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Abstract. This study was performed to compare the effects of neck dissection procedures on the prognosis of patients with pathological N1 (pN1) oral squamous cell carcinoma (OSCC), analyse factors affecting the prognosis, and provide a neck management strategy for clinical N1 (cN1) oral cancer. The study patients were divided into two groups according to the neck dissection: a selective neck dissection (SND) group (n = 85) and a radical or modified radical neck dissection (RND/MRND) group (n = 22). There was no statistically significant difference in recurrence rates at local, regional, and distant sites between the SND and RND/MRND groups. The 5-year overall survival was 68.3% for SND and 65.2% for RND/MRND patients (P = 0.590), while the 5year disease-specific survival was 70.4% for SND and 75.7% for RND/MRND patients (P = 0.715). Histological grade and postoperative radiotherapy were independent predictors of the outcome for SND patients. For histological grade II/III cases, 5-year overall survival (P = 0.004) and disease-specific survival (P = 0.002) outcomes differed significantly between patients treated with and without postoperative radiotherapy, with worse survival for patients not treated with radiotherapy. Therefore, SND appears appropriate for cN1 OSCC patients, and postoperative radiotherapy is recommended for those with histological grade II or III tumours.

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Oral cancer is the most common malignant tumour in the oral and maxillofacial region, and approximately 90% is oral squamous cell carcinoma (OSCC).^{1,2} Cervical lymph node metastasis is one of the most common biological features of OSCC and is the main factor that affects the prognosis of patients.^{3,4} The traditional view is that a therapeutic neck dissection should be performed for patients with neck metastasis confirmed by clinical evaluation or pathological examination (cN+/pN+). Therapeutic neck dissection mainly includes radical neck dissection (RND) or modified radical neck dissection (MRND).⁵ An elective neck dissection (END) should be performed in patients with a clinically node-negative neck (cN0), in whom there is a high

risk of occult metastasis; the main procedure in such cases is the selective neck dissection (SND).⁶ Cervical lymph node metastasis of OSCC mainly occurs at levels I–III, thus cN0 patients

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are usually treated with a supraomohyoid neck dissection.⁷

In recent years, with the rapid development of functional surgery, the preservation of function and patient quality of life have become important treatment goals.⁸ Therefore, the indications for SND have gradually been expanded. Previous reports have shown that SND can achieve a good prognosis in OSCC patients with single cervical lymph node metastasis that has a maximum diameter of ≤ 3 cm (cN1).⁹ However, most studies have had some limitations, such as a small sample size or short follow-up time, and there have been no pro-spective studies.^{10,11} Therefore, the use of SND for neck treatment in cN1 patients remains controversial.

The aims of this study were to analyse the effects of different neck dissections (RND/MRND or SND) on the prognosis of OSCC patients with pathological N1 nodal stage, analyse the factors affecting the prognosis of these patients, and summarize the neck treatments used in cN1 patients.

Materials and methods

Patients

The cases of a series of OSCC patients with pathologically confirmed neck metastasis (pN1), who were treated in of Oral the Department and Maxillofacial Peking Surgery at University School and Hospital of Stomatology between 2012 and 2016, were reviewed. Clinical information, including the primary tumour site, TNM staging, pathological grade, and type of neck dissection, as well as other demographic and clinical data, were retrieved from the electronic medical records system of the hospital. A total of 107 patients were enrolled. The following patient inclusion criteria were applied: (1) pathologically confirmed primary pN1 squamous cell carcinoma (SCC) of the oral cavity; (2) definitive surgery with neck dissection without previous surgical treatment; (3) no preoperative chemotherapy or radiotherapy. The patient exclusion criteria were as follows: (1) SCC originating from oropharyngeal sites; (2) surgical or adjunctive therapy before surgery.

The type of neck dissection performed was decided by an experienced chief surgeon. Postoperative radiotherapy (PORT) was recommended, although some patients refused additional treatment. In all cases, the primary tumour site was treated by radical resection aimed at 1.5-cm margins. The margins were confirmed by frozen section analysis intraoperatively and paraffin section analysis postoperatively to ensure that they were negative. The clinical nodal stage was determined using clinical signs, physical examination, and imaging techniques, such as enhanced computed tomography (CT). The pathological nodal stage was established based on lymph node metastasis, as determined by the Pathology Department. All patients were staged according to the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system (2017).^{12,13} Follow-up evaluations were conducted with physical examination

Table 1. C	Clinical and	pathological	characteristics	of the 1	07 study	patients with	ı pN1	OSCC
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		All patients,	Patients by neck d	issection group
		N = 107	SND, $n (\%)$ n = 85	RND/MRND, <i>n</i> (%) <i>n</i> = 22
Sex	Male	70 (65.4)	55 (64.7)	15 (68.2)
	Female	37 (34.6)	30 (35.3)	7 (31.8)
Median age (years)		55.5	55.5	53
Site	Oral tongue	45 (42.1)	37 (43.5)	8 (36.4)
	Floor of	13 (12.1)	10 (11.8)	3 (13.6)
	mouth			
	Upper gum	6 (5.6)	3 (3.5)	3 (13.6)
	Lower gum	23 (21.5)	17 (20)	6 (27.3)
	Buccal	18 (16.8)	16 (18.8)	2(9.1)
	mucosa			~ /
	Hard palate	2 (1.9)	2 (2.4)	0 (0.0)
Histological grade	Grade I	35 (32.7)	24 (28.2)	11 (50.0)
Histological grade	Grade II	68 (63.6)	57 (67.1)	11 (50.0)
	Grade III	4 (3.7)	4 (4.7)	0 (0.0)
cT classification	cT1	31 (29.0)	24 (28.2)	7 (31.8)
	cT2	51 (47.7)	40 (47.1)	11 (50.0)
	cT3	5 (4.7)	5 (5.9)	0 (0.0)
	cT4a	19 (17.8)	15 (17.6)	4 (18.2)
	cT4b	1 (0.9)	1 (1.2)	0 (0.0)
cN classification	cN0	62 (57.9)	56 (65.9)	6 (27.3)
	cN1	31 (29.0)	21 (24.7)	10 (45.5)
	cN2a	0 (0.0)	0 (0.0)	0 (0.0)
	cN2b	11 (10.3)	7 (8.2)	4 (18.2)
	cN2c	3 (2.8)	1 (1.2)	2(9.1)
pT classification	pT1	22 (20.6)	18 (21.2)	4 (18.2)
1	pT2	58 (54.2)	47 (55.3)	11 (50.0)
	pT3	6 (5.6)	4 (4.7)	2(9.1)
	pT4a	20 (18.7)	15 (17.6)	5 (22.7)
	pT4b	1 (0.9)	1 (1.2)	0 (0.0)
Postoperative	No	18 (16.8)	16 (18.8)	2(9.1)
radiotherapy	Yes	89 (83.2)	69 (81.2)	20 (90.9)

OSCC, oral squamous cell carcinoma; RND/MRND, radical or modified radical neck dissection; SND, selective neck dissection.

metastasis and four (two with OSCC of

the oral tongue and two with OSCC of

the floor of the mouth) had level V me-

tastasis. Moreover, among the 23 patients

who underwent a bilateral neck dissec-

tion, only one (OSCC of the oral tongue)

had contralateral lymphatic metastasis

Table 2. Ipsilateral and contralateral neck dissection according to type of neck dissection in 107 patients with pN1 OSCC.

		Type of neck	dissection	
Ipsilateral and contralateral	neck dissection	SND	MRND	RND
Ipsilateral	(n = 107)	85	18	4
Contralateral $(n = 23)$		22	1	0

OSCC, oral squamous cell carcinoma; RND/MRND, radical or modified radical neck dissection; SND, selective neck dissection.

and imaging studies as mentioned above. The patients were followed up every 3 months during the first 2 years, every 6 months until 5 years, and then annually thereafter.

This retrospective study was conducted according to the principles of the Declaration of Helsinki and its subsequent revisions, and was approved by the Institutional Review Board of Peking University School and Hospital of Stomatology (Approval No. PKUSSIRB-202171210). Informed consent or an acceptable alternative was obtained from all patients before study inclusion.

Statistical analysis

The χ^2 test or Fisher's exact test was performed to compare the effects of the different neck dissection procedures on postoperative recurrence. The 5-year overall survival rate (OS) and diseasespecific survival rate (DSS) were calculated by Kaplan–Meier method. A univariate analysis was performed using the log-rank test to identify factors that affected the survival rates. Variables that had prognostic potential suggested by the univariate analysis were subjected to multivariate analysis using a Cox proportional hazards regression model.

A two-tailed *P*-value of < 0.05 was considered to indicate statistical significance. The model was simplified using a stepwise selection method by removing variables that were negatively associated with survival or had *P*-values of ≥ 0.05 . The statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Patient demographic characteristics and neck management

A total of 107 patients were included in the study; 70 were male and 37 were female. The median age of the patients at the time of diagnosis was 55.5 years (range 36–82 years). The follow-up period ranged from 1 to 108 months, with a median time of 63 months. A summary of the clinical and pathological characteristics of the 107 patients is presented in Table 1.

All 107 OSCC patients received a neck dissection (107 ipsilateral, 23 contralateral) at the same time as the initial surgery. A bilateral neck dissection (n = 23) was performed when the primary SCC crossed the midline. Regarding the types of ipsilateral neck dissection performed, 73 patients received SND (I-III), 12 patients received SND (I-IV), 18 patients received MRND, and four patients received RND. Concerning the 23 patients who received treatment of the contralateral neck, 18 received SND (I-III), four received SND (I-IV), and one received MRND (Table 2). Among the 107 patients with pN1 OSCC, one (OSCC of the oral tongue) had level IV

(Table 3).

Recurrence and survival rates During follow-up, 24 of the 85 patients

(28.2%) treated with SND presented with local recurrence, 15 patients (17.6%) presented with regional recurrence, and four patients (4.7%) presented with distant metastasis. On comparison with the RND/MRND group, no statistically significant difference in the rates of local recurrence, regional recurrence, or distant metastasis was demonstrated (P > 0.05) (Table 4). Of the 15 SND group patients who presented with regional recurrence, three had recurrence in the dissected levels, 11 had recurrence in levels outside the previous neck dissection, and one had recurrence in both.

On analysis of the 89 patients who underwent both neck dissection and PORT, there was also no statistically significant difference in the rates of local recurrence, regional recurrence, or distant metastasis between the SND and RND/MRND groups, which ruled out possible interference from PORT (P > 0.05) (Table 5).

Table 3. Positive lymph node levels in 107 patients with pN1 OSCC.

	Lymph node level	Total 107 Necks ^a	SND 85 Necks ^a	RND/MRND 22 Necks ^a
Ipsilateral	Ι	68	57	11
1	II	27	21	6
	III	6	5	1
	IV	1	1	0
	V	4	0	4
Contralateral	Ι	1	1	0
	II	0	0	0
	III	0	0	0
	IV	0	0	0
	V	0	0	0

OSCC, oral squamous cell carcinoma; RND/MRND, radical or modified radical neck dissection; SND, selective neck dissection. ^aNumber of positive necks.

Table 4. Recurrences in 107 patients with pN1 OSCC.

		Type of neck di	ssection	P volue ^a
		SND	RND/ MRND	<i>I</i> -value
Number of patients		85	22	
Postoperative recurrence,	Local recurrence	24 (28.2)	9 (40.9)	0.251
n(%)	Regional	15 (17.6)	6 (27.3)	0.368
	recurrence Distant metastasis	4 (4.7)	3 (13.6)	0.151

OSCC, oral squamous cell carcinoma; RND/MRND, radical or modified radical neck dissection; SND, selective neck dissection. $a_{\chi^2}^{a}$ test or Fisher's exact test.

Table 5.	Recurrences	in	89 patients	with pN1	OSCC wh	o received	postoperative	radiotherapy.
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		Type of neck di	issection	<i>R</i> volue ^a
		SND	RND/ MRND 20 7 (35) 5 (25) 2 (10)	<i>I</i> -value
Number of patients		69	20	
Postoperative recurrence,	Local recurrence	17 (24.6)	7 (35)	0.358
n (%)	Regional recurrence	11 (15.9)	5 (25)	0.342
	Distant metastasis	3 (4.3)	2 (10)	0.313

OSCC, oral squamous cell carcinoma; RND/MRND, radical or modified radical neck dissection; SND, selective neck dissection. ${}^{a}\chi^{2}$ test or Fisher's exact test.

Overall, 29 of the 107 patients (27.1%) died of OSCC and five (4.7%) died from other causes. The 5-year OS rate was 68.3% for SND patients and 65.2% for RND/MRND patients (P = 0.590) during follow-up (median follow-up time of 63 months, range 1–108 months). Similarly, the 5-year DSS rate was 70.4% for SND patients and 75.7% for RND/MRND patients (P = 0.715) (Table 6, Fig. 1).

Factors affecting the prognosis of the 85 patients who underwent SND

On univariate analysis of the 85 patients with pN1 OSCC who underwent SND, histological grade III was found to be associated with lower OS (P < 0.001) and DSS (P < 0.001)(Table 7). The final stepwise selection in the Cox proportional hazards regression model revealed significantly worse OS (P < 0.001) and DSS (P < 0.001) outcomes in patients with histological grade III (reference category histological grade I) (Table 8). PORT was found to be associated with improved DSS in the univariate analysis (P = 0.033) (Table 7) and also in the multivariate Cox hazards regression analysis (P = 0.042) (Table 8).

In the multivariate Cox hazards regression analysis to determine whether PORT influenced postoperative 5-year survival in the 85 SND patients according to the pathological grade, 5-year OS (P = 0.004) and 5-year DSS (P = 0.002) in histological grade II/III cases was found to differ significantly between the SND group patients treated with and without PORT, with worse survival for those not treated with PORT (Table 9).

Discussion

Cervical lymph node metastasis is one of the most common biological features of OSCC and affects the prognosis of patients.³ More recently, the neck management of cN1 patients has become controversial, because many studies have reported that SND (I-III) can be applied in cN1 patients with the same prognosis as RND/MRND.⁹ An advantage of SND is a faster postoperative recovery because of the less extensive trauma and reduced complications of neck and shoulder function when compared with RND/MRND.¹ This retrospective study showed no statistically significant difference in the prognosis among patients with pN1 OSCC treated with different neck dissection: SND or RND/MRND. Therefore, it appears appropriate to perform SND (I-III) for cN1 OSCC.

Table 6.	Five-year	survival in	107 OSCC	patients with	pathological 1	N1 nodal stage
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		Type of neck d	lissection	D volue ^a
		SND	RND/MRND	I -value
Number of patients		85	22	
Five-year survival	OS (%)	68.3	65.2	0.590
-	DSS (%)	70.4	75.7	0.715

DSS, disease-specific survival; OSCC, oral squamous cell carcinoma; OS, overall survival; RND/MRND, radical or modified radical neck dissection; SND, selective neck dissection.

 $^{a}\chi^{2}$ test.



Fig. 1. Kaplan–Meier survival estimates according to neck management: (A) 5-year overall survival, and (B) 5-year disease-specific survival. SND, selective neck dissection; RND/MRND, radical or modified radical neck dissection.

Previous retrospective studies have confirmed that single cervical lymph node metastasis in OSCC mainly occurs at levels I-III, which provides a theoretical basis for SND (I-III) as a reasonable neck treatment for cN1 OSCC.15 Shah¹⁵ performed a retrospective study on 1119 patients with head and neck SCC who were treated with RND. The results showed that cervical lymph node metastasis was mainly concentrated within levels I-III, with a lower metastasis rate of 20% and 4% in levels IV and V, respectively. Moreover, of 776 patients with pN+, only 3.7% had level IV and V lymph node metastasis. In a study on 553 OSCC patients, Pantvaidya et al.¹⁶ found that 91% of positive lymph nodes were located at levels I-III, and

metastases at levels IV and V were rare (4.7% and 3.3%, respectively). Patel et al.17 performed a pathological examination on neck dissection specimens from 30 OSCC patients. The results showed that the cervical lymph node metastasis rates at levels I, II, III, IV, and V were 50%, 28.6%, 12%, 7%, and 2.4%, respectively. In the present study on patients with pN1 OSCC, only one patient had level IV metastasis and four had level V metastases. Moreover, only one case of contralateral lymphatic metastasis was observed among the patients who underwent a bilateral neck dissection (23 patients), indicating that unilateral SND (I-III) is appropriate for pN1 OSCC patients with primary lesions not crossing the midline. Klingelhöffer et al.¹⁸ conducted a cohort study involving 146 patients with unilateral SCC of the tongue not crossing the midline. Lymph node metastases were diagnosed in 50 patients (34.2%), but only two (1.1%) had contralateral lymph node metastases. Bilateral neck dissection showed no advantage regarding nodal relapse-free and overall survival when compared with unilateral neck dissection, irrespective of the initial N or T stage (P = 0.606).

There is ongoing controversy regarding the incidence of level IV metastases in oral tongue carcinoma. A systematic review on the prevalence of metastasis and involvement of level IV and V in OSCC showed many reports recommending level IV dissection in oral tongue carcinoma, possibly due to the tendency for early metastasis in tongue cancer.¹⁹ A possible reason may be that the tongue possesses an extensive lymphatic network. The results of a meta-analysis demonstrated low rates of skip metastasis to neck level IV in OSCC patients, with an overall involvement rate of 2.53% and skip metastasis rate of 0.50%.²⁰ Another recent systematic review indicated that in patients with cN0 oral tongue carcinoma, the rate of level IV involvement is less than 3%.²¹ In the present study, nine patients with SCC of the tongue or floor of the mouth underwent SND (I-IV), but only one had level IV metastasis. A strong correlation between site and level IV metastasis is unclear.

Previous studies have shown no statistically significant difference in postoperative neck recurrence rate or survival rate between N1 patients treated with SND and those treated with RND/MRND, which indicates that SND can remove 'risky lymph nodes' and preserve function without increasing the risk of control failure.^{11,22-26} López et al.²² confirmed that SND is an effective and safe surgical approach for patients with cN1 head and neck SCC, and SND can replace RND/MRND without compromising oncological outcomes. In a retrospective study of 68 cN1 necks, Yanai et al.¹¹ found that the regional control rate was 81.3% with SND and 83.0% with RND (P = 0.72), and the DSS rates were 81.3% and 80.0%, respectively (P = 0.94). In a series of 54 cN1-cN2a OSCC patients who underwent primary surgery combined with neck dissection. Shin et al.²³ found that the 2-year DSS rate was 71.8% in the RND group and 69.2% in the SND

			Tive-year	suivivai		
Variables		Number of patients	OS (%)	<i>P</i> -value ^a	DSS (%)	<i>P</i> -value ^a
Total		85	68.3		70.4	
Sex	Male	55	65.8	0.599	69.1	0.820
	Female	30	72.5		72.5	
Site	Oral tongue	37	64.2	0.788	64.2	0.770
	Floor of mouth	10	60		68.6	
	Upper gingiva	3	100		100	
	Lower gingiva	17	69.7		74.3	
	Buccal mucosa	16	78.6		78.6	
	Hard palate	2	50		50	
Histological grade	Grade I	24	81.1	< 0.001*	81.1	< 0.001*
	Grade II	57	66.8		69.7	
	Grade III	4	25		25	
cT classification	cT1	24	81.7	0.411	86.5	0.192
	cT2	40	58.5		58.5	
	cT3	5	60		60	
	cT4	16	75		80.4	
cN classification	cN0	56	67.6	0.478	70.7	0.453
	cN1	21	61.8		61.8	
	cN2	8	87.5		87.5	
pT classification	pT1	18	76.7	0.805	82.2	0.602
-	pT2	47	66.3		66.3	
	pT3	4	50		50	
	pT4	16	68.8		74	
Level of lymph node involvement	I	58	72.0	0.488	75.2	0.327
• •	II	21	63.7		63.7	
	III/IV	6	50		50	
Postoperative radiotherapy	No	16	50.8	0.061	50.8	0.033*
	Yes	69	72.1		74.8	

Table 7. Univariate analysis to determine the factors that influenced postoperative 5-year survival in the 85 patients treated with SND.

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DSS, disease-specific survival; OS, overall survival; SND, selective neck dissection.

^aLog-rank test.

 $^{*}P \leq 0.05.$

group, and the difference was not statistically significant (P = 0.823). Similar to DSS, the 2-year neck control rate also did not differ significantly between the groups (RND 88.0% vs SND 84.0%, P = 0.719). Likewise, in a previous retrospective study, the cN + (cN1-cN2b) group showed no statistically significant difference in 3-year DSS rate between the RND and SND groups (P > 0.05).²⁴ Schiff et al.²⁵ and Patel et al.²⁶ showed similar results in their retrospective studies. In the present study, no statistically significant difference in postoperative neck recurrence rate or survival rate was observed between pN1 patients treated with

SND and those treated with RND/MRND.

This retrospective study showed histological grade and PORT to be two independent predictors of the prognosis of patients with pN1 OSCC in both univariate analysis and multivariate analysis.

The clinical staging combined with histological features may be used to better predict tumour progression and to establish more suitable treatment plans. Kademani et al.²⁷ performed a retrospective study to highlight the importance of histological grade as an independent factor for predicting survival in OSCC patients. Thomas et al.²⁸

claimed a strong association between histological grade and survival in OSCC patients, and a high histological grade in early stage oral cavity cancer was associated with poorer survival and carried independent prognostic value. Through follow-up of 45 OSCC patients, Jing et al.²⁹ found a significant difference in recurrence rate among histological grades (P = 0.038) and established an association between lymph node involvement and poorly differentiated tumours. The World Health Organization (WHO) grading system has been adopted in the Pathology Department of Peking University School and Hospital of Stomatology;

Table 8. Multivariate Cox hazards regression model to determine the factors that influenced postoperative 5-year survival in 85 patients with SND.

Variable		OS	OS			DSS		
		HR	95% CI	P-value	HR	95% CI	P-value	
Histological grade	Grade I Grade II Grade II	Ref. 1.80	0.61-5.32	0.287	1.60	0.54-4.79	0.400	
Postoperative radiotherapy	Yes No	Ref. 2.24	9.73-581.18 0.94-5.39	< 0.001 * 0.071	2.52	8.91-526.25 1.04-6.15	< 0.001* 0.042*	

CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival; SND, selective neck dissection. *P < 0.05.

Variable		nological grade.	OS			DSS		
Histological grade	Postoperative radiotherapy	Number of patients	HR	95% CI	P-value	HR	95% CI	P-value
II/III	Yes No	50 11	Ref. 3.84	1.53–9.65	0.004*	4.47	1.73–11.52	0.002*
Ι	Yes No	19 5	Ref. 0.034	0–943.94	0.517	0.034	0–943.94	0.517

Table 9. Multivariate Cox hazards regression model to examine whether postoperative radiotherapy influenced postoperative 5-year survival in 85 patients with SND grouped by pathological grade.

CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival; SND, selective neck dissection. ${}^{*}P < 0.05$.

this system classifies tumours into grades I-III according to their epithelial differentiation (well, moderately, and poorly differentiated) based on the degree of keratinization, cellular and nuclear pleomorphism, and mitotic activity.³⁰ Lindenblatt et al.³¹ evaluated the prognosis of 53 OSCC patients through a retrospective study and found that the WHO grading system showed statistically significant associations with recurrence (P = 0.043) and disease-free survival (P = 0.031, log-rank test). Lin et al.³² reported that grade III tumours were associated with decreased recurrence-free survival (hazard ratio 1.973, 95% confidence interval 1.167-3.336) when compared with grade I/II tumours in a large cohort of 2535 OSCC patients from Changhua Christian Hospital. No significant differences were detected between grade I and II tumours, which is similar to the findings of the present study.

This retrospective study showed PORT to be significantly associated with DSS in both the univariate analysis and multivariate analysis, which indicates that PORT is also an independent predictor of the prognosis in pN1 patients. At the study hospital, patients who do not receive PORT tend to be older and more likely to suffer from co-morbidities. Thus, a negative pre-selection might have biased the survival analyses and limited the validity of OS as an outcome. Although the positive effect of PORT for patients with advanced OSCC has been verified substantially, the recommendation of PORT in intermediate-risk OSCC cases, such as pN1 without extracapsular spread, has been inconsistent in previous studies. A meta-analysis failed to clarify the effectiveness of PORT in pN1 OSCC patients, reporting a lack of significance and high heterogeneity of the outcome data, and stated that it was not possible to provide general treatment recommenda-³ A prospective study claimed tions.3

that PORT was associated with improved OS, DSS, and regional recurrence-free survival in pT1-2 pN1 oral cancer and should be recommended.³ Chen et al.³⁵ found that PORT was associated with improved survival in patients with pN1 OSCC, especially in those younger than 70 years of age and in those with pT2 disease. Liang et al.³ performed a meta-analysis on selective versus comprehensive neck dissection in cN+OSCC patients and concluded that cN+OSCC patients treated with SND combined with PORT and those treated with MRND/RND had comparable clinical outcomes for regional recurrence, OS, and DSS. However, the Clinical Practice Guideline of the American Society of Clinical Oncology (ASCO)³⁷ does not recommend PORT in pN1 cases with no further histological risk factors, such as perineural invasion or lymphovascular invasion. Therefore, prospective clinical trials are needed to address the current controversy regarding the application of PORT in pN1 cases.

This study found a significant correlation between histological grade and PORT. In the pN1 OSCC patients with histological grade II/III, PORT was observed to improve the survival rates. This suggests that histological grade may complement the TNM staging system and allow the surgeon to provide more appropriate therapy for patients. Very few studies have explored the connection between histological grade and PORT.

This study has several limitations. First, the data were collected from a single medical centre, thus the results may differ from those obtained in other geographical regions. Second, the outcome evaluation indexes did not include disease-free survival, because no accurate time at which the patients were diagnosed with a first recurrence could be determined, due to the limitations of the retrospective study design. Third, there may be some bias in the number and level of dissected lymph nodes.

In conclusion, the results of this retrospective study showed no statistically significant difference in the prognosis among patients with pN1 oral squamous cell carcinoma treated with the different neck dissections: SND or RND/MRND. Histological grade and postoperative radiotherapy were found to be independent predictors of the prognosis in these pN1 patients. In patients with histological grade II/III oral squamous cell carcinoma, postoperative radiotherapy may improve the survival rate. Therefore, it appears appropriate to perform SND (I-III) for cN1 oral squamous cell carcinoma and to perform postoperative radiotherapy when the histological grade is II or III. The conclusions of this study require further validation in prospective studies.

Ethical approval

Ethical approval was obtained from the Biomedical Institutional Review Board of Peking University School and Hospital of Stomatology (PKUSS-IRB-202171210).

Funding

None.

Competing interests

None.

Patient consent

This retrospective study obtained oral informed consent from the patients or their legal representative. An exemption from the need for signed informed consent was obtained.

References

- Funk GF, Karnell LH, Robinson RA, Zhen WK, Trask DK, Hoffman HT. Presentation, treatment, and outcome of oral cavity cancer: a National Cancer Data Base report. *Head Neck* 2002; 24:165–80. https://doi.org/10.1002/hed. 10004
- Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F, Soerjomataram I. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. *CA Cancer J Clin* 2017;67:51–64. https://doi.org/10. 3322/caac.21384
- Massano J, Regateiro FS, Januário G, Ferreira A. Oral squamous cell carcinoma: review of prognostic and predictive factors. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:67–76. https://doi.org/10.1016/j.tripleo.2005.07. 038
- 4. Amit M, Yen TC, Liao CT, Binenbaum Y, Chaturvedi P, Agarwal JP, Kowalski LP, Ebrahimi A, Clark JR, Cernea CR, Brandao SJ, Kreppel M, Zöller J, Fliss D, Bachar G, Shpitzer T, Bolzoni VA, Patel PR, Jonnalagadda S, Robbins KT, Shah JP, Patel SG, Gil Z. Clinical nodal stage is a significant predictor of outcome in patients with oral cavity squamous cell carcinoma and pathologically negative neck metastases: results of the International Consortium for Outcome Research. Ann Surg Oncol 2013;20:3575–81. https://doi.org/10.1245/s10434-013-3044-0
- Hamoir M, Silver CE, Schmitz S, Takes RP, Rinaldo A, Rodrigo JP, Robbins KT, Pitman KT, Medina JE, Ferlito A. Radical neck dissection: is it still indicated. *Eur Arch Otorhinolaryngol* 2013; 270:1–4. https://doi.org/10.1007/s00405-012-2237-7
- Coskun HH, Medina JE, Robbins KT, Silver CE, Strojan P, Teymoortash A, Pellitteri PK, Rodrigo JP, Stoeckli SJ, Shaha AR, Suárez C, Hartl DM, de Bree R, Takes RP, Hamoir M, Pitman KT, Rinaldo A, Ferlito A. Current philosophy in the surgical management of neck metastases for head and neck squamous cell carcinoma. *Head Neck* 2015;37:915–26. https://doi.org/10.1002/hed.23689
- Guo CB, Feng Z, Zhang JG, Peng X, Cai ZG, Mao C, Zhang Y, Yu GY, Li JN, Niu LX. Supraomohyoid neck dissection and modified radical neck dissection for clinically node-negative oral squamous cell carcinoma: a prospective study of prognosis, complications and quality of life. J Craniomaxillofac Surg 2014; 42:1885–90. https://doi.org/10.1016/j. jcms.2014.07.007
- Spalthoff S, Zimmerer R, Jehn P, Gellrich NC, Handschel J, Krüskemper G. Neck dissection's burden on the patient:

functional and psychosocial aspects in 1652 patients with oral squamous cell carcinomas. *J Oral Maxillofac Surg* 2017; 75:839–49. https://doi.org/10.1016/j.joms. 2016.09.037

- Rodrigo JP, Grilli G, Shah JP, Medina JE, Robbins KT, Takes RP, Hamoir M, Kowalski LP, Suárez C, López F, Quer M, Boedeker CC, de Bree R, Coskun H, Rinaldo A, Silver CE, Ferlito A. Selective neck dissection in surgically treated head and neck squamous cell carcinoma patients with a clinically positive neck: systematic review. *Eur J Surg Oncol* 2018; 44:395–403. https://doi.org/10.1016/j.ejso. 2018.01.003
- Barzan L, Talamini R, Franchin G, Pin M, Silvestrini M, Grando G, Galla S, Savignano MG, Armas G, Margiotta F, Vanoni V, Magri E, Grandi C. Effectiveness of selective neck dissection in head and neck cancer: the experience of two Italian centers. *Laryngoscope* 2015;**125**:1849–55. https://doi.org/10. 1002/lary.25296
- 11. Yanai Y, Sugiura T, Imajyo I, Yoshihama N, Akimoto N, Kobayashi Y, Hayashi K, Fujinaga T, Shirasuna K, Takenoshita Y, Mori Y. Retrospective study of selective submandibular neck dissection versus radical neck dissection for N0 or N1 necks in level I patients with oral squamous cell carcinoma. J Oncol 2012;2012:634183https://doi.org/10.1155/ 2012/634183
- Doescher J, Veit JA, Hoffmann TK. The 8th edition of the AJCC Cancer Staging Manual: updates in otorhinolaryngology, head and neck surgery. *HNO* 2017; 65:956–61. https://doi.org/10.1007/ s00106-017-0391-3
- Moeckelmann N, Ebrahimi A, Tou YK, Gupta R, Low TH, Ashford B, Ch'ng S, Palme CE, Clark JR. Prognostic implications of the 8th edition American Joint Committee on Cancer (AJCC) staging system in oral cavity squamous cell carcinoma. Oral Oncol 2018;85:82–6. https://doi.org/10.1016/j.oraloncology. 2018.08.013
- Gane EM, Michaleff ZA, Cottrell MA, McPhail SM, Hatton AL, Panizza BJ, O'Leary SP. Prevalence, incidence, and risk factors for shoulder and neck dysfunction after neck dissection: a systematic review. *Eur J Surg Oncol* 2017; 43:1199–218. https://doi.org/10.1016/j. ejso.2016.10.026
- Shah JP. Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. *Am J Surg* 1990;**160**:405–9. https://doi.org/10.1016/ s0002-9610(05)80554-9
- Pantvaidya GH, Pal P, Vaidya AD, Pai PS, D'Cruz AK. Prospective study of 583 neck dissections in oral cancers: implications for clinical practice. *Head Neck*

2014;**36**:1503–7. https://doi.org/10.1002/ hed.23494

- Patel S, Singh I, Gulati A, Khurana N. A study on neck nodes in oral cancers, with special reference to skip metastasis. *Indian J Otolaryngol Head Neck Surg* 2019;71:474–81. https://doi.org/10.1007/ s12070-018-1360-1
- Klingelhöffer C, Gründlinger A, Spanier G, Schreml S, Gottsauner M, Mueller S, Meier JK, Reichert TE, Ettl T. Patients with unilateral squamous cell carcinoma of the tongue and ipsilateral lymph node metastasis do not profit from bilateral neck dissection. Oral Maxillofac Surg 2018;22:185–92. https://doi.org/10.1007/ s10006-018-0690-1
- Altuwaijri AA, Aldrees TM, Alessa MA. Prevalence of metastasis and involvement of level IV and V in oral squamous cell carcinoma: a systematic review. *Cureus* 2021;13:e20255https://doi.org/10.7759/ cureus.20255
- 20. Warshavsky A, Rosen R, Nard-Carmel N, Abu-Ghanem S, Oestreicher-Kedem Y, Abergel A, Fliss DM, Horowitz G. Assessment of the rate of skip metastasis to neck level IV in patients with clinically node-negative neck oral cavity squamous cell carcinoma: a systematic review and meta-analysis. JAMA Otolaryngol Head Neck Surg 2019;145:542–8. https://doi.org/10.1001/jamaoto.2019.0784
- Weisz Shabtay N, Ronen O. Level IV neck dissection as an elective treatment for oral tongue carcinoma—a systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 2020; 130:363–72. https://doi.org/10.1016/j. 0000.2020.04.810
- 22. López F, Fernández-Vañes L, García-Cabo P, Grilli G, Álvarez-Marcos C, Llorente JL, Rodrigo JP. Selective neck dissection in the treatment of head and neck squamous cell carcinoma patients with a clinically positive neck. *Oral Oncol* 2020;102:104565https://doi.org/10.1016/j. oraloncology.2020.104565
- Shin YS, Koh YW, Kim SH, Choi EC. Selective neck dissection for clinically node-positive oral cavity squamous cell carcinoma. *Yonsei Med J* 2013;54:139–44. https://doi.org/10.3349/ymj.2013.54.1.139
- 24. Feng Z, Li JN, Niu LX, Guo CB. Supraomohyoid neck dissection in the management of oral squamous cell carcinoma: special consideration for skip metastases at level IV or V. J Oral Maxillofac Surg 2014;72:1203–11. https:// doi.org/10.1016/j.joms.2013.12.008
- 25. Schiff BA, Roberts DB, El-Naggar A, Garden AS, Myers JN. Selective vs modified radical neck dissection and postoperative radiotherapy vs observation in the treatment of squamous cell carcinoma of the oral tongue. Arch Otolaryngol Head Neck Surg 2005;

131:874–8. https://doi.org/10.1001/ archotol.131.10.874

- Patel RS, Clark JR, Gao K, O'Brien CJ. Effectiveness of selective neck dissection in the treatment of the clinically positive neck. *Head Neck* 2008;30:1231–6. https:// doi.org/10.1002/hed.20870
- Kademani D, Bell RB, Bagheri S, Holmgren E, Dierks E, Potter B, Homer L. Prognostic factors in intraoral squamous cell carcinoma: the influence of histologic grade. J Oral Maxillofac Surg 2005;63:1599–605. https://doi.org/10. 1016/j.joms.2005.07.011
- Thomas B, Stedman M, Davies L. Grade as a prognostic factor in oral squamous cell carcinoma: a population-based analysis of the data. *Laryngoscope* 2014; 124:688–94. https://doi.org/10.1002/lary. 24357
- Jing J, Li L, He W, Sun G. Prognostic predictors of squamous cell carcinoma of the buccal mucosa with negative surgical margins. *J Oral Maxillofac Surg* 2006; 64:896–901. https://doi.org/10.1016/j. joms.2006.02.007
- Sarradin V, Siegfried A, Uro-Coste E, Delord JP. WHO classification of head and neck tumours 2017: main novelties and update of diagnostic methods. *Bull Cancer* 2018;105:596–602. https://doi.org/ 10.1016/j.bulcan.2018.04.004
- 31. Lindenblatt Rde C, Martinez GL, Silva LE, Faria PS, Camisasca DR, Lourenço

Sde Q. Oral squamous cell carcinoma grading systems—analysis of the best survival predictor. *J Oral Pathol Med* 2012;**41**:34–9. https://doi.org/10.1111/j. 1600-0714.2011.01068.x

- Lin NC, Hsu JT, Tsai KY. Survival and clinicopathological characteristics of different histological grades of oral cavity squamous cell carcinoma: a single-center retrospective study. *PLoS One* 2020; 15:e0238103https://doi.org/10.1371/ journal.pone.0238103
- 33. Moergel M, Meurer P, Ingel K, Wendt TG, Al-Nawas B. Effectiveness of post-operative radiotherapy in patients with small oral and oropharyngeal squamous cell carcinoma and concomitant ipsi-lateral singular cervical lymph node metastasis (pN1): a meta-analysis. Strahlenther Onkol 2011;187:337–43. https://doi.org/10.1007/s00066-011-2206-x
- 34. Alsharif U, Steller D, Falougy M, Tharun L, Rades D, Hakim SG. The benefit of postoperative radiotherapy and extending neck dissection in pT1–2 oral squamous cell carcinoma with a single ipsilateral cervical lymph node metastasis (pN1). Anticancer Res 2022;42:97–104. https://doi.org/10.21873/anticanres.15462
- 35. Chen MM, Harris JP, Hara W, Sirjani D, Divi V. Association of postoperative radiotherapy with survival in patients with N1 oral cavity and oropharyngeal

squamous cell carcinoma. JAMA Otolaryngol Head Neck Surg 2016; 142:1224–30. https://doi.org/10.1001/ jamaoto.2016.3519

- 36. Liang L, Zhang T, Kong Q, Liang J, Liao G. A meta-analysis on selective versus comprehensive neck dissection in oral squamous cell carcinoma patients with clinically node-positive neck. *Oral Oncol* 2015;51:1076–81. https://doi.org/10.1016/j.oraloncology.2015.10.005
- 37. Koyfman SA, Ismaila N, Crook D, D'Cruz A, Rodriguez CP, Sher DJ, Silbermins D, Sturgis EM, Tsue TT, Weiss J, Yom SS, Holsinger FC. Management of the neck in squamous cell carcinoma of the oral cavity and oropharynx: ASCO Clinical Practice Guideline. J Clin Oncol 2019;37:1753–74. https://doi.org/10.1200/jco.18.01921

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