. Results were expressed in terms of Hazard Ratio (HR) and 95% confidence intervals (CI).

Three proposals for a new nodal classification of the TNM were developed, considering ON, LD or a combination of both. Risk stratification in terms of survival and recurrence of each nodal classification was assessed with the log-rank test and Kaplan Meier method. Correction for multiple comparisons according to Holm method was performed for each nodal classification. Akaike information criterion (AIC), Bayesian information criterion (BIC), and Nagelkerke pseudo-R^2 index were calculated and compared between the new proposals of N categorization and the current N classification (TNM 8th edition).

Multivariable Cox proportional hazard model was adopted to determine the independent prognostic role of proposed N-classifications in pN+ patients. Schoenfeld residuals were evaluated for the assessment of proportional hazards assumption; variance inflation factors (VIF<5) were estimated to exclude multi-collinearity between covariates.

Statistical analysis was performed using R (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria); p values < 0.05 were considered statistically significant.

Results

Demographics and clinical presentation

Three-hundred-seven patients were included in the study. The mean age was 58.9 years (SD 17.1, range 6–91), with an almost equal gender distribution (1.03:1 male to female ratio). Patients were affected by primary parotid and submandibular carcinoma in 93.2% and 6.8% cases, respectively. Preoperative evidence of cervical and intraparotid node involvement (cN+) was identified in 23.3% and 14.7% of cases, respectively. The cohort characteristics are summarized in Table 1.

Histopathology of nodal metastasis

The number and largest dimension of cervical and parotid lymph-nodes are detailed in Table 1. Nodal metastasis at final pathology report (pN+) were observed in 95/303 (31.4%) patients: overall, intraparotid and cervical NM were diagnosed in 66/298 (22.1%) and 74/303 (24.4%) cases, respectively. Preoperative imaging failed to identify occult cervical and intraparotid metastasis in 20.0% and 20.1% of cases, respectively. Almost half of pN+ patients had both intraparotid and cervical node metastasis (45/95, 47.4%), whereas exclusive intraparotid and cervical node metastasis were less frequently observed (21/

Table 1
Descriptive statistics of the cohort of patients. mRND - modified Radical Neck Dissection, RND - Radical Neck Dissection, SD - Standard Deviation, SND - Selective Neck Dissection.

Variable		N.	%
Participant Institutions	Brescia	203	66.1%
	Birmingham	46	15.0%
	San Raffaele - Milan	45	14.7%
	Genova	13	4.2%
Mean age ± SD (range) - yr	58.9 ± 17.1 (6–91)		
Gender	Female	151	49.2%
	Male	156	50.8%
Primary site	Submandibular gland	21	6.8%
	Parotid gland	286	93.2%
Mean H time ± SD (range) - days	5 ± 4.2 (1–34)		
Clinical signs on presentation	Pain	55/265	20.7%
	Skin alteration	17/273	6.2%
	Facial palsy	36/273	13.2%
Parotid tumor extension at the time of surgery	Superficial lobe	154/266	57.9%
	Deep lobe	35/266	13.2%
	Extensive/both lobes	49/266	18.4%
	Masseteric process	12/266	4.5%
	Parotid tail	16/266	6.0%
Parotid surgery	Less than superficial parotidectomy	3/274	1.1%
	Superficial parotidectomy	121/274	44.1%
	–Extended superficial parotidectomy	(12)	(9.9%)
	Total parotidectomy	101/274	36.9%
	–Extended total parotidectomy	(24)	(23.8%)
	Radical parotidectomy	49/274	17.9%
	–Extended radical parotidectomy	(33)	(67.3%)
Nodal dissection for parotid malignancies	No ND performed	126/282	44.7%
	ND performed	156/282	55.3%
	–Super-selective ND (II or II-III)	(64)	(41.0%)
	–Selective ND (II-IV)	(48)	(30.8%)
	–mRND/RND (I-V)	(42)	(26.9%)
	–Not otherwise specified	(2)	(1.3%)
Nodal dissection for submandibular malignancies	No ND performed	5/21	23.8%
	ND performed	16/21	76.2%
	–Super-selective ND (I)	(7)	(43.7%)
	–Selective ND (I-III/IV)	(4)	(25.0%)
	–mRND/RND (I-V)	(5)	(31.3%)
Histology	Mucoepidermoid Carcinoma (MEC)	63/307	20.5%
	Acinic Cell Carcinoma (AcCC)	48/307	15.6%
	Salivary Duct Carcinoma (SDC)	37/307	12.0%
	Adenoid Cystic Carcinoma (AdCC)	35/307	11.4%
			8.1%

Table 1 (*continued*)

Variable		N.	%
	Adenocarcinoma Not Otherwise Specified (ADC NOS)	25/307	
	Carcinoma Ex-Pleomorphic Adenoma (CEPA)	31/307	10.1%
	Basal cell adenocarcinoma	10/307	3.2%
	Poorly differentiated carcinoma	10/307	3.2%
	Myoepithelial carcinoma	10/307	3.2%
	Epithelial-myoepithelial carcinoma	9/307	2.9%
	Primitive salivary squamous cell carcinoma	8/307	2.6%
	Mammary analogue secretory carcinoma	5/307	1.6%
	Oncocytic carcinoma	5/307	1.6%
	Carcinosarcoma	4/307	1.3%
	Lymphoepitelial carcinoma	3/307	1.0%
	Intraductal carcinoma	2/307	0.6%
	Sebaceous adenocarcinoma	1/307	0.3%
	Polymorphous adenocarcinoma	1/307	0.3%
Grading	Low-grade	138/297	46.5%
	Intermediate-grade	39/297	13.1%
	High-grade	120/297	40.4%
Mean primary tumor major diameter ± SD (range) - mm	27.3 ± 17.6 (3–100)		
Margin status	R0	179/305	58.7%
	R1	126/305	41.3%
Extraglandular Extension	Absent	187/291	64.3%
	Present	104/291	35.7%
	–Facial Nerve infiltration	(35)	12.4%
	–Connective tissue/fat infiltration	(56)	20.7%
	–Muscles infiltration	(28)	10.4%
	–Bone infiltration	(8)	2.9%
	–Cartilage infiltration	(4)	1.5%
	–Dermal/epidermal infiltration	(34)	11.4%
Perineural invasion	Pn0	173/302	57.3%
	Pn1	129/302	42.7%
Lymphovascular invasion	V0	194/281	69.0%
	LV1VI+	87/281	31.0%
Nodal metastasis	No nodal metastasis	208/303	68.6%
	Overall pN+ (cervical and/or intraparotid)	95/303	31.4%
	–Cervical pN+	74/303	24.4%
	–Intraparotid pN+	66/298	22.1%
Location of nodal metastasis	Exclusive intraparotid pN+		22.1%

(*continued on next page*)

Table 1 (*continued*)

Variable		N.	%
		21/95	
	Exclusive cervical pN+	29/95	30.5%
	Both intraparotid and cervical pN+	45/95	47.4%
Number of metastatic nodes - median (range)			
–overall	3 (1–72)		
–cervical	3 (1–72)		
–intraparotid	2 (1–12)		
Major diameter of nodal metastasis ± SD (range) - mm			
–overall	15.4 ± 10.7 (0.5–50)		
–cervical	15.8 ± 11.0 (0.5–50)		
–intraparotid	11.2 ± 8.5 (1–45)		
Presence of Extra-Nodal Extension (ENE)	Overall ENE+	56/91	61.5%
	Cervical ENE+	41/71	59.1%
	Intraparotid ENE+	26/62	41.9%
Adjuvant treatment	No	107/277	38.6%
	Yes	170/277	61.4%
T status (according to TNM classification – 8th edition)	pT1	91/299	30.4%
	pT2	75/299	25.1%
	pT3	62/299	20.7%
	pT4a	71/299	23.8%
N status (according to TNM classification – 8th edition)	N0	229/303	75.6%
	pN1	11/303	3.6%
	pN2a	5/303	1.7%
	pN2b	28/303	9.2%
	pN2c	0/303	0%
	pN3a	0/303	0%
	pN3b	30/303	9.9%
Staging of disease	stage I	86/297	29.0%
	stage II	63/297	21.2%
	stage III	49/297	16.5%
	stage IV	99/297	33.3%

95 [22.1%] and 29/95 [30.5%], respectively). Overall, the median number of metastatic nodes was 4 (range: 1–72; mean: 9.95), with a median largest diameter of 13.5 mm (range: 0.5–50 mm; mean: 15.4 mm). ENE was observed in 41/71 (59.2%) and 26/62 (41.9%) of cervical and intraparotid NM, respectively. The number of intraparotid NM was strongly associated with the presence of cervical NM at logistic regression ($p < 0.001$; Fig.S1). Frequency of cervical NM involvement was 100% in patients bearing 4 or more intraparotid NM. The ON of metastatic nodes and their LD were associated with a higher rate of ENE at logistic regression ($p = 0.04$ and $p = 0.05$, respectively; Fig. S2, S3).

Staging

The pT and pN categories, as well as the definitive staging of disease, are shown in Table 1. Cervical NM were diagnosed in 24.4% of patients. The majority of pN+ cases were classified as pN2b (9.2%) or pN3b (9.9%); pN1 and pN2a were rarely observed (3.6% and 1.7%, respectively). No bilateral NM (pN2c category) nor NM with the largest diameter >60 mm (pN3a category) were observed.

Survival analysis

Follow-up data were available for 295 patients (12 lost at follow-up, 3.9%). Median follow-up was 51 months (inter-quartile range [IQR]: 82.7, mean: 75.8 months, range: 3–292). At the end of the present study (April 2020), 63.4% of patients were alive without disease and 6.4% were alive with recurrence. Patients died more frequently because of the disease (18.0%) rather than other causes (9.8%). In 2.4% of cases, cause of death was not established. Disease persistence or recurrence was found in 27.0% of patients, with a median interval to first recurrence of 16.5 months (range: 1–126 months). Local failure was diagnosed in 12.1% (median interval: 14 months, range: 1–59 months), regional failure in 7.4% (median interval: 12 months, range: 1–56 months), and distant metastasis in 21.6% of cases (median interval: 16 months, range: 0–202 months). Survival data and univariate analysis of major prognostic factors on survival and recurrence are shown in Table S1 and S2. Of note, tumor grading, PNI, LVI, margin status and pT categories (pT1-4) were associated with a worse outcome in terms of OS, DSS and RFS.

Current pN classification (TNM 8th edition) was not able to correctly stratify patients: at multiple pairwise comparison only the difference between survival of pN0 vs pN2b and pN0 vs pN3b patients were statistically significant (adjusted p-value using the Holm method). In pN+ patients no statistically significant difference could be appreciated according to current classification (Fig. S4).

ENE did not significantly impact on OS ($p = 0.194$, Fig. 1), DSS ($p = 0.134$), RFS ($p = 0.159$), LRFS ($p = 0.229$), RRFS ($p = 0.941$) and DRFS

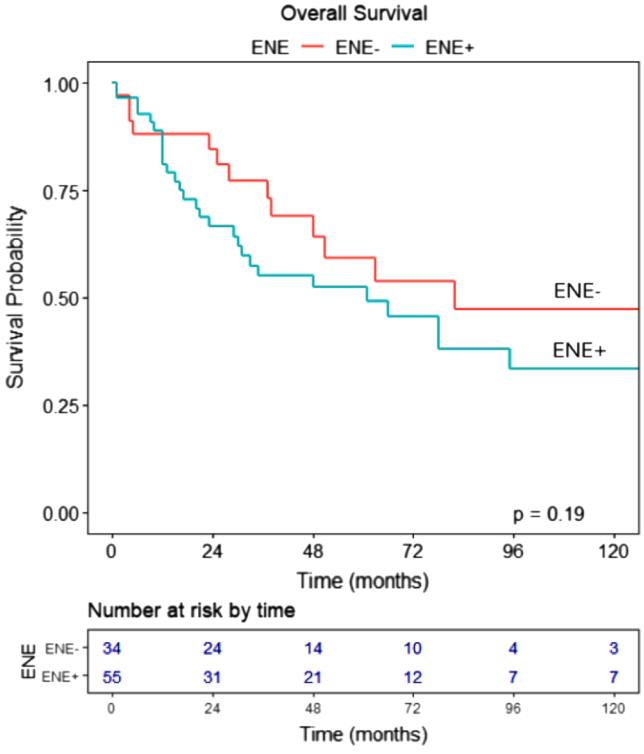

Fig. 1. Kaplan Meier survival curves showing no statistically significant difference between pN+ ENE+ and pN+ ENE- patients.

($p = 0.265$). Metastasis to cervical nodes was a strong negative prognostic factor for all survival outcomes ($p < 0.001$). The presence of intraparotid NM was also associated with a worse outcome in all survival estimates ($p \leq 0.01$). Univariate analysis using Cox proportional regression model showed that ON (HR: 1.04, 95% CI 1.02–1.05; $p < 0.001$) and LD (HR: 1.73 per cm increase, 95% CI 1.48–2.02; $p < 0.001$) of nodal metastasis significantly affected OS.

Multivariable analyses (Table 2) proved the independent prognostic role of ON and LD, adjusted for major prognostic covariates, in terms of OS; conversely, they confirmed the negligible role of ENE and the inadequacy of current N classification (TNM 8th ed.).

Proposal of novel N classifications

Considering the limited value of different pN+ categories in survival stratification, data on NM were thoroughly analyzed to build a more reliable classification of N status. Intraparotid nodes were considered within the overall count of dissected nodes, laterality was not considered since no cases of contralateral NM were encountered. Similarly, ENE was not considered as a prognostic factor since it was not a statistically significant variable at univariate and multivariable analyses. The ON and LD of metastatic lymph-nodes were therefore the only factors considered.

With the X-tile analysis (Fig. 2), the optimal cut-offs in terms of OS for ON and LD of nodal metastasis were determined. According to minimum p- and maximum χ^2- values of log rank test, ideal cutoff point in the ON was ≥ 4 ($p = 0.001$, $\chi^2 = 10.17$), and in the LD was ≥ 20 mm ($p < 0.001$, $\chi^2 = 11.53$).

According to these findings, nodal classifications based on the ON and LD of NM were formulated.

N-classification 1 (based on overall number of metastatic nodes)

- N0: no intraparotid or cervical nodal metastasis,
- N1: <4 intraparotid and/or cervical nodal metastasis,
- N2: ≥4 intraparotid and/or cervical nodal metastasis.

N-classification 2 (based on largest diameter of the overall count of metastatic nodes)

- N0: no intraparotid or cervical nodal metastasis,
- N1: nodal metastasis with the largest diameter < 20 mm,
- N2: nodal metastasis with the largest diameter ≥ 20 mm.

Combining data of the ON and LD of metastatic nodes, 4 classes of pN + patients could be identified:

- patients with 1–3 nodal metastasis with the largest diameter < 20 mm,
- patients with 1–3 nodal metastasis with the largest diameter ≥ 20 mm,
- patients with ≥ 4 nodal metastasis with the largest diameter < 20 mm,
- patients with ≥ 4 nodal metastasis with the largest diameter ≥ 20 mm.

According to pattern of survival at univariate analysis (Fig. S5), these classes were reformulated in terms of nodal disease burden, conceiving a third classification, as follows.

N-classification 3 (based on number and largest diameter of the overall count of nodal metastasis)

- N0: no intraparotid or cervical nodal metastasis,
- N1 (low nodal disease burden): 1–3 nodal metastasis with the largest diameter < 20 mm,
- N2 (high nodal disease burden): ≥ 4 nodal metastasis and/or at least one nodal metastasis with the largest diameter ≥ 20 mm.

All indices estimating the trade-off between prediction accuracy and simplicity of the model (i.e., AIC and BIC) and those expressing how comprehensively models can explain data (i.e., Nagelkerke pseudo-R) were in favor of the novel N-classifications as compared to the 8th

Table 2
Multivariable analysis showing the independent role of the overall number of nodal metastasis (ON) and their largest diameter (LD) as prognosticators in terms of OS. Conversely, current N status (TNM 8th edition) fails to adequately stratify patients. PNI - Perineural invasion; LVI - Lymphovascular invasion; ENE - Extra-nodal extension.

Variable		OS								
		Multivariable analysis			Multivariable analysis			Multivariable analysis		
		HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age (years)		1.06	1.03–1.08	**<0.001**	1.06	1.04–1.08	**<0.001**	1.06	1.03–1.08	**<0.001**
Grading	low									
	intermediate	1.75	0.62–4.90	0.289	1.48	0.49–4.49	0.49	1.74	0.63–4.84	0.290
	high	2.81	1.38–5.71	**0.004**	2.87	1.32–6.25	**0.008**	2.99	1.47–6.05	**0.002**
pT	pT1									
	pT2	1.31	0.50–3.42	0.584	1.22	0.44–3.35	0.698	1.24	0.47–3.23	0.664
	pT3	1.97	0.82–4.75	0.132	2.26	0.94–5.43	*0.068*	2.02	0.84–4.85	0.116
	pT4	2.26	0.92–5.55	*0.075*	2.35	0.94–5.88	*0.068*	2.00	0.80–4.98	0.137
Surgical margins	R0									
	R1	1.26	0.74–2.13	0.393	1.22	0.70–2.12	0.486	1.30	0.75–2.24	0.349
PNI	Pn0									
	Pn1	1.31	0.61–2.82	0.482	1.53	0.69–3.40	0.293	1.26	0.62–2.56	0.522
LVI	V0									
	V1	1.32	0.71–2.43	0.376	0.96	0.48–1.90	0.903	1.16	0.63–2.16	0.630
ENE	N0									
	ENE-	1.15	0.54–2.44	0.708	0.75	0.30–1.87	0.539	–	–	–
	ENE+	0.98	0.44–2.16	0.951	0.74	0.26–2.06	0.561	–	–	–
Overall Number of nodal metastasis (ON) - N.		1.02	1.01–1.05	**0.045**	–	–	**–**	–	–	–
Largest Diameter of nodal metastasis (LD) - cm		–	–	–	1.50	1.06–2.13	**0.023**	–	–	–
N staging (TNM 8th ed.)	N0	–	–	**–**	–	–	–			
	N1	–	–	**–**	–	–	–	1.89	0.63–5.65	0.254
	N2a	–	–	**–**	–	–	–	1.19	0.34–4.15	0.781
	N2b	–	–	**–**	–	–	–	1.53	0.71–3.29	0.281
	N3b	–	–	**–**	–	–	–	2.05	0.93–4.49	*0.074*

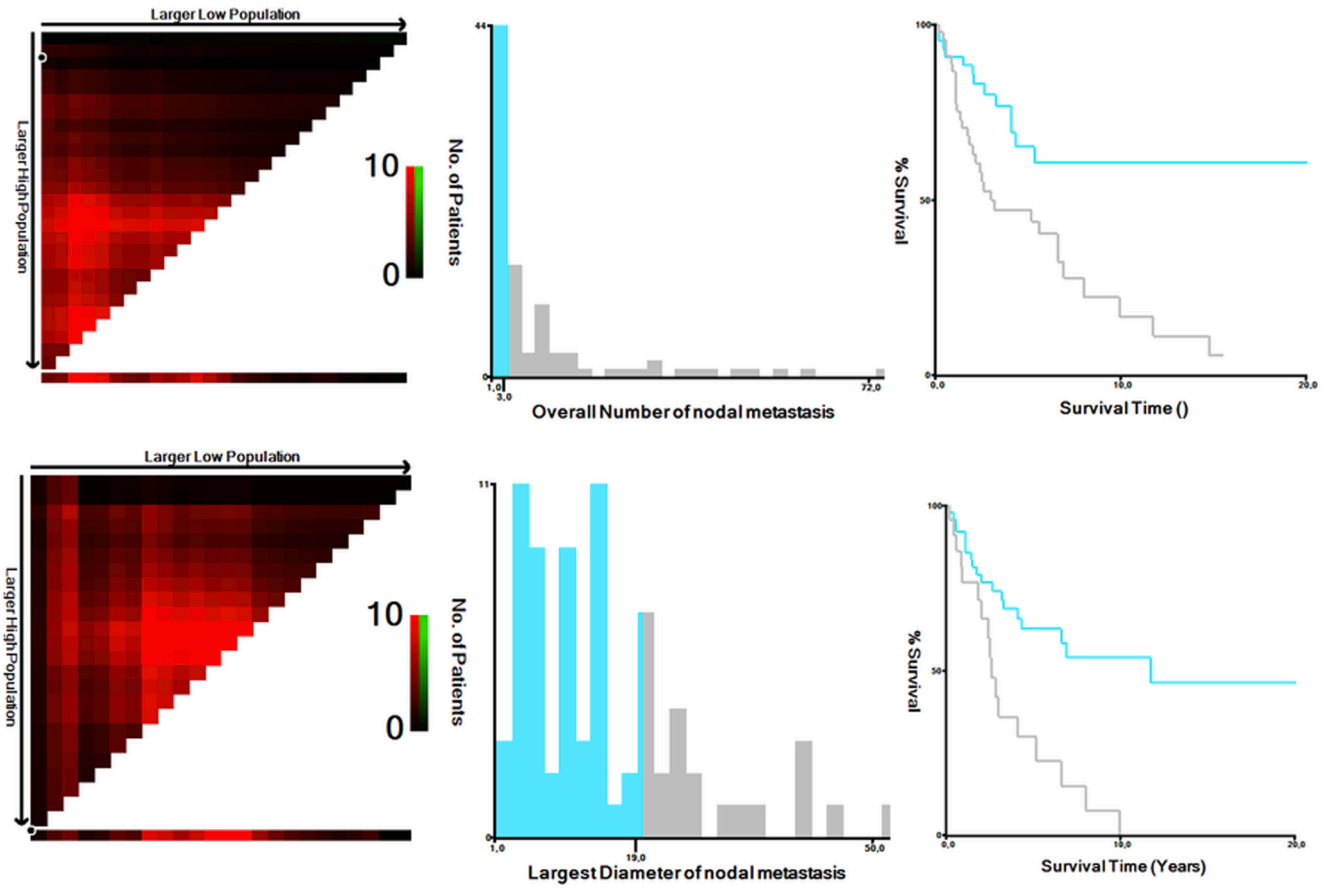

Fig. 2. X-tile analysis of OS in our multicenter cohort of patients. The optimal cutoff values were determined according to the minimum p- and maximum χ^2 test values: ≥4 for overall number ($p = 0.001$, $\chi^2 = 10.17$), and ≥20 mm for largest diameter of nodal metastasis ($p < 0.001$, $\chi^2 = 11.53$).

TNM Edition N-classification (Table 3).

The univariate analysis (Fig. 3a–c, Table 3) showed that each of the 3 new nodal classifications effectively stratify patients in terms of survival outcomes ($p < 0.001$). For each new proposal of N classification, a statistically significant difference between all sub-categories was demonstrated at multiple pairwise comparison (p-value adjusted for multiple comparisons using the Holm method). Further, to assess performance in survival stratification in pN+ patients, nodal high-risk profiles (ON ≥ 4, LD ≥ 20 mm, or high burden of nodal disease) adjusted for major prognostic covariates in the clinical setting,

Table 3
Univariate analysis of the three N classifications proposed and of the current N status (TNM 8th edition) using log-rank test and Cox proportional hazard regression. For each new proposal of N classification, a statistically significant difference between all sub-categories was demonstrated at multiple pairwise comparison (p-value adjusted for Holm method). Conversely, only the difference between survival of pN0 vs pN2b and pN0 vs pN3b patients were statistically significant when considering current N status (TNM 8th edition). * Nagelkerke pseudo-R^2.

	Log-rank test			Cox proportional hazard regression					
	5-y OS	95% CI	p-value	HR	95% CI	p-value	AIC	BIC	pseudo-R^{2*}
N classification 1									
pN0	83.1%	77.6–89.1%	**<0.001**				849.64	854.59	0.281
Overall number of NM = 1–3	65.9%	51.3–84.6%		2.02	1.10–3.71	**0.024**			
Overall number of NM ≥ 4	44.7%	31.7–63.0%		5.90	3.68–9.45	**<0.001**			
N classification 2									
pN0	83.1%	77.6–89.1%	**<0.001**				776.74	781.53	0.248
Largest diameter of NM < 20 mm	63.2%	50.3–79.4%		2.69	1.60–4.52	**<0.001**			
Largest diameter of NM ≥ 20 mm	30.0%	14.6–61.6%		8.00	4.46–14.32	**<0.001**			
N classification 3									
pN0	83.1%	77.6–89.1%	**<0.001**				831.96	836.89	0.291
Low nodal disease burden	66.2%	49.0–89.4%		1.98	0.99–3.96	**0.05**			
High nodal disease burden	44.3%	31.8–61.6%		5.83	3.67–9.26	**<0.001**			
Current N staging (TNM 8th ed.)									
pN0	82.5%	77.1–88.3%	**<0.001**				857.82	867.73	0.253
pN1	53.0%	27.7–100%		2.83	1.01–7.90	**0.047**			
pN2a	–	–		4.48	1.38–14.60	**0.013**			
pN2b	53.8%	36.6–79.2%		4.21	2.29–7.75	**<0.001**			
pN3	50.2%	34.1–74.0%		4.89	2.91–8.20	**<0.001**			

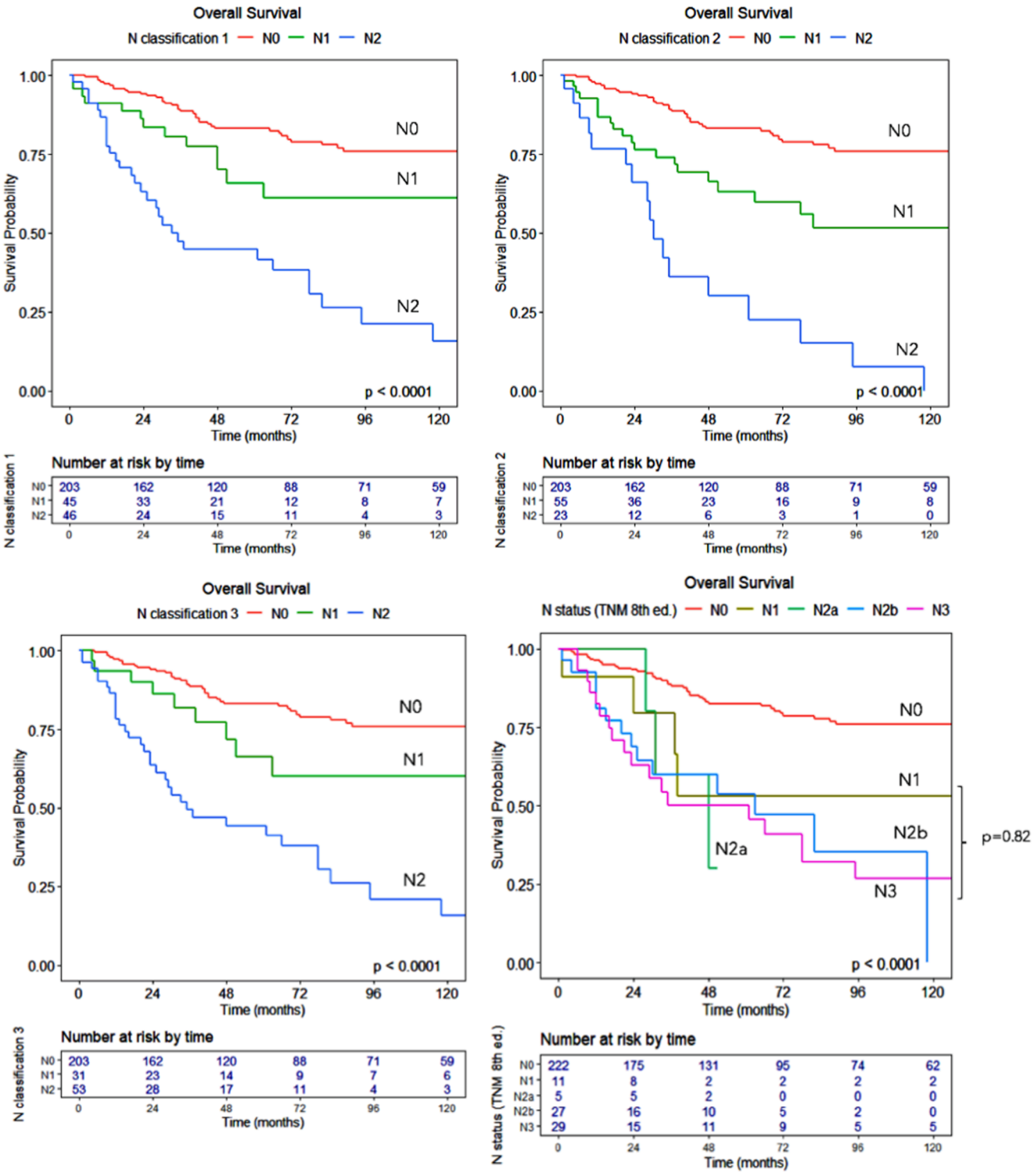

Fig. 3. Kaplan Meier survival curves showing the accurate stratification in terms of survival offered by each of the N classifications proposed; conversely, current N status (TNM 8th edition) does not show to properly stratify pN+ patients. (a) N classification 1, based on overall number of nodal metastasis; (b) N classification 2, based on the largest diameter of nodal metastasis; (c) N classification 3, based on overall number and largest diameter of nodal metastasis; (d) N-status according to current TNM 8th edition (see also Fig. S4).

confirmed to be strong independent prognostic factors (Table S3).

Discussion

The present study confirmed that in MSG carcinoma increasing nodal involvement is a strong negative prognostic impact on survival. Data herein presented showed also that current N-categories do not allow for reliable prognostic stratification. This is probably due to the complete absence in clinical reality of some factors defining the levels of the current N-classification (no bilateral nodal involvement nor lymph-node with a diameter>6 cm), and to the lack of prognostic relevance of ENE. Conversely, it highlights the paramount importance of considering

parotid lymph-nodes as well as lateral cervical lymph-nodes.

Nodal prognostic factors

Nodal status (pN+ vs pN0) is considered among the most important prognostic factors in MSG carcinoma [6,7,27–33]. Our overall rate of nodal involvement was 31.4%, in keeping with previously reported figures, which range between 11.8% and 37% [1,4,9,14,30,34]. Interestingly, our series, which also includes patients with exclusive parotid lymph-node involvement, has values comparable with those reported by Klussmann et al. who performed a very similar histologic analysis [9]. In addition to the simple, dichotomic distinction between N0 and N+ patients, we broadened our analysis to identify which nodal factors affected prognosis.

Parotid lymph-nodes

O'Brien et al. in their pivotal paper on metastatic cutaneous squamous cell carcinoma (SCC) of the parotid gland, should be credited with the first attempt to conceive a specific nodal classification considering also parotid nodes [35]. The issue of metastasis to parotid lymph-nodes when dealing with primary parotid carcinoma is also well known, [1,9,11,36] but the prognostic relevance is probably underestimated. Klussmann et al. discovered that a not negligible rate of patients had parotid lymph-node involvement that proved to increase the risk of recurrence at univariate analysis [9]. Lim et al. clearly demonstrated that: (i) parotid lymph-node involvement was associated with a higher risk of lateral neck involvement, (ii) patients classified as N0 but with parotid lymph-node metastasis had a significantly worse DSS and a higher risk of recurrence than patients completely free of any nodal localization [10]. Also, Olsen et al. advocated deep lobe parotidectomy in presence of high-grade parotid cancer and/or in case of superficial parotid lymph-node and/or lateral neck involvement [11].

Our data demonstrate that disease localization to parotid lymph-nodes *per se* implies an increased risk of lateral neck involvement and a significant impact on survival. These findings underline not only the importance of a specific lymphatic drainage pathway in which the parotid gland may be a halfway station between the tumor and the neck, but also the inherent prognostic relevance of parotid nodal involvement. This led us to advance the proposal to include parotid nodes within the new N-classification and, once more, supports the concept that excision of the deep lobe, whenever indicated, should be considered an essential step in the treatment of the primary lesion and of the nodal basin.

Extra-nodal extension

ENE has been historically considered one of the most important survival predictors in head and neck cancer and for this reason has also been included among nodal prognosticators for salivary gland cancer, despite inconclusive and somewhat conflicting results. Meyer et al. in their analysis on 128 patients with parotid gland cancer, were not able to demonstrate any impact of ENE on survival; moreover, a higher number of ENE+ nodes was not associated with a worse prognosis [16]. Coversely, Yoo et al. found that ENE independently affected the risk of nodal recurrence [34]. Hong et al, in a cohort of 87 patients with high-grade salivary gland cancer, found that ENE independently affected only DFS. [15] Aro et al. [17] and Hsieh et al. [37] demonstrated that ENE did not have any impact on survival. It is worth mentioning, however, that a recent report did identify ENE as one of the most important prognostic predictors [18].

In our cohort of patients, ENE was identified in 61.5% of cases, higher than the values reported in the literature (31–57%) [5,18,19], but it failed to demonstrate any influence on survival. Our data, moreover, seem to suggest that ENE is directly correlated with increasing number and dimension of lymph-nodes (Fig. S2, S3).

Number and dimensions of nodes

In recent years, attention has been directed towards the burden of lymphatic involvement in the field of salivary gland cancer. Consequently, parameters such as number of involved nodes and nodal ratio (NR) were evaluated. Suzuki et al. discovered that a NR of $\geq$ 0.38 was associated with a significantly shorter overall survival time [19]. Similarly, Hong et al. showed that a NR $>$ 0.4 had an independent impact on OS, DFS, and DSS in high-grade salivary gland malignancies [15]. Aro et al., in a National Database analysis on major and minor salivary gland cancers, identified number of positive lymph-nodes as the strongest prognostic factor whereas other nodal factors such as size had no impact on survival [17]. Lee et al. identified number of positive nodes as a main nodal prognostic factor [18].

Our results are in keeping with these recent experiences as regards the number of involved nodes [17,19]. X-tile analysis identified $\geq$4 lymph-nodes as the cutoff between low- and high nodal burden patients. A similar cutoff was identified by Qian et al., who analyzed 8668 patients with MSG carcinoma from the SEER database, found that $>$ 4 positive lymph-nodes, and a NR $>$ 0.15 independently affected DSS [25]. Whilst strongly supporting these findings as regards the number of involved lymph-nodes as a predictor of survival, our experience identifies maximal nodal dimension $\geq$20 mm rather than ENE as a prognosticator. We decided not to rely upon NR for two reasons: first, the relationship between nodal yield and survival may be not linear, and second, apart from extent of neck dissection, there are other factors that may alter the relationship between nodal yield and NR [38–41].

Proposal of a novel N-classification

The inability of current N-categories to differentiate between prognostic groups prompted us to redefine and simplify them by including only the number and maximum diameter of metastatic nodes. Recently, two similar attempts have been made: Aro et al. stratified patients in 4 categories mainly according to number of positive nodes: N0, N1 (1–2 N+), N2 (3–21 N+), N3 (>22 or ENE+) [17]. Lee et al., conversely, preferred to stratify their cohort of 172 patients with intermediate/high-grade tumors of major and minor salivary glands into 3 categories: N0, N1 (1 LN+), N2 ($\geq$2N+ and/or ENE+) [18]. Both proposals were found to be superior to the current TNM system and allowed a more precise prognostic stratification.

According to our models, we prefer to advance three systems of N-classification according to the number and/or largest dimension of metastatic lymph-nodes. These models, all of which were found to be better than the current N-categories in prognostic stratification with an independent impact on survival, were conceived to depict the burden of nodal involvement. This was statistically confirmed by all employed indices (AIC, BIC, Nagelkerke pseudo-R^2) once again demonstrating the superiority of these models compared to the 8th TNM Edition N-classification. Among our 3 models, the second and third are apparently the most promising, but their validation and assessment in an external, larger cohort is essential to identify the most effective one.

Points of strength and limitations of the study

A point of strength of our analysis is that all histological subtypes and tumor grades, not only intermediate- or high-grade tumors, were included and that only tumors arising in MSG, as dictated by TNM, have been evaluated. Moreover, we did not retrieve data from national databases and, consequently, we were able to analyze in detail all information pertaining to surgical procedure, histologic findings, and pattern of recurrence. Furthermore, we could demonstrate that involvement of parotid lymph-nodes is of paramount prognostic importance.

The main limitation of the study is its retrospective, observational nature. Second, nodal status could be assessed only in those patients who underwent any type of neck dissection. Lastly, the data set in this

study has been used to define the variables of interest and estimate the prognostic ability of the models constructed. External validation in an independent cohort of patients is required to exclude overfitting and verify the generalizability of our findings.

Conclusions

In this study, high tumor grade, high T-category and nodal involvement confirmed their prognostic relevance in MSG carcinoma. The current N-classification failed to demonstrate a satisfactory prognostic potential. Conversely, increasing overall number and diameter of nodes, including those contained within the parotid gland, proved to stratify survival of patients more accurately. Three proposals of a novel N-classification based upon number of lymph-nodes, their largest diameter, and a combination of both, have been advanced.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2020.105076.

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