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Predictive Index for Lymph Node Management of Major Salivary Gland Cancer

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Objectives/Hypothesis: To find the risk factors of lymph node (LN) metastasis of salivary gland cancer and draw a scheme for LN management.

Study Design: Hospital-based retrospective study.

Methods: The records of salivary gland cancer patients treated at the Department of Head and Neck Surgery, Cancer Hospital, Fudan University, were entered in a database, and 219 consecutive patients with carcinomas of major salivary glands primarily operated on between January 1998 and January 2011 were chosen for univariate and multivariate analysis to identify risk factors for LN involvement.

Results: Fifty-eight (26.5%) patients had LN involvement. Factors associated with cervical LN involvement on univariate analysis included pathologic type, male sex, shorter duration of preoperative course, facial paralysis, advanced T stage, and major nerve, soft tissue, lymphatic/vascular (L/V), neural/perineural, and extracapsular invasion. Multivariate analysis identified major nerve invasion, histologic type, L/V invasion, and extracapsular invasion as significant factors for LN involvement. The proportion of patients with LN involvement with low (105), middle (61), high (34), and super high (19) predictive index scores based on the four risk factors were 3.8%, 27.9%, 55.9%, and 94.7%, respectively.

Conclusions: A predictive index using the clinicopathologic factors described in this report can effectively stratify patients into risk groups for nodal metastasis. Comprehensive management based on this risk index should improve treatment outcomes for patients with salivary gland cancer.

Key Words: Salivary gland cancer, lymph node, predictive index, neck dissection, radiation.

Level of Evidence: 2b.

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INTRODUCTION

Salivary gland carcinoma is a rare disease, comprising a minimum of 24 histologic types and representing 1% to 5% of all head and neck carcinomas.[1–4] In Shanghai, China, the standardized incidence rates of malignant neoplasms of the salivary glands are 0.45 and 0.40 per 100,000 female and male inhabitants, respectively.[5] No prospective clinical trials have been conducted on any aspect of the curative treatment of primary salivary gland carcinomas because of its low incidence and varied biological behavior.[3]

Cervical lymph node (LN) involvement is associated with decreased survival of patients with salivary gland cancers.[2,4,6–8] However, there is no consensus on the management of the neck. Clinically positive LNs are treated by surgical neck dissection (ND), often followed by radiation therapy. Patients with clinically negative cervical lymph nodes (cN0) may be treated with an elective ND and/or radiotherapy. Evidence-based guidelines that indicate which patients will present with LN metastasis are currently lacking in the literature, although some risk factors have been built.[2,7,9] The limitations of published literature to date have included the small patient series, and the research results of decades of patient enrollment have been adulterated over time by the complex and changing pathological classification of salivary gland tumors.[10]

In the current study of 219 consecutive patients, tumor characteristics known by clinicians who are facing the decision of whether or not to treat the cervical LN were examined for their association with neck metastasis by both univariate and multivariate analysis. A simple prognostic index based on the identified risk factors was established, and a proposed treatment algorithm was produced to predict LN metastasis and to identify patients for ND and/or irradiation.

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TABLE I.
Lymph Node Involvement Frequency of Salivary Gland Cancer by Histologic Type.

Histologic Type	Total Cases	cN0	pN+ (%)	pN1+ (%)	pN2+ (%)	Risk Group
Mucoepidermoid Ca	51	47	10 (19.6)	2 (3.9)	8 (15.7)	
Low grade	28	27	2 (7.1)	1 (3.6)	1 (3.6)	Low
Intermediate grade	16	16	4 (25)	0	4 (25)	Middle
High grade	7	4	4 (57.1)	1 (14.3)	3 (42.9)	High
Adenoid cystic Ca	38	36	5 (13.2)	2 (5.3)	3 (7.9)	Middle
Salivary duct Ca	29	17	17 (58.6)	7 (24.1)	10 (34.5)	High
Acinic cell Ca	28	28	0	0	0	Low
Lymphoepithelial Ca	23	11	13 (56.5)	0	13 (56.5)	High
AdenoCa NOS	17	9	9 (52.9)	1 (5.9)	8 (47.1)	High
Ca ex PA	12	11	1 (8.3)	0	1 (8.3)	Low
PLGA	7	7	0	0	0	Low
Epithelial-Myoepithelial Ca	3	3	0	0	0	Low
Squamous cell Ca	3	2	2 (66.6)	1 (33.3)	1 (33.3)	High
Myoepithelial Ca	2	2	0	0	0	Low
Small cell Ca	2	2	0	0	0	Low
Carcinosarcoma	1	1	0	0	0	Low
Oncocytic carcinoma	1	0	1 (100)	0	1 (100)	High
Basal cell adenocarcinoma	1	1	0	0	0	Low
Cystadenocarcinoma	1	1	0	0	0	Low
Sum	219	178	58(26.5)	13 (5.9)	45 (20.5)	

N1 and N2 were defined as American Joint Committee on Cancer staging manual 2010. The values used for multivariable analysis of low, middle, and high risk were weighted as 1, 2, and 3, respectively.

cN0 = clinically negative cervical lymph node; pN+ = pathological lymph node involvement; Ca = carcinoma; NOS = not otherwise specified; PA = pleomorphic adenoma, PLGA = pleomorphic low-grade adenocarcinoma.

MATERIALS AND METHODS

Patient Enrollment

The records of patients with salivary gland tumors who were treated at the Department of Head and Neck Surgery, Cancer Hospital, Fudan University, Shanghai, China, were entered in a database. This research was approved by the institution's ethics committee. Because of the different clinical courses and LN drainage of persistent/recurrent disease and primary cases, and minor and major salivary gland cancer, only patients primarily operated for major salivary gland cancer were included in this research.[6] The pathologic classification of salivary gland carcinoma was significantly updated in 1996 by the Armed Forces Institute of Pathology (AFIP), and the most recent WHO classification is almost identical to the AFIP system.[10] Therefore, only patients with primary salivary gland cancers who were treated after January 1998 were included in this study, for a total of 219 consecutive cases of primary major salivary gland carcinoma operated on from January 1998 to January 2011 (Table I). TNM stages were reclassified according to the 2010 American Joint Committee on Cancer staging system.

Diagnostic Work-Up and Treatment

The patients underwent ultrasound, computed tomography (CT), magnetic resonance imaging, and fine-needle aspiration before surgery. Frozen section (FS) biopsy was done for all patients during surgery. The final pathology reports were based on hematoxylin-eosin staining, and when necessary immunohistochemical analysis. A comprehensive management plan based on histopathologic results and intraoperative findings was formulated by a multidisciplinary team that included the surgeons and the radiation and medical oncologists. For clinically suspicious LNs identified by preoperative diagnostic examinations (cN+), therapeutic ND was performed. For malignant tumors with cN0 neck (no suspicious LNs were found preoperatively), a selective ND was carried out according to the results of the FS and the surgeons' intraoperative assessment based on the tumor size and invasion.

Statistical Analysis

Clinical and pathological factors potentially associated with LN metastasis were identified and examined individually for their effect on LN involvement using the Pearson double-sided χ^2 test (Table II). Statistically significant factors were then included in a multivariate logistic regression model by forced entry and in forward stepwise fashion with an odds ratio significance cutoff of .05 (Table III). The four most significant factors (with six predictive index scores) were combined into a categorical variable of 24 groups representing all possible combinations of each predictive index score (Table IV). Finally, patients were stratified into low, middle, high, and super high-risk groups based on the total predictive index scores. This four-group categorical variable was then reentered in the logistic regression with the same covariate controls (Table V). A receiver operator curve was generated for the prognostic index of LN involvement in salivary gland cancer (Fig. 1). Kaplan-Meier survival curves for patients with different statuses of LN involvement and risk categories were generated (Fig. 2 and Table VI). All of the statistical analyses were performed using SPSS 17 (SPSS, Inc., Chicago, IL) software.

RESULTS

Clinicopathologic Characteristics of Major Salivary Gland Carcinomas

The histological type and clinical characteristics are listed in Tables I and II. The median age of patients was

TABLE II.
Patient Characteristics, Clinicopathologic Factors, and Correlation With Lymph Node Involvement in Univariate Analysis.

Category Variables	Total No. of Cases	pN+, No. (%)	*P*
Preoperative assessment			
Sex			<.01
Female	101	14 (13.9)	
Male	118	44 (37.3)	
Age, yr			.536
>50	111	32 (28.8)	
≤50	108	26 (24.1)	
Primary site			0.450
Parotid	157	38 (24.2)	
Submandibular	58	19 (32.8)	
Sublingual	4	1 (25.0)	
Preoperative course, mo			.050
>9	111	23 (20.7)	
≤9	108	35 (32.4)	
Facial paralysis			.003
Yes	23	12 (52.2)	
No	196	46 (23.5)	
Intraoperative assessment			
Tumor size, mm			.002
≤20	84	11 (13.1)	
20–40	108	37 (34.3)	
>40	27	10 (37.0)	
Facial nerve invasion			
Yes	55	25 (45.5)	<.01
No	102	13 (12.7)	
Major nerve invasion			<.01
Yes	71	32 (45.1)	
No	148	26 (17.6)	
Soft tissue invasion			<.01
Yes	104	40 (38.5)	
No	115	18 (15.7)	
T stage			<.01
T1	59	4 (6.8)	
T2	55	17 (30.9)	
T3	48	13 (27.1)	
T4	57	24 (42.1)	
Microscopic examination			
Histologic type			<.01
High risk	80	46 (57.5)	
Middle risk	54	9 (16.7)	
Low risk	85	3 (5.2)	
Lymphatic/vascular invasion			<.01
Yes	18	14 (77.8)	
No	201	44 (21.9)	
Neural/perineural invasions			.002
Yes	60	25 (41.7)	
No	159	33 (20.8)	
Extracapsular invasion			.001
Yes	43	21 (48.8)	
No	176	37 (21.0)	
Muscle invasion			.216
Yes	9	4 (44.4)	
No	210	54 (25.7)	

Numerical Variables	pN+, Mean ± SE	pN−, Mean ± SE	*P*
Age, yr	53.07 ± 16.081	49.43 ± 17.458	.166
Preoperative course, mo	42.03 ± 108.763	34.70 ± 66.259	.549
Tumor size, mm	3.25 ± 1.453	2.57 ± 1.407	.002
Lymph nodes detected, no.	27.93 ± 17.552	7.52 ± 8.585	.000

pN+ = pathological lymph node involvement; pN− = pathological lymph node negative; SE = standard error.

50 years (range, 11–85 years); the male:female ratio was 118:101. Forty-one patients presented with clinically apparent cervical LN metastasis (cN+, 18.7%). NDs were performed in 61.2% (134/219) of the patients, which included all the cN+ cases and 52.2% of cN0 patients (93/178). Neck dissection levels included 23 cases of submandibular ND (level IB), 59 supraomohyoidal ND (level I-III), 15 cases of modified radical ND (level I-V), and 37 cases of radical ND (level I-V). Pathologically confirmed metastatic LN was identified in 26.5% (58/219) of the patients, which included 40 cases for cN+ cases (97.6%, 40/41) and 18 cases for cN0 cases (10.1%, 18/178). One cN+ case was pathologic LN negative (pN−) after ND. Median follow-up time for all patients was 19 months (range, 1–140 months).

Histological Type and Frequency of LN Involvement

The distribution of histological type and LN involvement is listed in Table I. The histologic types were stratified into three groups according to the LN metastasis risk as low (<10%), middle (10%–30%), and high (>40%). The designations of low, middle, and high risk were weighted as 1, 2, and 3, respectively, for predictive analysis. The grades of different histological types were analyzed for their association with LN metastasis individually, and only the grade of mucoepidermoid carcinoma was found to be significant as listed at Table I.

Clinicopathologic Characteristics Possibly Associated With LN Involvement

To arrive at a model that illustrates the relative importance of findings commonly available to physicians considering ND or radiation, the clinicopathologic factors identified as significant on univariate analysis (Table II) were included in a multivariate logistic regression of LN involvement (Table III). Controlling for all factors listed, major nerve invasion, histologic type, lymphatic/vascular (L/V) invasion (Fig. 3a) (reported by the pathologist according to the primary tumor histological slides), and extracapsular invasion (Fig. 3b) (reported by the

TABLE III.
Multivariate Logistic Regression of Clinicopathologic Factors in Lymph Node Metastasis.

Variable (Index)	Expβ (95% CI)	*P*	β(SE)
Major nerve invasion (1)	3.841 (1.679-8.787)	.001	1.346 (0.422)
Histologic type		<.01	
Low risk (1)			
Middle risk (2)	4.276 (1.002-18.224)	.050	1.453 (0.740)
High risk (3)	34.599 (9.115-131.335)	<.01	3.544 (0.681)
Lymphatic/vascular invasion (1)	10.282 (2.514-42.051)	.001	2.330 (0.719)
Extracapsular invasion (1)	2.744 (1.068-7.047)	.036	1.009 (0.481)
Constant	0.014	<.01	−4.253 (0.690)

Exp(β) = odds ratio; CI = confidence interval; SE = standard error.

pathologist according to the primary tumor histological slides) were found to be statistically significant predictors of regional nodal metastasis. When the total risk was calculated according to these four variables, six predictive indices and 24 risk groups were generated as listed in Table IV. The area under the receiver operator curve (Fig. 1a) using these six predictive indices to predict LN involvement was 0.878 (95% confidence interval [CI], 0.830-0.925). Because the LN involvement frequency of index 1, index 2, index 5, and index 6 were overlapping, four risk groups (low, middle, high, and super high) based on the LN involvement frequency and predictive indices generated from the significant risk factors were identified (Table V). When controlled for all the risk factors by univariate analysis (Table II), these four risk classifications are statistically significant

TABLE IV.
Frequency of Lymph Node Involvement for a Predictive Index Generated by All Combinations of the Four Significant Risk Factors.

Index	Variable	No. of Cases	pN+ (%)	N1/N2
1	Low risk without adverse features	58	0	
2		47	4 (8.5)	2/2
	Low risk and major nerve invasion	11	1 (9.1)	1/0
	Low risk and LV invasion	0	0	
	Low risk and extra capsular invasion	10	0	
	Middle risk without adverse features	26	3 (11.5)	1/2
3		61	17 (27.9)	2/15
	Low risk and major nerve/LV invasion	2	1 (50)	0/1
	Low risk and major nerve/extra capsular invasion	4	1 (25.0)	0/1
	Low risk and LV/extra capsular invasion	0	0	
	Middle risk and major nerve invasion	16	4 (25.0)	1/3
	Middle risk and LV invasion	2	1 (50.0)	0/1
	Middle risk and extra capsular invasion	4	0	
	High risk without adverse features	33	10 (30.3)	1/9
4		34	19 (55.9)	6/13
	Low risk with three adverse features	0	0	
	Middle risk and major nerve/extra capsular invasion	0	0	
	Middle risk and major nerve/LV invasion	1	0	
	Middle risk and major nerve/extra capsular invasion	4	0	
	Middle risk and LV/extra capsular invasion	0	0	
	High risk and major nerve invasion	18	10 (55.6)	3/7
	High risk and LV invasion	4	4 (100)	0/4
	High risk and extra capsular invasion	7	5 (71.4)	3/2
5		17	16 (94.1)	2/14
	Middle risk and three adverse features	1	1 (100)	0/1
	High risk and major nerve/LV invasion	2	2 (100)	1/1
	High risk and major nerve/extra capsular invasion	10	10 (100)	1/9
	High risk and LV/extra capsular invasion	4	3 (75)	0/3
6	High risk and three adverse features	2	2 (100)	1/1

pN+ = pathological lymph node involvement; LV = lymphatic/vascular.

TABLE V.
Frequency and Pattern of Lymph Node Involvement in Major Salivary Gland Cancer Patients by Risk Group.

Risk Group	Total Index	pN+/Total Cases (%)	OR (95% CI)	*P*	LN Metastasis Level (%)			pN+/Total cN0 Cases (%)	LN Metastasis Level, cN0 (%)		
					1 Level	Level II	>Level II		1 Level	Level II	>Level II
Low (ref)	1, 2	4/105 (3.8)			50	50		2/103 (1.9)	50	50	
Middle	3	17/61 (27.9)	9.76 (3.10-30.67)	<0.01	41.2	23.5	35.3	6/50 (12.0)	83.3	16.7	
High	4	19/34 (55.9)	31.98 (9.57-106.93)	<0.01	26.3	21.1	52.6	5/19 (26.3)	40	40	20
Super high	5, 6	18/19 (94.7)	454.50 (48.00-4303.34)	<0.01	22.2	27.8	50.0	5/6 (83.3)	20	60	20

Lymph node levels: 1 level represents intra/paraparotid or level IB lymph nodes, level II represents 1 level and level II, >;level II represents metastasis beyond level II.

OR = odds ratio; CI = confidence interval; LN = lymph node; cN0 = clinically negative cervical lymph node.

predictors of regional nodal metastasis. The area under the receiver operator curve (Fig. 1b) using this four-risk group stratification to predict LN involvement was 0.864 (95% CI, 0.808-0.920).

Survival Analysis of LN Involvement and Risk Stratification

The overall survival rates at 5 and 10 years for all patients were 87.3% and 76.1%, respectively. Disease-free survival at 5 and 10 years for all the patients was 65.6% and 57.6%, respectively. The 5-year overall survival and disease-free survival rates for LN negative and positive cases are shown in Figure 2a and 2b and Table VI, respectively. After the LN involvement risk index was produced (Table V), the survival data were analyzed for the four risk groups. The 5-year overall survival and disease-free survival for low, middle, high, and super high-risk groups are shown in Figure 2c and 2d and Table VI.

Postoperative Radiation of Salivary Gland Cancer

Postoperative radiation was performed in 45.7% (100/219) of the patients. The number of patients who received radiation therapy in the low, middle, high, and super high-risk groups were 31.4%, 54.1%, 61.8%, and 68.4%, respectively. The postoperative radiation plan was based on the pathological report and intraoperative assessment and was fashioned by a multidisciplinary team, which included the surgeons and the radiation and medical oncologists. Clinical target volumes for the postoperative radiation of salivary gland cancer were defined as high-risk region (dose 60 Gy/30 Fx) and low-risk region (dose 50–54 Gy/25–27 Fx). The radiation technique included conventional two-dimensional and three-dimensional conformal radiation, and intensity-modulated radiotherapy (IMRT), which has been routinely used since 2007. Univariate analysis of patients without and with radiation showed that those patients with male gender, facial nerve paralysis, extraparenchymal extension, major nerve invasion, high histological grade, advanced T classification, LN metastasis, and advanced TNM staging, which were all adverse factors for prognosis, received more radiation. Although no significant differences were found for the 5-year overall survival rate (89.9% vs. 85.0%, $P = .401$) and disease-free survival rate (67.1% vs. 63.7%, $P = .582$) of patients without and with radiation. All these suggested that postoperative radiation can redeem the adverse impact on prognosis of risk factors and improve the survival of patients with adverse features.

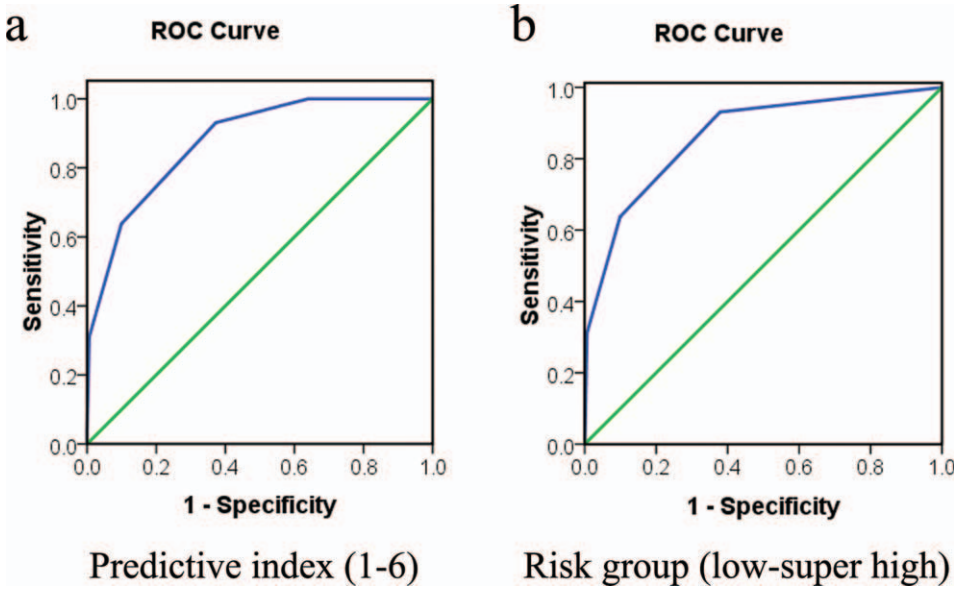

Fig. 1. The area under the receiver operator curve (ROC) for predicting lymph node involvement by using predictive indices. (a) Index 1 to 6 listed in Table IV. (b) Risk groups low to super high listed in Table V. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

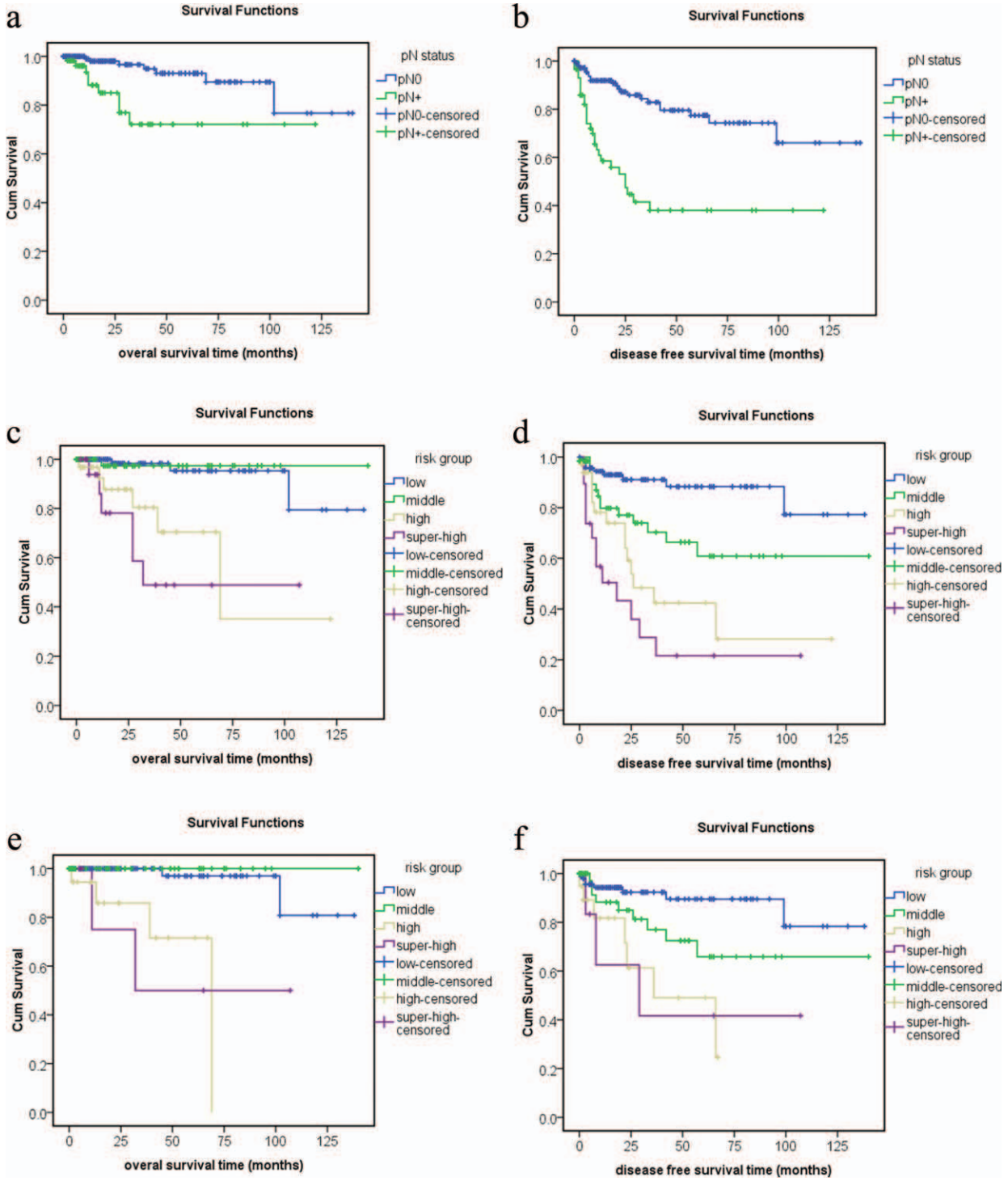

Fig. 2. Survival analysis of salivary gland cancer. (a,b) The overall survival (OS) and disease-free survival (DFS) in lymph node (pN) positive and negative patients. (c,d) The OS and DFS of patients in low-, middle-, high- and super high-risk lymph nodes involvement. (e,f) The OS and DFS of patients with cN0 neck in low-, middle-, high- and super high-risk lymph nodes involvement. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

LN Metastasis Pattern and Risk of Neck Recurrence

The patients who were included were also divided into three groups based on the involved LN levels: one level (intra/paraparotid or level IB), level II (one level and level II), and >level II (metastasis beyond level II). The LN metastasis patterns of the four risk groups are listed in Table V. The neck LN recurrence rate was 5.9% (13/219). The detailed clinicopathologic characteristics of patients with recurrence are listed in Table VII. The median time to recurrence was 6 months (range, 5–25 months).

TABLE VI.
The Survival Analysis of Different Lymph Node Status and Risk Group.

Classification	5-Year Overall Survival		5-Year Disease-Free Survival	
	Rate, %	Log rank χ^2 (*P*)	Rate, %	Log Rank χ^2 (*P*)
Lymph node status	Fig. 2a	10.224 (.001)	Fig. 2b	30.559 (<.001)
Positive (pN+)	72.1		38.0	
Negative (pN−)	93.0		77.4	
Risk group	Fig. 2c	31.187 (<.001)	Fig. 2d	41.102 (<.001)
Low	95.3		88.3	
Middle	97.4		60.8	
High	70.4		42.3	
Super high	48.8		21.6	
Risk group for cN0 cases	Fig. 2e	30.297 (<.001)	Fig. 2f	17.603 (0.001)
Low	97.0		89.5	
Middle	100		65.9	
High	71.5		49.0	
Super high	50.0		41.7	

pN+ = pathological lymph node involvement; pN− = pathological lymph node negative; cN0 = clinically negative cervical lymph node.

Validation of Prognostic Index of LN Involvement for the CN0 Neck

The clinical significance of a prognostic index for LN metastasis is greater for patients with cN0 cervical LN, because patients with occult LN metastasis will benefit from neck dissection and/or irradiation. Of the patients who presented with cN0 neck (178), occult LN metastasis was found in 18 cases (11.1%), which included eight pN1 cases and 10 pN2 cases. The frequency of occult LN involvement and level of low, middle, high, and super high-risk cN0 patients are listed in Table V. There were two cases with occult LN metastases beyond level II, which included one T3N2M0 adenocarcinoma not otherwise specified case with extracapsular extension and one T4N2M0 salivary duct carcinoma case with L/V invasion and facial nerve invasion. The 5-year overall survival rate and disease-free survival rates for low, middle, high, and super high-risk patients with cN0 neck are shown in Figure 2e and 2f and Table VI. The radiation frequency of low, middle, high, and super high-risk patients with cN0 neck were 31.1%, 50.0%, 68.4%, and 100%, respectively ($P < 0.01$).

DISCUSSION

Salivary gland carcinomas have a low incidence, wide histological variability, and variety of treatment options. The management of the neck in major salivary gland malignancies, in particular the treatment of the cN0 neck, is controversial. Three basic steps to achieve an individual plan for cervical LN management in salivary gland cancer are patient selection criteria (follow-up or selective neck management), treatment choice

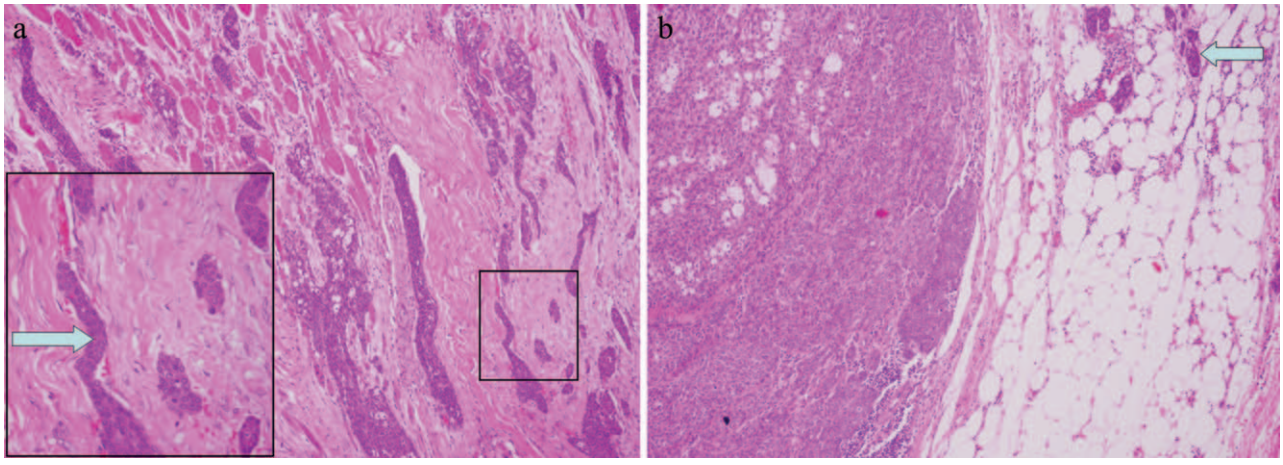

Fig. 3. Lymphatic/vascular invasion and extracapsular invasion of salivary gland cancer. (a) Lymphatic/vascular invasion, intermediate grade mucoepidermoid carcinoma (hematoxylin-eosin ×100). The arrowhead indicates the invasive loci in the vessel surrounded by erythrocytes. (b) Extracapsular invasion, adenocarcinoma not otherwise specified. The arrowhead indicates the extracapsular invasive loci (hematoxylin-eosin ×40). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE VII.
Clinicopathologic Characteristics of Recurrent Neck Cases After Primary Treatment.

No.	Sex	Age, yr	Site	Facial Paralysis	cN	Neck Dissection	Tumor Size, cm	Pathology Type	Risk Group	T	No. Metastasis/ Examined LNs	Stage	Radiation	Primary Site Recurrence	Recurrence Time, mo
1	M	40	P	No	N0	Level I-V	1.5	MEC-middle	Middle	III	6/25	IV	No	No	5
2	M	68	P	Yes	N0	No	2.8	SDC	High	IVa	0/2*	IV	No	Yes	22
3	M	48	P	No	N2	Level I-V	3.5	LEC	High	II	29/29	IV	Yes	No	6
4	M	39	P	No	N2	Level I-V	2.5	LEC	High	IVa	75/86	IV	Yes	No	6
5	M	54	P	Yes	N1	Level I-V	3	MEC-high	High	IVa	29/34	IV	Yes	Yes	6
6	F	30	P	No	N2	M- Level I-V	2.5	LEC	High	II	21/47	IV	Yes	No	13
7	M	78	P	Yes	N1	M- Level I-V	3	Oncocytic Ca	S-high	II	20/29	IV	Yes	Yes	2
8	M	55	P	Yes	N1	Level I-V	4	AC NOS	S-high	IVa	17/28	IV	Yes	No	11
9	F	80	P	No	N1	Level II, III	3.7	SDC	S-high	IVa	14/18	IV	Yes	No	3
10	M	59	P	No	N2	M- Level I-V	10	LEC	S-high	IVb	21/36	V	Yes	No	2
11	M	61	Sm	No	N2	M- Level I-V	3	AC NOS	Middle	III	12/17	IV	No	Yes	5
12	M	62	Sm	No	N0	Level I, II, III	2	LEC	Middle	I	2/6	IV	No	No	6
13	M	66	Sm	No	N2	M- Level I-V	2.5	AC NOS	High	III	1/18	IV	No	Yes	25

*These two lymph nodes were intraparotid lymph nodes. LN = lymph node; P = parotid gland; MEC = mucoepidermoid carcinoma; SDC = salivary duct carcinoma; LEC = lymphoepithelial carcinoma; M- Level I-V = modified therapeutic neck dissection; Ca = carcinoma; AC NOS = adenocarcinoma not otherwise specified; Sm = submandibular gland.

(operation and/or radiation), and method of treatment (ND level and target volume of IMRT plan).

The approach to clinically positive nodal disease is well documented. Therapeutic ND followed by postoperative radiation is the accepted treatment for patients with clinically obvious cervical nodal involvement. Many studies have shown that there is improved locoregional control and increased survival with postoperative radiation,[11] and the current National Comprehensive Cancer Network (NCCN) guidelines recommend that all patients with LN metastasis receive postoperative radiation. The extent of ND and radiation is determined by the grossly involved LN levels and should cover all of the potentially involved levels. Because none of the LN involved in low-risk patients in the current study were beyond level II (Table V), upper ND (level I-III) and radiation may be enough for low-risk patients if there are no involved LN beyond level II detected on a preoperative CT scan. More than half of the high-risk (52.5%) and super high-risk (50%) patients had metastatic LN beyond level II. The ND and radiation should include the total neck in these patients. For middle-risk patients, if the preoperative CT scan and intraoperative assessment show clinically positive LN beyond level II, total ND should be performed. Otherwise, supraomohyoidal ND may be enough.

Treatment of the clinically negative neck has been more controversial, which included observation, elective ND, and prophylactic radiation.[12] The goal of the treatment is to eradicate micrometastatic disease. A systematic review of recent existing literature on nodal involvement and treatment of the neck reveals that 32 of 137 elective LN dissections (23%, weighted average; range, 20%–33%) have positive nodes in the specimen.[12] The discrepancy between the reported number of occult metastases and reported regional recurrence rates (3%–8%) is a measure of the effectiveness of elective neck treatment by either elective ND or radiotherapy.[12] In a landmark study, Armstrong et al. reviewed the records of 407 patients with cN0 neck treated at Memorial Sloan-Kettering Cancer Center between 1939 and 1982 and reported that 12% had occult LN involvement.[13] Multivariate analysis revealed that tumor size and grade were significant risk factors for occult LN metastasis, and neck treatment was only recommended for high-grade and larger tumors. Medina suggests that elective radiation therapy instead of ND should be performed for patients in whom postoperative radiation therapy is indicated by the characteristics of the primary tumor.[14] Ferlito et al. recommend basing the decision for elective ND mainly on the histologic type of the primary tumor.[15] There have been other reports recommending surgery, in particular recent reports from Europe.[7,16,17] Chen et al. found that level II is the most common site of nodal recurrence, and histology and T stage are the most important prognostic indicators for neck recurrence.[1]

Two out of 103 low-risk patients with cN0 neck were found with occult cervical LN metastasis on histopathology (Table V), and none of these 103 patients developed neck recurrence during the follow-up (Table VII). The two patients with LN metastasis were adenoid cystic carcinomas without any adverse features. For low-risk pathologic

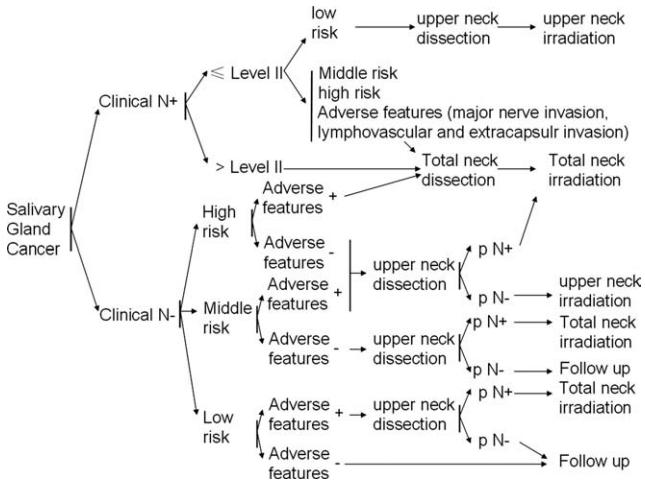

Fig. 4. A cervical lymph node management algorithm for major salivary gland cancer. Pathologic-type risk grouping (as listed in Table I) for lymph node metastasis is not equivalent to the Word Health Organization histological grade stratification, and factors indicating neck radiation are not the same as for primary site radiation. The upper neck represents level I-III for submandibular gland cancer and sublingual gland cancer, and level II-III for parotid gland cancer, respectively.

type carcinomas (Table I: low grade mucoepidermoid carcinoma, acinic cell carcinoma, carcinoma expleomorphic adenoma, pleomorphic low-grade adenocarcinoma) without any adverse features (Index 1, Table IV), ND may be deferred for the cN0 neck due to the zero frequency of LN involvement (Table IV) and neck recurrence (Table VII). For the patients with total predictive indices of 2 and 3 (Table IV), an upper ND (level I-III) along with the primary resection is recommended. This level of ND is chosen because there were no LN metastases beyond level II (Table V). For high- and super high-risk patients (total index 4–6, Table IV), therapeutic ND (level I-V) should be performed because 40% (10/25) of these patients had clinically occult neck metastasis and 20% (2/10) of the LNs were located beyond level II in current study.

If dissected nodes are positive in the cN0 patient, the neck should be treated with postoperative radiation therapy as described above for patients with clinically positive LN. Except for the pN+ cases, the NCCN guidelines also recommend postoperative radiation for patients with adenoid cystic carcinoma and adverse features (intermediate or high-grade tumor, close or positive margins, neural/perineural invasion, and L/V invasion). If dissected nodes are negative, and no other indications for primary site radiation exist, the treatment choice should be balanced between the cost and morbidity of radiation and the patient's benefit. There were no recurrent neck cases among low-risk or middle-risk patients with pN0 neck in this study (Table VII). Thus, for low- and middle-risk patients with pN0 neck, careful follow-up may be appropriate. For high- and super high-risk patients with pN0 neck, there are at least three reasons to support postoperative radiation. First, the 5-year disease-free survival rate for high- and super high-risk cN0 patients were 44.2% and 0%, respectively, the higher relapse rate deserved for more intensified postoperative treatment. Second, most of the high- and super high-risk patients are those with adverse features and are recommended for radiation by NCCN guidelines. Third, there was one high-risk pN0 case among 13 cases with neck recurrence (Table VII). The clinical target volume (CTV) planned should cover the upper neck in the middle-risk group and the total neck in the high- and super high-risk group because none of the middle-risk cN0 patients had lymph node involvement beyond level II, whereas 20% of high- and super high-risk cN0 patients had positive lymph nodes beyond level II in current study.

To further develop the guidelines for neck management in patients with major salivary gland cancer, a management algorithm was generated according to the findings in this study and a review of the literature, and is presented as Figure 4. The 5-year overall survival (87.3%) of this series of patients exceeds treatment results reported elsewhere in the literature (46%–81%).[12] Six out of 13 neck recurrence cases (cases 1, 2, and 9–12) (Table VII) were treated insufficiently according to the algorithm (Fig. 4). These types of patients should benefit from the guidelines presented in this study. For the other seven neck recurrence cases (cases 3–8 and 13) (Table VII) with the standard therapy recommended by this report, postoperative concurrent chemoradiotherapy might be warranted, because concurrent chemoradiotherapy has resulted in excellent local control in a subgroup of salivary gland cancer patients with adverse prognostic factors.[18] Further research to assess these guidelines for overtreatment, particularly for low- and middle-risk patients, is warranted.

The retrospective nature of this analysis, the heterogeneity of tumor histologic types, and a patient population limited to one institution have limited the conclusions that can be drawn from these data. However, the relatively low incidence, the multiple histopathologic subtypes, and the behavior patterns of salivary gland cancers have precluded large randomized analyses or prospective trials of homogenous patient populations. Previously published studies have often included patients who were treated during a span of more than 2 decades, with wide variations in surgical techniques and pathologic classifications. In contrast, the current study examined more than 200 patients who were treated within a relatively short period (13 years), during which the latest pathologic classification of tumors has become widely used. The current research also elaborates patterns of LN involvement in different risk groups and discusses ND levels and CTV planning for radiation.

CONCLUSION

Using a predictive index based on pathologic-type risk stratification, major nerve invasion, extracapsular invasion, and lymphatic/vascular invasion can effectively separate patients into risk groups for nodal metastasis. Comprehensive management based on this index, including surgery and radiation, will improve treatment outcomes for patients with salivary gland cancer. The

precision of this predictive index is subject to the limitations of data from one institution and should be validated in further clinical studies.

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